CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-278

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-278

INFORMATION REQUEST LETTER

Celgene Corporation
Attention: Dr. Steve Thomas
Vice President, Regulatory Affairs and Project Management
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas:

Please refer to your October 25, 2000 new drug application for [redacted] (*d-threo*-methylphenidate HCl) oral tablets, 2.5mg, 5mg, and 10mg.

We are reviewing the Chemistry section of your submission and have the following information request. We need your prompt written response to continue our evaluation of your NDA.

1. Refer to page 01 0008 in Volume 1.1 and to page 04 00415 in Volume 1.4. Please provide the Drug Master File number and an updated Letter of Authorization that references the assigned Drug Master File, Type II.

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301) 594-5537.

Sincerely,

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-278

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice Pres., Regulatory Affairs and Project Mgmt.
7 Powder Horn Drive
Warren, New Jersey 07059
USA

Dear Dr. Thomas:

Please refer to the meeting between representatives of your firm and FDA on March 14, 2001. The purpose of the meeting was to discuss [redacted] decision not to manufacture commercial batches of d-threo-methylphenidate, and Celgene's subsequent proposal to amend the NDA to include an alternative commercial drug product manufacturer. [redacted]

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-278

INFORMATION REQUEST LETTER

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Regulatory Affairs and Project Man
7 Powder Horn Drive
Warren, NJ 07059
USA

Dear Dr. Thomas:

Please refer to your October 25, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADEMARK(dexmethylphenidate hydrochloride) 2.5mg, 5.0mg, and 10.0mg tablets.

We also refer to your Desk Copy dated September 4, 2001.

We are reviewing the Chemistry, manufacturing, and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. [redacted] has been sent an Information Request dated September 7, 2001.

2. Please refer to your response Number 5 on page 2 of the Desk Copy and pages 2346 – 2352 in the May 21, 2001 (BC)Amendment. Please provide a revised Certificate of Analysis for each [redacted] drug substance batch such that the impurities are correctly identified.

3. Please refer to your response Number 3 on page 4 in the Desk Copy and refer to pages 33 – 34 in the Desk Copy. We do not accept your proposal in regards to the 2.5mg tablets. As stated in the August 21, 2001 Approvable Letter, the Impurity specification limits for each tablet strength should be consistent. Please provide a revised regulatory specifications for the drug product.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call Donald N. Klein, Ph.D. Review Chemist, at (301) 594-5537.

Sincerely,

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-278

INFORMATION REQUEST LETTER

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice-President, Regulatory Affairs and Project Management
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted](dexmethylphenidate hydrochloride) Tablets, 2.5mg, 5.0mg, and 10.0mg.

We are reviewing the Chemistry section of your submissions and have the following information request. We need your prompt written response to continue our evaluation of your NDA.

Please refer to the following pages: 5/21/01 Desk Copy, page 2286; 2/20/01 (BL)Amendment, pages 605- 608; and Volume 1.13, pages 3801 – 3826. Please provide the complete USAN information for dexmethylphenidate hydrochloride, i.e., chemical name(s), structure, CAS Registry number. Also, please revise the proposed labeling and package insert to reflect the USAN assignment.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-5504.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-278

INFORMATION REQUEST LETTER

Celgene Corporation
Attention: Steve Thomas, Ph.D.
VP Regulatory Affairs & Project Management
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas:

Please refer to your October 25, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (dexmethylphenidate hydrochloride) 2.5, 5.0, and 10.0mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Please refer to the following pages: 2/20/01 N(BC) amendment, pp. 605 – 608; 6/25/01 N(BC) amendment, p. 3218; and 6/25/01 Desk Copy, p. 3218. Please provide a copy of the draft proposed container label for each strength, 2.5mg, 5.0mg, and 10.0mg.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-5504.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC 1, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-278

INFORMATION REQUEST LETTER

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice-President, Regulatory Affairs and Project Management
7 Powder Horn Drive
Warren, NJ 07059

Dear Dr. Thomas:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (methylphenidate hydrochloride) Tablets.

We are reviewing the Chemistry section of your submissions and have the following information request. We need your prompt written response to continue our evaluation of your NDA.

Refer to page 4 01242 in Appendix 4.17 in Volume 1.7. Please revise the Stability Trial Initiation Form such that the example refers to the proposed drug product [redacted] Tablets instead of [redacted] Capsules.

If you have any questions, call Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-5504.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-278

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice Pres., Regulatory Affairs and Project Mgmt.
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas

Please refer to your new drug application (NDA) dated October 25, 2000, received October 25, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (dexmethylphenidate HCl) 2.5 mg, 5 mg, and 10 mg Tablets.

We also refer to our November 13, 2001, Approval letter which stated that your proposed trade name Focalin® was under review by the FDA Office of Post-marketing and Risk Assessment (OPDRA).

OPDRA has concluded that your proposed trade name is acceptable. Therefore, in order to avoid any further delay, we recommend that you submit a 'Special Supplement-Changes Being Effected' labeling supplement for this trade name.

If you should have any questions, please call Ms.Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-278

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice Pres., Regulatory Affairs and Project Mgmt.
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas

Please refer to your new drug application (NDA) dated October 25, 2000, received October 25, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (dexmethylphenidate HCl) 2.5 mg, 5 mg, and 10 mg Tablets.

We acknowledge receipt of your submissions dated:

November 22, 2000	December 4, 2000	December 5, 2000
December 28, 2000	December 29, 2000	January 12, 2001
January 30, 2001	February 13, 2001	February 14, 2001
February 20, 2001	March 8, 2001	March 15, 2001
April 9, 2001	April 25, 2001	May 7, 2001
May 18, 2001	May 21, 2001	June 15, 2001
June 19, 2001	June 20, 2001	June 21, 2001
June 25, 2001	July 3, 2001	July 10, 2001
July 12, 2001		

This new drug application provides for the use of TRADENAME for the treatment of attention deficit disorder.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Phase 4 Commitment

Please commit to performing a study in juvenile rats in order to examine the effects of d-methylphenidate on developing systems, with particular emphasis on neurobehavioral and reproductive parameters. A proposed protocol for such a study should be submitted for our review.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Ms.Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

25 October 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Central Documents Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Submission of New Drug Application

Ladies and Gentlemen:

Pursuant to 21 CFR Part 314, please find enclosed the submission of New Drug Application, NDA 21-278 for *d-threo*-methylphenidate hydrochloride tablets [redacted] Celgene Corporation (Celgene) is submitting this NDA for *d-threo*-methylphenidate hydrochloride for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 to 17 years. Two adequate and well controlled studies demonstrate that *d-threo*-methylphenidate HCl is effective in the treatment of ADHD in children when used in doses up to 20 mg/day, given in two divided doses in the morning and mid-day (approximately 4 hours apart). The drug was safe and well-tolerated. Six hundred and eighty-four children with ADHD have been exposed to *d-threo*-methylphenidate hydrochloride, 426 of them for at least 6 months and 146 for at least 1 year. This experience is supported by the more than 40 years of commercial use of racemic methylphenidate. Access to NDA 10-187 for Ritalin® has been granted by Novartis Pharmaceuticals Corporation and a Letter of Authorization is enclosed. When *d*- and *d,l-threo*-methylphenidate are administered in equimolar doses, exposure to *d*-MPH is comparable.

Celgene has studied *d-threo*-methylphenidate HCl in children aged 6 to 17 years. As requested by the Division of Neuropharmacological Drug Products, Celgene commits to conduct further studies in children under the age of 6 years following approval of this NDA.

This NDA is being submitted in paper and electronic form. All applicable sections of the NDA are provided in paper format except Items 11 and 12 (Case Report Tabulations and Case Report Forms), which are submitted in electronic format. Tabulations for one

Phase 1 Study (Study *d*-MPH/PK-00-001) are provided in paper copy. A summary of the electronic portions is provided below.

Electronic Submission Overview

The electronic submission follows the Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – NDAs" (January 1999). Item 11 (Case Report Tabulations – CRT) and Item 12 (Case Report Forms – CRF) are included in this electronic NDA. In addition, copies of this letter (cover.pdf), a signed Form 356h (356h. pdf), and the NDA Table of Contents (ndatoc.pdf) are included on the CD- ROM. The information has been placed in a main folder named N21278. Inside this directory there are two subfolders:

- **crt Folder (Case Report Tabulations)**

  Located in this subfolder are the data sets for Celgene studies *d*-MPH/PK-99-001, 97-M-01, 97-M-02, 97-M-03, 97-M-04, and 97-M-05. [Note: tabulations for Study *d*-MPH/PK-00-001 are not available electronically and are included as a paper copy.]

- **crf Folder (Case Report Forms)**

  Located in this subfolder are the case report forms for patients that either discontinued due to an adverse event or experienced serious adverse events during the course of the study for Celgene Protocols 97-M-02, 97-M-03, 97-M-04, and 97-M-05. (No adverse events resulted in discontinuation in Studies *d*-MPH/PK-99-001, *d*-MPH/PK-00-001, and 97-M-01, nor were there any serious adverse events in these studies.)

The following is a description of the electronic media being provided for this NDA:

File Size: 180 MB
Number of CDs: 1 (included in Archive Copy, Volume 1.1)
The NDA electronic submission is virus free. The Virus Scan program used was McAfee VShield version 4.0.3.

Please address any questions regarding NDA 21-278 to Dr. Steve Thomas, 732 805 3914.

Sincerely,

Steve Thomas

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

NDA 21-278

NOV - 3 2000

Celgene Corporation
Attention: Steve Thomas, Ph.D.
Vice President, Regulatory Affairs
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas :

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: *d-threo*-methylphenidate HCl Tablets [redacted]

Therapeutic Classification: Standard (S)

Date of Application: October 25, 2000

Date of Receipt: October 25, 2000

Our Reference Number: 21-278

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 25, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 25, 2001 and the secondary user fee goal date will be February 25, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Anna M. Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

/S/

John S. Purvis 11/3/00 (for)
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4164

5 December 2000

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 004
General Correspondence: Response to Questions (Clinical)

Dear Dr. Katz:

This submission is in response to the Division's questions pertaining to the Integrated Summary of Safety. Please refer to the facsimile sent by Ms. Anna Homonnay-Weikel, R. Ph. (Project Manager, Division of Neuropharmacological Drug Products) dated 4 December 2000. The Division's questions are stated below, verbatim and in bold, followed by Celgene Corporation's responses.

1. **It is stated in the second study that the dose may be increased in increments of up to [redacted] Is this a typo?**

The "second study" pertains to Protocol 00-M-07, to be conducted in adult patients with ADHD. The maximum *d*-MPH dose is correctly stated [redacted] This protocol was submitted to IND [redacted]

2. **What is the safety cut-off date for the data that has been submitted? Are all other studies completed?**

All studies for which data were included in the NDA were completed, and consequently no cut-off date was used. These studies are listed in In-text Table 1 of the ISS.

The cut-off date for the three recently initiated studies is 20 October 2000; these studies are briefly described in Section 3.2 of the ISS. There are no other ongoing studies. Information regarding any serious adverse events and adverse events resulting in discontinuation from any of these studies will be included in the Safety Update.

The cut-off date for the published literature is 11 August 2000.

3. **We note that there is a 5% table in the submission. Is there a 1% table in this submission as well?**

With respect to the double-blind, placebo-controlled trials, the incidence of treatment-emergent adverse events that occurred in 2 or more of the patients in any one treatment group is summarized in In-text Table 18 of the ISS. Since there were 46 to 82 patients in the double-blind treatment groups, this table corresponds to adverse events that occurred with an incidence of approximately 2.5 to 4%, depending on treatment group. The complete tabulation of all adverse events by treatment group is in Table 9 (Appendix 1 of the ISS); given the sample sizes, this table is in effect a "1% table".

When considering all pediatric patients exposed to *d*-MPH, whether in a double-blind study or an open-label study, adverse events occurring with an incidence of 2% or more are summarized in In-text Table 22 of the ISS. This table was derived from the complete tabulation of adverse events, provided in Table 9 (Appendix 1 of the ISS).

4. **What were the normal ranges that were used for the laboratory values since these could not be located in the submission?**

As described in Sections 4.7.1.1 and 4.7.1.2 of the ISS, published normal ranges were used for the majority of the clinical laboratory analytes because the central laboratory did not have pediatric normal ranges. Based on a review of the methods used, the following sources were used as the most appropriate for serum biochemistry, hematology, and urinalysis laboratory normal ranges:

- The normal ranges for serum biochemistry parameters were obtained from Pediatric Reference Ranges, Second Edition. Soldin SJ et al. (eds), published by American Association of Clinical Chemists (AACC) Press, Washington, D.C., 1997. [redacted] adult normal ranges were used for electrolytes (sodium, potassium, chloride) and bicarbonate, which do not change with age.

- The normal ranges of [redacted] were used for the hematology parameters.
- [redacted] adult normal ranges were used for urine pH and specific gravity.

Copies of the normal ranges cited above are included in Appendix 3 of the ISS.

5. **Were there any post-baseline ECGs performed?**

There were no post-baseline ECGs performed.

Please do not hesitate to call with any questions.

Sincerely,

Steve Thomas STP

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

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

4 January 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

JAN - 3 2001

RECEIVED HFD-120

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 007
General Correspondence: Response to Requests

Dear Dr. Katz:

This submission is in response to the Division's requests received *via* facsimile from Ms. Anna M. Homonnay-Weikel, R. Ph. (Project Manager, Division of Neuropharmacological Drug Products) dated 20 December 2000. The Division's requests are stated below, verbatim and in bold, followed by Celgene Corporation's responses.

1. **Another desk copy of the Abuse Liability package.**

A desk copy of the Abuse Liability package was hand-delivered to the document control room at 1451 Rockville Pike, HFD-120 on 3 January 2001 to the attention of Ms. Anna M. Homonnay-Weikel.

2. **Response to the following information request for Study 97-M-02: Please refer to p 82, section 3.7.3 of Volume 1.2. In the submission in Table 3.19, VISIT 7 takes place at Week 4. However, the efficacy data set does not have VISIT 007.**

Study 97-M-02 was a 4-week double-blind, randomized, placebo-controlled study that was preceded by a 1-week single-blind, placebo, lead-in phase. A total of seven study visits occurred over a period of 6 weeks. In the data set listings (included as Appendix 3 in the final report for Study 97-M-02), results are presented according to the overall Study Week Number (Study Weeks 000 through 006 in the column labeled "Week

Number") rather than according to the Visit Number. The correlation between Study Visit Number and Week Number is presented in the following table.

Study 97-M-02 Visit Schedule

Screening	1-week Single Blind Placebo	4-week Double Blind Treatment				
(Visit 1)	(Visits 2-3)	Baseline (Visit 3)	Week 1 (Visit 4)	Week 2 (Visit 5)	Week 3 (Visit 6)	Week 4 (Visit 7)
Week 000	Week 001	Week 002	Week 003	Week 004	Week 005	Week 006

Efficacy was evaluated at Study Visits 2 through 7, which corresponds to Study Weeks 001 through 006 in the efficacy data set listings; there is no Study Week 007. Thus, in Table 3.19 of Section 3.7.3 (Volume 1.2, NDA 21-278), reference to Visit 7 (which takes place at the end of the 4-week double-blind treatment phase) corresponds to overall Study Week 006 in the efficacy data set listings.

Please do not hesitate to call with any questions.

Sincerely,

Steve Thomas

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

DUPLICATE

CENTER FOR DRUG EVALUATION AND RESEARCH

JAN 16 2001

RECEIVED HFD-120

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

12 January 2001

NEW CORRESP
N000(C)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-*threo*-methylphenidate HCl Tablets (Attenade™)
Serial No. 008
General Correspondence: Response to FDA Requests

Dear Dr. Katz:

This submission is in response to the Division's requests received *via* facsimile from Ms. Anna M. Homonnay-Weikel, R. Ph. (Project Manager, Division of Neuropharmacological Drug Products) dated 21 December 2000. The Division's requests are stated below, verbatim and in bold, followed by Celgene Corporation's responses.

1. **Please verify that the following submitted electronic data sets for Study PK-00-001 are as follows:**

   Pla1.xls.xls: **contains *d-threo*-methylphenidate plasma concentrations (ng/mL)**
   Pla3.xls.xls: **contains *d-threo*-ritalinic acid plasma concentrations (ng/mL)**

We confirm that the above referenced electronic data sets for PK-00-001 contain the described plasma data.

Appendix 4-40 (and Appendix 6.3.3) is a report on a comparative dissolution study in three different media [redacted] to demonstrate the similarity between the 2.5 mg commercial formulation and the 2.5 mg clinical formulation with respect to *in vitro* dissolution characteristics. (Refer also to Volume 1.3, Section 4.3.10.1, page 04 00103). At the 6 January 2000 pre-NDA meeting, Celgene had asked FDA for confirmation that the comparative dissolution study was adequate to demonstrate equivalence between the commercial and clinical formulas. FDA had replied that the study was acceptable (IND [redacted]

5. **Please provide any available solubility and permeability data to enable classification of your drug according to the Biopharmaceutics classification. This will help in deciding whether a biowaiver may be granted for certain situations that may arise in the NDA review.**

Celgene is submitting herewith the following supporting documentation:

- Comparative Solubility Report (ATTACHMENT A):
  "Equilibrium solubility of d-threo-Methylphenidate Hydrochloride [redacted]

- Permeability References (ATTACHMENT B):

  1) Redalieu E, Bartlett MF, Waldes LM, Darrow WR, Egger H, and Wagner WE. A Study of Methylphenidate in man with Respect to its Major Metabolite. Drug Metabolism and Disposition 1982; 10(6):708-709.

  2) Faraj BA, Israili ZH, Perel JM, Jenkins ML, Holtzman SG, Cucinell SA, and Dayton PG. Metabolism and Disposition of Methylphenidate-^{14}C: Studies in Man and Animals. J Pharm Exper Ther 1974; 191(3):535-547.

Please do not hesitate to call with any questions.

Sincerely,

Steve c.A

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

DUPLICATE

CENTER FOR DRUG EVALUATION AND RESEARCH

JAN 23 2001

RECEIVED HFD-120

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

23 January 2001

NEW CORRESP
N000(C)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 009
General Correspondence: Response to FDA Requests

Dear Dr. Katz:

This submission is in response to a telephone conversation with Dr. Koti, the statistical reviewer, on 12 January 2001. Dr. Koti requested that Celgene Corporation provide him with a diskette for Study 97-M-02 and Study 97-M-03 containing the following information: patient identification, treatment assignment, and baseline value, final value, and change from baseline for the Teacher SNAP-ADHD rating scale and for the Investigator's Clinical Global Impression-Improvement of Illness scale (CGI-I). Because the CGI-I is itself a measure of change and was not assessed at baseline, only the final CGI-I value is reported. Data for Study 97-M-03 is limited to the double blind phase only.

Enclosed please find a diskette containing the following data sets:

1. An Excel spreadsheet containing a Celgene "visit to week" map for Studies 97-M-02, 97-M-03, 97-M-04, and 97-M-05.

2. A SAS data set for Study 97-M-02 containing the following data columns:
   - PID = Patient Identification
   - TSNAPB1 = Double-blind Baseline Teacher Score #1 from Visit 3 (Week 2)
   - TSNAPB2 = Double-blind Baseline Teacher Score #2 from Visit 3 (Week 2)

- TSNAPB = Mean Double-blind Baseline Teacher Score from Visit 3 (Week 2)
- TSNAPF1 = Double-blind Final Teacher Score #1 from Visit 7 (Week 6)
- TSNAPF2 = Double-blind Final Teacher Score #2 from Visit 7 (Week 6)
- TSNAPF = Mean Double-blind Final Teacher Score from Visit 7 (Week 6)
- TSNAPC = Change in Teacher Score from Baseline to Final
- TLABEL = -Treatment Assignment
- CGI_I = CGI-I score from final visit of the double blind treatment phase Visit 7 (Week 6)

3. A SAS data set for Study 97-M-03 containing the following data columns:
   - PID = Patient Identification
   - TSNAPB1 = Double-blind Withdrawal Baseline Teacher Score #1 from Visit 8 (Week 7)
   - TSNAPB2 = Double-blind Withdrawal Baseline Teacher Score #2 from Visit 8 (Week 7)
   - TSNAPB = Mean Double-blind Withdrawal Baseline Teacher Score from Visit 8 (Week 7)
   - TSNAPF1 = Double-blind Withdrawal Final Teacher Score #1 from Visit 10 (Week 9)
   - TSNAPF2 = Double-blind Withdrawal Final Teacher Score #2 from Visit 10 (Week 9)
   - TSNAPF = Mean Double-blind Withdrawal Final Teacher Score from Visit 10 (Week 9)
   - TSNAPC = Change in Teacher Score from Baseline to Final
   - TLABEL = -Treatment Assignment
   - CGI_I = CGI-I score from final visit of the double blind treatment phase Visit 10 (Week 9)

Please do not hesitate to call with any questions.

Sincerely,

Steve Thomas BWC

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

Desk Copy: Dr. Koti, Division of Biometrics, with diskette

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

23 January 2001

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 010
Status of Nonclinical Pharmacokinetic Bridging Studies/Request for Teleconference

Dear Dr. Katz:

The Division of Neuropharmacological Drug Products has previously agreed that Celgene Corporation is not required to conduct lifetime carcinogenicity studies of *d*-MPH provided exposure to *d*-MPH in 2-year rodent carcinogenicity studies conducted by the National Toxicology Program (using dosing with *d,l*-MPH; NTP, 1995[1]) was adequate to assess the carcinogenic potential in humans receiving therapeutic doses of *d*-MPH. Because the NTP studies did not include pharmacokinetic blood sampling, Celgene has conducted bridging dietary pharmacokinetic studies to estimate the exposure to *d*-MPH achieved in the NTP studies. As described previously in [redacted] (submitted 5 October 2000) and in the original submission of NDA 21-278 (dated 25 October 2000), the Celgene-sponsored bridging dietary pharmacokinetic studies are to be completed in three parts:

- Part 1: Pilot 14-Day Dietary Pharmacokinetic Studies In Mice And Rats (Studies 079-008-PK and 079-009-PK, respectively);
- Part 2: Main 28-Day Bridging Dietary Pharmacokinetic Studies in Mice and Rats (Studies 079-005-PK and 079-006-PK, respectively);
- Part 3: Repeat Main 28-Day Bridging Dietary Pharmacokinetic Studies in Mice and Rats (Protocol R00-0533-A and Study 079-014-PK, respectively).

---

[1]National Toxicology Program (1995) Technical Report on the toxicology and carcinogenesis studies of methylphenidate hydrochloride in F344/N Rats and B6C3F$_1$ Mice. National Toxicology Program Report NTP-TR 439, NIH Publication No. 95-3355.

The final reports for Part 1 and Part 2 of this project were included in the original submission of NDA 21-278. The Division has previously agreed that it is acceptable to submit final reports for the repeat 28-day mouse study (Protocol R00-0533-A) and the repeat 28-day rat study (Study 079-014-PK) within 180 and 90 days, respectively, of the submission of NDA 21-278 [redacted] 14 August 2000).

With respect to Part 3, the repeat of the 28-day bridging dietary pharmacokinetic study in rats (Study 079-014-PK) was recently completed. Results in the high dose (1000 ppm) males are anomalously low compared with the previous study (Study 079-006-PK) and with the other dose groups. The availability of the final report is therefore delayed by approximately 2 weeks, pending further investigation of the findings. Celgene is currently undertaking an audit of the contract and analytical laboratories in an attempt to identify the potential source of error. Preliminarily, the observation appears to be the result of mis-dosing.

Celgene requests a telephone call with the Division to discuss how best to proceed. We would like to schedule this call for the week of 5 February, after submission of the report.

Sincerely,

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

Desk Copy:

Ms. Anna M. Homonnay-Weikel, R.Ph.
HFD-120, Room 4025

DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

CENTER FOR DRUG EVALUATION AND RESEARCH

FEB 14 2001

RECEIVED HFD-120

14 February 2001

ORIG AMENDMENT

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

N- BD

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 013
Nonclinical Pharmacokinetic Bridging Studies/Request for Teleconference

Dear Dr. Katz:

As described previously in Serial No. 010 to NDA 21-278 (submitted 23 January 2001), the repeat of the 28-day bridging dietary pharmacokinetic study in rats (Study 079-014-PK) described in Part 3 was recently completed. Results in the high dose (1000 ppm) males were anomalously low compared with the previous study (Study 079-006-PK) and with the other dose groups. The availability of the final report was therefore delayed, pending further investigation of the findings.

In an attempt to identify the potential source of error, Celgene undertook audits of [redacted] on 17 January 2001 and of [redacted] on 19 January 2001. Based on these audits, the observation appears to be due to an animal husbandry error at [redacted] which resulted in rats from two groups having no or limited access to water during the last week of the study. Affected were all of the males in the high dose (1000ppm) groups (Groups 3 and 4), and some of the males in the middle dose (500 ppm) group (Group 2). This error, which went unnoticed by the personnel responsible for the conduct of the study at [redacted] resulted in markedly reduced feed consumption in these animals. As a result of reduced feed and water consumption, there were substantial decreases in body weight in the affected animals. The reduction in body weight and feed consumption in the Group 3 and 4 males are shown in the figures below. Since fewer of the animals in the middle dose males were affected by the water access problem; the mean change in feed consumption and body weight in this group was much less substantial.

[redacted]

Since the route of administration for *d,l*-MPH in this study was through the feed, the resulting plasma levels of *d,l*-MPH analytes in the affected animals were reduced congruently with the reduction in food intake in these animals. Thus, the integrity of the study was compromised and the resulting pharmacokinetic data from the high dose males are considered invalid. Therefore, the study will be repeated.

[redacted] has agreed to again repeat the study (Study No. 079-015-PK), and it is scheduled to begin in mid April. Several refinements have been made to the study design in order to prevent further errors:

1. Body weights will be measured weekly for the first 3 weeks of the study and daily for the last week of the study.
2. Feed consumption will be measured weekly for the first 3 weeks of the study and daily for the last week of the study.
3. A control group receiving 0 ppm *d,l*-MPH will be included to provide a reference for food consumption and weight gain.
4. Water will be provided *via* both an automatic watering system and water bottles.

Celgene stresses that the results of this study were compromised only in the males; the data from all dose groups in the females are comparable with the previous study (Study 079-006-PK). Although the attached protocol includes both sexes, we propose that this study be repeated only in the males. This will avoid the unnecessary sacrifice of additional animals.

It is estimated that the final report will be submitted to the Division mid September 2001. Celgene requests a telephone conversation with the Division to discuss the adequacy of this approach. We would like to schedule this call as soon as possible.

Sincerely,

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

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

February 28, 2001

Robert Seevers, Team Leader
Division of Neuropharmacological Drug Products, HFD-120

Fax: (301) 594-2859 **Page 1 of 2**

NDA 21-278 (oral d-*threo*-methylphenidate for the treatment of attention deficit hyperactivity disorder)

RE: Chemistry Manufacturing and Controls information

Dear Dr. Seevers

I am writing to update you on the status of an important chemistry issue that was brought to our attention on Tuesday February 27th. The manufacturer of d-*threo*-methylphenidate hydrochloride (d-MPH) tablets named in our NDA number 21-278, [redacted] advised Celgene Corporation (Celgene) on that date that they will no longer consider being the commercial supplier for this drug product. We subsequently found out that The Director of [redacted] Branch and informed a contact their that FDA should not undertake a previously scheduled early March [redacted] on Celgene's NDA 21-278 as [redacted] was no longer interested in supplying commercial material to Celgene. Celgene is unable to understand [redacted] rationale in this regard as our company has invested very substantial resources, over a number of years, in supporting [redacted] role as a potential supplier of d-MPH drug product. Furthermore, Celgene had been assisting in preparations for the [redacted] up to Friday February 23 with no indications that [redacted] was considering this action.

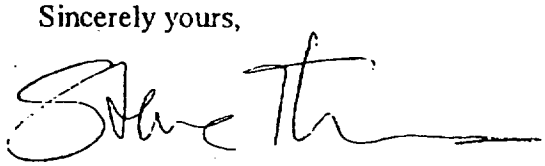
Clearly, a [redacted] is required as expeditiously as possible to validate the information in NDA 21-278 pertaining to clinical and regulatory batches generated at their facility. This validation is needed for your on-going review and is independent of any review of suitability of [redacted] as a potential commercial supplier of drug product. We will be informing the [redacted] Field Branch of our concerns, coincident with this communication and will urge them to undertake the [redacted] as scheduled.

Celgene has already identified an alternate manufacturer for the drug product and discussions with this potential manufacturer are nearing completion. We will be submitting a plan to you March 9 2001, that will outline the data Celgene intends to submit in an amendment to NDA 21-278 to support an alternate commercial manufacturer of drug product. Once you have had an opportunity to review the Celgene proposal to amend the NDA, we would like to meet with Division chemists to discuss the proposed NDA amendment and the implications such an amendment may have on potential approval timelines and expiration dating.

Lastly, Celgene is in discussions with [redacted] about this issue as we hope that they will reconsider their decision and we expect to have more information by the end of this week. We will update the Division as soon as we complete these discussions with [redacted]

Please do not hesitate to call me if you have questions or need additional information.

Sincerely yours,



Steve Thomas, Ph.D.
V.P., Regulatory Affairs and Project Management
Celgene Corporation

cc: Project Manager NDA 21-278
Division of Neuropharmacological Drug Products, HFD-120
4th Floor Document Room
U.S. Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732 271 4184

March 8th 20001

Robert Seevers, Team Leader
Division of Neuropharmacological Drug Products, HFD-120

Fax: (301) 594-2859 **Page 1 of 35**

NDA 21-278 (oral d-*threo*-methylphenidate for the treatment of attention deficit hyperactivity disorder)

RE: Chemistry Manufacturing and Controls information

Dear Dr. Seevers

Please refer to fax correspondence dated February 28th 2001.

In light of the recent, unexpected, decision of [redacted] not to manufacture commercial batches of d-*threo*-methylphenidate hydrochloride (d-MPH) tablets (2.5, 5 and 10 mg), Celgene proposes to amend NDA 21-278 to include an alternate commercial manufacturer of drug product, [redacted]

Celgene seeks the assistance and advice of FDA in understanding how the impact of this very unusual situation may be reduced given the information described below. Specifically, Celgene is seeking the most rapid route to a possible approval accepting that one option may result in a foreshortened initial expiration dating period for drug product at the time of approval.

Celgene also seeks to understand if other issues, for example field inspection access to [redacted] held NDA data, may impact on the review and approval of the NDA.

Celgene wishes to obtain Agency input on the amount, type and timing of stability data to be provided in an amendment to NDA 21-278 that would identify [redacted] as the commercial manufacturer of drug product. Please find attached a summary package of information to support a request for a telecon at your earliest convenience, and preferably within the next 5 business days, if possible

Alison Smith is available to set up the telecon. She can be reached at (732) 271-4152 or by email at asmith@celgene.com.

Please do not hesitate to call me if you have questions or need additional information. Thank you very much for your assistance.

Sincerely yours,

Steve Thomas, Ph.D.
V.P., Regulatory Affairs and Project Management
Celgene Corporation

cc: Teresa Wheelous
Division of Neuropharmacological Drug Products, HFD-120
4th Floor Document Room
U.S. Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4194

3 April 2001

CENTER FOR DRUG EVALUATION
AND RESEARCH

APR - 3 2001

RECEIVED HFD-120

Teresa Wheelous
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Response to FDA Requests: Desk copy of
Revised Proposed Labeling
(Revision 1: Date 15 February 2001)

Dear Ms. Wheelous:

Enclosed please find revised Proposed Labeling (Revision 1: Date 15 February 2001) for *d-threo*-methylphenidate HCl Tablets [redacted] This additional copy is being submitted as a follow-up to the electronic copy e-mailed to you by Dr. Michelle Price on 30 March 2001. The revision was first submitted to the NDA 21-278 as Serial No. 014 on 16 February 2001. It addresses the following error in the original Proposed Labeling, submitted with the NDA on 25 October 2000:

- Figure 1 was incorrect and lacked necessary descriptive text.

Figure 1 has been replaced, and the text, which is highlighted in bold, has been added. Please feel free to contact me with any questions.

Sincerely,

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

Mara Stiles
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936
Tel (973) 781-3771
Fax (973) 781-6325
Internet: mara.stiles@pharma.novartis.com

NOVARTIS

May 30, 2001

DESK COPY

Request for Consultation

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20857

Dear Dr. Katz:

This is with respect to Celgene Corporation's pending NDA 21-278 for dexmethylphenidate tablets. Per executed licensing agreement between Celgene and Novartis, Novartis has obtained an exclusive license to dexmethylphenidate worldwide except for Canada and will become the owner of NDA 21-278 upon approval of the NDA. The trademark to be used with dexmethylphenidate will be the trademark of Novartis.

Novartis proposes the following trademark for dexmethylphenidate tablets:

Proposed tradename: [redacted]

FDA review of the proposed trademark [redacted] is requested in conjunction with the review of Celgene's NDA 21-278. The primary action date for NDA 21-278 is August 25, 2001.

If there are any questions or comments, please contact me at (973) 781-3771.

Sincerely,

Mara Stiles

Mara Stiles
Associate Director
Drug Regulatory Affairs

Celgene

DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey, 07059
Tel: 732-271-1001
Fax: 732-271-1383

25 June 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

JUN 25 2001

RECEIVED HFD-120

ORIGINAL AMENDMENT

N(BC)

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
Dexmethylphenidate HCl Tablets
Serial No. 028
Chemistry, Manufacturing, and Controls: Response to Information Requests from Dr. Robert Seevers (4 June 2001)

Dear Dr. Katz:

This Chemistry, Manufacturing, and Controls amendment contains Celgene Corporation's responses to Dr. Seevers' recent request for additional Chemistry, Manufacturing, and Controls information. Please refer to the facsimile sent by Dr. Robert Seevers (Chemistry Team Leader, Division of Neuropharmacological Drug Products) dated 04 June 2001. A partial response was previously submitted (Serial No. 026, 19 June 2001). Dr. Seevers' request is stated below, verbatim and in bold, followed by Celgene Corporation's responses.

> **Please refer to the following pages: 5/21/01 Desk Copy, page 2286; 2/20/01 (BL) Amendment, pages 605 – 608; and Volume 1.13, pages 3801 – 3826. Please provide the complete USAN information for dexmethylphenidate hydrochloride, i.e., chemical name(s), structure, CAS Registry number. Also, please revise the proposed labeling and package insert to reflect the USAN assignment.**

The complete USAN information for dexmethylphenidate hydrochloride was submitted in Serial No. 026 on 19 June 2001.

The proposed labeling and package insert has been revised to reflect the USAN assigment and is included in this submission. Please note that two additional revisions

have been made to the proposed labeling and package insert for dexmethylphenidate hydrochloride tablets. These are described below.

1. The proposed trade name for dexmethylphenidate hydrochloride tablets has been changed from [redacted]

2. The manufacturing information has been changed from "Manufactured by [redacted] for Celgene Corporation" to "Manufactured by [redacted] for Novartis Pharmaceutical Corporation."

Please do not hesitate to call with any questions.

Sincerely,

Steve Thomas mtp

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

Desk copy to: Dr. Donald Klein, Review Chemist

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: July 2, 2001

To: Dr. Steve Thomas	**From:** Teresa Wheelous
Company: .Celgene	Division of Division of Neuropharmacological Drug Products
Fax number: (732) 271-4184)	**Fax number:** (301) 594-2859
Phone number:	**Phone number:** (301) 594-2850
Subject: NDA 21-278 [redacted]	
Total no. of pages including cover: 1	

Dr. Thomas,

In preparation for the action schedule for August 24, 2001 the following information is needed:

1. New labeling, carton, and container labeling for the new name [redacted] (2 copies)
2. Debarment Statement
3. Financial Disclosure Information
4. Your copy of the End of Phase 2 Meeting Minutes [redacted]

Thank you,

Teresa

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 594-2850. Thank you.

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

July 6th 20001

Donald Klein, Review Chemist
Division of Neuropharmacological Drug Products, HFD-120

Fax: (301) 594-2859 **Page 1 of 10**

NDA 21-278: oral dexmethylphenidate HCl (d-MPH) for the treatment of attention deficit hyperactivity disorder

Re: Chemistry, Manufacturing and Controls

Dear Dr. Klein,

Please refer to the information request from Dr. Seevers, dated 7/2/01, and to page 003052 of Celgene's June 19th 2001 CMC amendment.

- In response to Dr. Seevers' 7/2/01 request for additional Chemistry, Manufacturing and Controls information, copies of the draft proposed container labels for each strength, 2.5, 5 and 10 mg, are attached. There are two copies for each label; the first is actual size and the second is enlarged two-fold.
- Also attached is the Certificate of Analysis for the third and final pilot scale batch of 10 mg d-MPH tablets manufactured by [redacted]

This information will also be submitted as a CMC amendment to the NDA early next week.

Please do not hesitate to call me if you have questions or need additional information. Thank you very much for your assistance.

Sincerely yours,

Steve Thomas, Ph.D.
V.P., Regulatory Affairs and Project Management
Celgene Corporation

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

FAX COVER SHEET

To: Teresa Wheelous	
Organization: Division of Neuropharmacological Drug Products Food and Drug Administration	
Fax: (301) 594-2859	**Voice:**
From: Steve Thomas, Ph D Vice President, Regulatory Affairs and Project Management Celgene Corporation	
Subject: Carton Label and Packaging / New Proposed Tradename Dexmethylphenidate [redacted] NDA 21-278	
Date: 6 July 2001	**No. pages (including this sheet): 1**

Further to your facsimile dated 2 July 2001, I would like to inform you that the packaging artwork (there is no secondary packaging) will be available from our licensee, Novartis, by early next week. These materials are in response to the request in item 1. They will be submitted to you immediately upon receipt, together with the responses to requests in items 2 through 4.

I would also like to take this opportunity to confirm that there are at present no other outstanding requests necessitating a response from Celgene.

A new tradename is being proposed for dexmethylphenidate, [redacted] This name was included in the revised draft labeling recently submitted (Serial No. 028, dated 25 June 2001). Please advise on the procedure for requesting approval of this name by the Office of Post-Marketing Drug Risk Assessment. Specifically, it is our understanding that this process can be undertaken using the proposed draft labeling. If not, what are the additional materials required in order to initiate this process? Also, you indicated that the committee requires approximately 45 days in order to reach an opinion. If there is failure to reach agreement on a tradename before 24 August, what is the impact on the action, assuming the product would otherwise be approved?

This letter will be sent as an official submission. I look forward to your response. Please do not hesitate to call with any additional questions.

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

July 10th 20001

Donald Klein, Review Chemist
Division of Neuropharmacological Drug Products, HFD-120

Fax: (301) 594-2859 **Page 1 of 7**

NDA 21-278: oral dexmethylphenidate HCl (d-MPH) for the treatment of attention deficit hyperactivity disorder

Re: Chemistry, Manufacturing and Controls, bottle labels

Dear Dr. Klein,

Please refer our fax submission of 7/6/01.

A minor revision has been made to the bottle labels as submitted to you last week. Specifically, the statement "Protect from light and moisture" has been added. As before, attached are two copies of the label for each tablet strength, one each at actual size and one of each enlarged 200%.

The revised bottle labels will be submitted as an amendment to the NDA.

Please do not hesitate to call me if you have questions or need additional information.

Sincerely yours,

Steve Thomas, Ph.D.
V.P., Regulatory Affairs and Project Management
Celgene Corporation

Received
9/5/01

Celgene

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

September 4th 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 05 2001

RECEIVED HFD-120

Donald Klein, Review Chemist
Division of Neuropharmacological Drug Products, HFD-120
1451 Rockville Pike
Rockville, MD 20852

NDA 21-278 (oral dexmethylphenidate for the treatment of attention deficit hyperactivity disorder)

Re: Responses to Chemistry, Manufacturing and Controls and Clinical Pharmacology and Biopharmaceutics Issues Contained in the August 21st Approvable Letter

Dear Dr. Klein,

Please find attached a desk copy of our responses to the CMC and Biopharm. issues contained in the approvable letter for NDA 21-278. This information will be formally submitted to the NDA with the complete resubmission of data requested in the approvable letter.

Please do not hesitate to call me if you have questions or need additional information. Thank you very much for your assistance.

Sincerely yours,

Alison Smith RAC
Manger, Regulatory Affairs/CMC

Celgene Corporation
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Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 07 2001

RECEIVED HFD-120

6 September 2001

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Building WOC 2
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
4th Floor Document Room – HFD-120
Rockville, MD 20857

20.1

Re: NDA 21-278
Dexmethylphenidate HCl Tablets
Serial No. 037
Proposed Trade Name

DUPLICAT

N-C
NEW CORRESPONDENCE

Dear Dr. Katz:

As stated in the August 21, 2001 approvable letter sent *via* facsimile, the Office of Post-Marketing Drug Risk Assessment has recommended that the trade name [redacted] not be accepted. Celgene Corporation (Celgene) together with our licensee, Novartis, intends to provide information in support of this trade name.

Celgene will respond to all remaining deficiencies and issues raised in the approvable letter, and requests that such a submission be considered a complete response. Specifically, Celgene would like to request that trade name discussions between the Agency and Novartis be considered a separate issue. Dr. Roy Dodsworth of Novartis indicated to Celgene (per a discussion he had with you and Dr. Thomas Laughren of the Division of Neuropharmacological Drug Products on Tuesday, the 4th of September) that separating the trade name discussion from the other approvable letter issues would be acceptable. We would be most grateful if the Division would provide us with written confirmation that separate review tracks are appropriate and that therefore approval could occur prior to an agreement being reached on tradename.

If you have any concerns regarding this submission, do not hesitate to contact me at (732) 805-3914.

Sincerely,

Steve Thomas

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

NEW CORRESPONDENCE

Celgene DUPLICATE

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey, 07059
Tel: 732-271-1001
Fax: 732-271-1383

13 September 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

SEP 14 2001

RECEIVED HFD-12

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
Dexmethylphenidate HCl Tablets
Serial No. 038
Proposed Trade Name

Dear Dr. Katz:

As stated in Serial No. 037, submitted on 6 September 2001, Celgene Corporation (Celgene) together with our licensee, Novartis, intends to provide information regarding the trade name. This letter serves as authorization from Celgene that Novartis be allowed to directly discuss issues pertaining to the trade name with the Agency. Celgene also authorizes Novartis to submit any introductory promotional materials directly to the Agency and to the Division of Drug Marketing, Advertising, and Communications.

If you have any concerns regarding this submission, do not hesitate to contact me at (732) 805-3914.

Sincerely,

Steve Thomas, PhD

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

NEW CORRESPONDENCE

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 201 503 7500
Fax 201 503 6325

18 September 2001

Russell Katz, MD, Director
Division of Neuropharmacological
Drug Products, HFD-120
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

DUPLICATE

SEP 21 2001
HFD-120

NDA No. 21-278
Dexmethylphenidate HCl Tablets
Proposed Tradename
General Correspondence

N - C

Dear Dr. Katz:

Reference is made to the above-listed approvable New Drug Application sponsored by Celgene Corporation of Warren, New Jersey. Further reference is made to correspondence from Celgene to your office dated 13 September 2001 (copy attached), in which Celgene authorized your office to accept correspondence directly from Novartis related to trade name issues. This is a consequence of the Agency's rejection of the previously proposed [redacted] as the prospective trade name for dexmethylphenidate HCl tablets. For your information, Novartis Pharmaceuticals Corporation holds exclusive North American Marketing rights to this product, and will launch, promote and market same subsequent to its final approval.

In the approvable letter for Celgene's NDA dated 21 August 2001, the Agency noted that the name [redacted] was not acceptable to FDA's Office of Post-Marketing Drug Risk Assessment due to concern over potential confusion with Ritalin with the possibility for medication errors. Novartis has carried out extensive testing of the [redacted] trade name with both prescribers and dispensing pharmacists and have determined that the concern from OPDRA is not warranted. Results of these tests can be provided upon request. Nevertheless, in an effort to ameliorate the perceived concerns from OPDRA, Novartis would like to revise the pending trade name by adding an additional [redacted] at the end resulting in the name [redacted] It is our belief that the use of [redacted] should eliminate any and all concern that OPDRA might have concerning possible mix-ups. Having two "crossed letters" at the end of the name should obviate any chance for confusion with Ritalin in either the written or spoken word.

We request that you send this revised trade name to OPDRA for evaluation and approval. Once we have received confirmation from your office that [redacted] is an acceptable name, we shall then revise the pending labeling which was submitted by Celgene as part of their complete response on 14 September 2001 , and which employed "TRADENAME" in lieu of the actual proprietary name.

We trust that the submission and review of the above-described trade name will conclude any issues related thereto, and look forward to your confirmation of its acceptability.

Should you have any questions related to this issue, please contact the undersigned at 973-781-3250.

Sincerely,

Roy W Dodsworth
Executive Director, Drug Regulatory Affairs
Global Therapeutic Area Head, Neuroscience

Copy: Steve Thomas, PhD, Vice President, Celgene Corporation
Ms. Theresa Wheelous, Project Manager, HFD-120

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

24 September 2001

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

Re: NDA 21-278
Dexmethylphenidate HCl Tablets
Serial No. 040
General Correspondence

Dear Dr. Katz

Please refer to Celgene's responses to the approvable letter for Dexmethylphenidate HCl tablets (NDA 21-278) submitted 14 September 2001 (Serial No. 039). Celgene seeks to confirm the action date for this resubmission.

I look forward to your response. Please do not hesitate to contact me at (732) 805-3914 if you have any questions or need additional information.

Sincerely,

Steve Thomas

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: October 11, 2001

To: **Dr. Steve Thomas**	**From:** Teresa Wheelous
Company: Celgene	Division of Division of Neuropharmacological Drug Products
Fax number: (732) 271-4184)	**Fax number:** (301) 594-2859
Phone number:	**Phone number:** (301) 594-2850

Subject: **NDA 21-278 TRADENAME Comment**

Total no. of pages including cover: 1

Dr. Thomas

The following is a Biopharmaceutics Comments regarding the 9/14/01 response to the approvable letter:

The Office of Clinical Pharmacology & Biopharmaceutics (OCPB) maintains the recommendation of a revised *in vitro* dissolution specification of Q = [redacted] dissolved at **30 min**, and does not accept the sponsor's proposed retention of a Q = [redacted] at 45 min as an interim specification.

It should be noted that the USP monograph specification of Q = [redacted] at 45 min describes the *in vitro* specifications for *d,l-threo*-methylphenidate, not for dexmethylphenidate. The proposed Q = [redacted] dissolved at 30 min, may serve as an interim specification until the *in vitro* dissolution data is available from the accelerated, intermediate and long-term stability batches specified by the sponsor. If the specified stability batches fail to meet a Q = [redacted] at 30 minutes, the sponsor can submit the new *in vitro* dissolution data together with the revised *in vitro* dissolution specifications. A discussion regarding the potential impact on the *in vivo* performance of the tablets is requested to justify the change of the *in vitro* specification. The new data and revised *in vitro* dissolution specifications, including the justification regarding the *in vivo* performance of the change should be submitted as a supplement, at the same time as the first annual report to NDA 21-278. This supplement should be a separate submission from the annual report.

Thank you,

Teresa

Mara Stiles
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080
Tel (973) 781-3771
Fax (973) 781-6325
Internet: mara.stiles@pharma.novartis.com

NOVARTIS

October 25, 2001

NDA 21-278
Dexmethylphenidate HCl tablets
2.5, 5 and 10 mg

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, MD 20857

Dear Dr. Katz:

We refer to our Sept 13 and 28, 2001 correspondence regarding the tradename for approvable NDA 21-278 for dexmethylphenidate. As noted in those letters, Celgene Corporation has provided authorization for Novartis to discuss issues pertaining to the tradename directly with the Agency.

The proposed tradename of [redacted] was revised per September 13 letter to [redacted]

At this time, we are providing an alternate tradename in the event the proposed tradename is not found to be acceptable.

The following is the proposed alternate tradename for this product:

Focalin™

Please note that the market research provided as volume 2 of our September 28, 2001 submission included Focalin™.

We look forward to rapidly reaching a conclusion on the tradename for this product so that the tradename will be agreed upon in time for the November 14 action date for this application.

If there are any questions or comments, please contact me at (973) 781-3771.

Sincerely,

Mara Stiles

Mara Stiles
Associate Director
Drug Regulatory Affairs

Copy: OPDRA (HFD-400)

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 732-271-1001
Fax 732-271-4184

DUPLICATE

16 February 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

FEB 16 2001

RECEIVED HFD-120

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike, HFD-120
Rockville, MD 20852

NC

Re: NDA 21-278
d-threo-methylphenidate HCl Tablets [redacted]
Serial No. 014
Corrections to Proposed Labeling

Dear Dr. Katz:

Enclosed please find revised Proposed Labeling for *d-threo*-methylphenidate HCl Tablets [redacted] This revision addresses the following error in the original Proposed Labeling, submitted with NDA 21-278 on 25 October 2000:

- Figure 1 was incorrect and lacked necessary descriptive text.

Figure 1 has been replaced, and the text, which is highlighted in bold, has been added. Please feel free to contact me with any questions.

Sincerely,

Steve Thomas PWC

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