

For each of the following four categories of events of interest, please provide a tabular summary of requested information for all spontaneous or literature reports, foreign and domestic, serious<sup>1</sup> and non-serious (except as otherwise noted), received from January 1, 2000 through June 30, 2005.

Please include string search of reporter verbatim terms, as well as MedDRA (or other safety dictionary used by Sponsor, such as COSTART) coded events, which may include or reflect the following clinical conditions (events of interest):

- **Signs and/or symptoms of psychosis/mania**
  - Hallucination (*any type, including visual, auditory, tactile, mixed, etc*)
  - Delusion (*any type including somatic, persecutory, grandeur, reference*)
  - Schizophrenia (*any type*)
  - Psychotic disorder
  - Transient psychosis
  - Acute psychosis
  - Paranoia
  - Childhood psychosis
  - Schizophreniform disorder
  - Schizoaffective disorder
  - Catatonia
  - Mania
  - Hypomania
  
- **Suicidal ideation and behavior**
  - Depression suicidal
  - Gun shot wound
  - Intentional self-injury
  - Non-accidental overdose
  - Overdose
  - Self injurious behavior
  - Self injurious ideation
  - Self-mutilation
  - Suicidal ideation
  - Suicide attempt
  - Completed suicide
  
- **Aggression and violent behavior**
  - Aggression
  - Anger

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<sup>1</sup> Regulatory definition of serious adverse event (CFR 312.32): "Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

- Hostility
- Homicidal ideation
- Sexual offense
- Murder
- Imprisonment
- **Miscellaneous psychiatric events (include events with serious outcome only)**
  - Abnormal behavior
  - Agitation
  - Amnesia
  - Confusional state
  - Depressed mood
  - Depression
  - Disorientation
  - Emotional disorder
  - Emotional distress
  - Feeling abnormal
  - Memory impairment
  - Mood altered
  - Mood swings
  - Personality change
  - Thinking abnormal
  - Anxiety
  - Fearfulness
  - Phobia
  - Panic attack
  - Sleep disturbance
  - Tics
  - Obsessive or compulsive behavior
  - Trichotillomania

Please provide a tabular summary (see Attachment 1 for a sample tabular summary format) of each case with the following information:

- File ID number;
- Country of origin;
- Reporter type (i.e., health professional, consumer, literature, legal);
- Patient age;
- Patient gender;
- Suspect drug(s);
- Concomitant drug(s);
- Dose, duration, and indication for therapy with <drug name>;
- Reporter verbatim adverse effects;
- MedDRA Preferred Term (or other coded events as applicable);
- Is this event an exacerbation of a pre-existing condition (yes or no);
- Patient medical history and/or comorbid conditions;
- Past psychiatric history or comorbid conditions other than ADHD;

- Has patient been diagnosed with a seizure disorder (yes or no);
- Is drug abuse suspected (yes or no);
- Is drug overdose suspected or reported (yes or no);
- Serious outcome, if any (i.e., death, hospital admission, life-threatening, medically important, etc);
- Dechallenge (i.e., did event resolve or improve after drug was stopped);
- Rechallenge (i.e., did event recur after drug was restarted); does patient have a family history of bipolar disorder or psychosis (yes or no).

Please provide a separate tabular summary for each of the four categories described above (i.e., psychosis, suicidal events, aggression/violence, and miscellaneous serious psychiatric events). In addition, please provide capsule summaries for each of these reports in an appendix, sorted by file ID number, for each of the four categories. If feasible, please submit this information in electronic format, with hyperlink by File ID number from each report listed in the table to a capsule summary in the appendix.

## **2. Analysis of clinical trial database**

For the adverse events of interest described above, we request that you conduct a search of your clinical trial database for patients of all ages. Please include string search of reporter verbatim terms, as well as MedDRA (or other safety dictionary used by Sponsor, such as COSTART) coded events, which may include or reflect the adverse events of interest. Please enumerate these adverse events in your clinical trials with <drug name> and include a line listing of all patients in your clinical trials with <drug name> who experienced these events, along with summary frequency counts for these events. Please include not only patients who received <drug name> but also those treated with placebo or an active control, and those treated during open label run-in periods and during open label extensions. Please provide a separate enumeration of two categories of post-treatment events: those occurring in the first 48 hours after the end of treatment, and a second category occurring after 48 hours and up to 30 days after the last dose of study medication. The tabular list of individual patients should include routine clinical information as specified in the attached template (see Attachment 2 for sample table). Please list events occurring during double-blind treatment, open label treatment, and after treatment in separate tables, as shown. There should be one row for each distinct event, so that some patients may have multiple rows, even for the same type of event (e.g., a patient might have a hallucination during week 1 and then again during week 4.) For adverse events designated as “serious” or as reasons for premature treatment discontinuation, we ask that you also provide a brief narrative summary of each case and the case report form.

In addition, we ask that you include a brief synopsis of the study design for the relevant clinical trials. The format for a clinical study synopsis suggested in the ICH E3 Guidance on clinical study reports would be sufficient. Please be sure to indicate the location of the trial if it was conducted outside the U.S., and whether the trial involved outpatients or inpatients (we expect that the majority of these studies were conducted in outpatient settings).

Finally, in order to make comparisons between treatments, we ask that you provide the relevant exposure information (numbers of patients and patient-years) for all treatments studied. Please

stratify the data according to open label run-in, open label extension, or double blind treatment; gender; and age group (age less than or equal to 12 years, age 13-17 years, and age over 17 years). We expect that some patients may contribute both open label and double blind exposure.

Please include a count of events that occurred during study treatment for each category of events and stratum. Each category of event should be counted only once for any given patient, e.g., if a patient has distinct events in the category of "suicidal ideation and behavior" during weeks 2 and 4, this would count as only 1 such event for that patient. (Events occurring after the end of study treatment will appear in the tabular listing of events but should not be included here. Similarly, events from clinical pharmacology studies should be included in the tabular listing of events but please omit those studies from this summary of clinical trial data.) Attachment 3 provides a sample table which suggests a format for this information; if feasible, please provide this in an electronic spreadsheet format. As an additional secondary analysis, please provide similar displays of data limited to the subgroups of patients who completed the randomized, double blind trials.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manager, at (301) 594-5793.

Sincerely,  
*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Acting Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Attachments

**ATTACHMENT I**  
**SIGNS AND/OR SYMPTOMS OF PSYCHOSIS OR MANIA**  
**<DRUG NAME>**

**Tabular Summary of Spontaneous or Literature Reports for Events of Interest<sup>2</sup>**  
**Sponsor Received Date from January 1, 2000 through June 30, 2005**

File ID number	Country of origin	Reporter type <sup>3</sup>	Patient age (years)	Sex	Suspect drug(s)	Concomitant drug(s)	Dosage of <drug name> (total daily dose in mg)	Duration of therapy <sup>4</sup>	Indication for therapy with <drug name>	Reporter verbatim adverse event(s)	MedDRA Preferred Term(s) <sup>5</sup>	Exacerbation of pre-existing condition? (yes or no)
4297425	US	C	6	M	<drug name>	atropine drops	36	NR	ADHD	"seeing bugs and insects crawling on the floor" "being afraid"	hallucination NOS; headache	No
4370915	Germany	HP	11	M	<drug name>	pipamperone	36	42 days	ADHD	"optical and acoustic hallucinations, abnormal thinking, paranoid thoughts"	hallucination, visual; thinking abnormal; hallucination auditory; paranoia	No
4416161	US	HP	6	F	<drug name>	None	18, increased to 54	Few months	ADHD	"seeing bugs over her and having them coming out of her feet and hands" "screaming"	hallucination, visual	No

<sup>2</sup> Reports resulting from string search of reporter verbatim terms, as well as MedDRA (or other applicable coding dictionary) Preferred Terms (PTs), which may reflect the following clinical conditions: hallucination (any type, including visual, auditory, tactile, mixed, etc), delusion (any type including somatic, persecutory, grandeur, reference), schizophrenia (any type), psychotic disorder, transient psychosis, acute psychosis, paranoia, childhood psychosis, schizophreniform disorder, schizoaffective disorder, catatonia, mania, hypomania. Search includes both foreign and domestic, serious and non-serious reports received from all spontaneous or literature sources between Jan 1, 2000 through June 30, 2005.

<sup>3</sup> Reporter type: HP (health professional), C (consumer), LIT (literature), LEG (legal), O (other)

<sup>4</sup> Indicate duration of therapy with <drug name> at time of adverse event onset; provide estimate if exact number of days is not reported (e.g., "few days", "several years")

<sup>5</sup> Or other coding dictionary used by Sponsor, such as COSTART

SIGNS AND/OR SYMPTOMS OF PSYCHOSIS OR MANIA  
<DRUG NAME> (Continued from previous page)

File ID number (cont'd)	Patient medical history and/or comorbid conditions	Patient psychiatric history (other than ADHD)	Diagnosis of seizure disorder (yes or no)	Is drug abuse suspected <sup>6</sup> (yes or no)	Overdose <sup>7</sup> (yes or no)	Serious outcome (if any) <sup>8</sup>	Positive dechallenge (yes or no) <sup>9</sup>	Positive rechallenge (yes or no) <sup>10</sup>	Family history of bipolar disorder or psychosis (yes or no)
4297425	Strabismus	NR	No	No	No	IMP	N/A	N/A	NR
4370915	NR	Schizoaffective disorder	No	No	No	H	No	N/A	Yes (schizophrenia)
4416161	NR	NR	No	No	No	IMP	Yes	N/A	NR

<sup>6</sup> Indicate whether drug abuse with <drug name> and/or other drug(s) was reported or suspected

<sup>7</sup> Indicate whether overdose with <drug name> and/or other drug(s) was reported or suspected (i.e., amount taken by patient exceeded maximum recommended dosage)

<sup>8</sup> Serious outcomes: D (death), LT (life-threatening), H (required or prolongs hospitalization), DIS (disabling), IMP (other medically important), N (non-serious)

<sup>9</sup> Did event resolve or improve after drug was stopped; if drug was not stopped indicate not applicable (N/A)

<sup>10</sup> Did event recur after drug was restarted; if drug was not restarted indicate not applicable (N/A)



ATTACHMENT 3

Sample table for clinical trial exposure and event data

Trial	Treatment assignment	Gender	Age category	N	Person-time (days)	Psychosis/mania events (n)	Suicidal events (n)	Aggression events (n)
123	Placebo	M	≤12	22	294	1	1	2
123	Placebo	F	≤12	8	103	0	0	1
123	Methylphenidate 20 mg etc.	M	≤12	25	305	0	0	1

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/s/

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Thomas Laughren  
9/14/2005 12:16:05 PM

## MEMORANDUM OF TELECON

DATE: April 15, 2005

Time: 9:30-11:00 am

APPLICATION NUMBERS: NDA 21-121, 21-259, 21-475, 21-419, 10-187, 21-284, 18-029, 21-278, 21-514

**BETWEEN:**

Name: McNeil Consumer and Specialty Pharmaceuticals  
Novartis Pharmaceuticals Corporation  
UCB Pharma, Inc.  
Tyco Healthcare / Mallinckrodt  
Noven Pharmaceuticals, Inc.

**AND**

Name: Russell Katz, M.D., Division Director  
Thomas Laughren, M.D., Psychiatric Clinical Team Leader  
Paul Andreason, M.D., Psychiatric Clinical Team Leader  
Glenn Mannheim, M.D., Clinical reviewer  
Barry Rosloff, Ph.D., Pharmacology/Toxicology Supervisor  
Judy Racoosin, M.D., Safety Group Team Leader  
Richardae Taylor, Pharm.D., Regulatory Project Manager  
Division of Neuropharmacological Drug Products, HFD-120

**SUBJECT:** Meeting to discuss recent paper published regarding cytogenetic effects in children treated with methylphenidate

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**Background:**

An article (in press) on the subject of potential cytogenetic effects in children treated with methylphenidate recently came to the Division's attention<sup>1</sup>. The Division arranged a meeting with the sponsors of all methylphenidate products to discuss the Agency's current thinking regarding this paper and what role the Agency expects the sponsors of methylphenidate products to play in further evaluating the problem.

**Teleconference:**

Dr. Katz started the meeting by discussing the recent paper that will be published and the need for the teleconference. Dr. Katz told the sponsors that the Agency wants them to work together to rapidly evaluate this concern with a cross-sectional study of children on methylphenidate, on

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**1 Cytogenetic effects in children treated with methylphenidate**

Randa A. El-Zein<sup>a</sup>, Sherif Z. Abdel-Rahman<sup>b</sup>, Matthew J. Hay<sup>b</sup>, Mirtha S. Lopez<sup>a</sup>, Melissa L. Bondy<sup>a</sup>, Debra L. Morris<sup>b</sup>, Marvin S. Legator<sup>b</sup>, CANCER LETTERS xx(2005)1-8; available at [www.sciencedirect.com](http://www.sciencedirect.com)

a.Department of Epidemiology, Box 189, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

bDepartment of Preventive Medicine and Community Health, The University of Texas Medical Branch, 2.102 Ewing Hall, Galveston, TX 77555-1110, USA

Received 22 November 2004; received in revised form 6 January 2005; accepted 10 January 2005

alternative drug treatments for ADHD, and a control group on non-psychiatric medications. Dr. Katz explained that this design was chosen because a cross-sectional study could be done rapidly in children already taking these drugs, even though this would not provide a definitive answer. In preparation for a cross-sectional study, Dr. Katz asked each sponsor to prepare and submit a draft protocol. It was noted that the actual conduct of the study may involve multiple sponsors and the NIH.

In addition, Dr. Katz suggested that sponsors might begin thinking about study designs to try to replicate the study that was described in the paper that is soon to be published.

There will be another meeting between the Agency, each of the sponsors, and the NIH to discuss the specifics of the study.

The Agency is still interpreting the available data from the study that was the subject of the recent paper and we are attempting to obtain additional information that may help in interpreting the findings from that study.

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Richardae Taylor, Pharm.D.  
Regulatory Health Project Manager, HFD-120

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

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Russell Katz  
5/3/05 10:44:49 AM



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO ( <i>Division/Office</i> ): <b>Controlled Substance Staff RKW2 RM 1205 HFD-009 5515 Security Lane</b>		FROM: HFD-120/ Division of Neuropharmacological Drug Products		
DATE July 5, 2005	IND NO.	NDA NO. 21-514	TYPE OF DOCUMENT Response to Not approvable letter	DATE OF DOCUMENT June 28, 2005
NAME OF DRUG methylphenidate transdermal system	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE <b>6-month clock, due date for application is 12/28/05</b>	
NAME OF FIRM: Noven Pharmaceuticals, Inc.				
<b>REASON FOR REQUEST</b>				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
<p>On April 25, 2003, the Division issued a not-approvable letter for NDA 21-514 for methylphenidate transdermal system (reference IND 54,732). Noven and their co-development partner Shire have submitted their response to that action. This submission is entirely electronic and is located in the EDR: The network path location is:  <u>\\CDSESUB1\N21514\N 000\2005-06-28</u></p> <p>Please review the submission and provide any comments.  Thanks!</p>				
SIGNATURE OF REQUESTER Richardae Taylor, Pharm.D. Regulatory Project Manager 301-594-5793 taylorr@cderr.fda.gov		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> X MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Richardae Taylor  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO ( <i>Division/Office</i> ): HFD-420/Director, Division of Medication Errors and Technical Support; PKLN Rm. 6-34		FROM: HFD-120/ Division of Neuropharmacological Drug Products		
DATE July 5, 2005	IND NO.	NDA NO. 21-514	TYPE OF DOCUMENT Response to Not approvable letter & Tradename Proposal	DATE OF DOCUMENT June 28, 2005
NAME OF DRUG Methylphenidate Transdermal System	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG ADHD	DESIRED COMPLETION DATE <b>November 1, 2005</b>	
NAME OF FIRM: Noven Pharmaceuticals, Inc.				
<b>REASON FOR REQUEST</b>				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
<p>On April 25, 2003, the Division issued a not-approvable letter for NDA 21-514 for methylphenidate transdermal system (reference IND 54,732). Noven and their co-development partner Shire have submitted their response to that action and have proposed a new trade name, "Daytrana". This submission is entirely electronic and is located in the EDR: The network path location is: <u>\\CDSESUB1\N21514\N_000\2005-06-28</u></p> <p>The due date for this application is 12/28/05. Please review the new proposed name and provide feedback for the Division by 11/1/05.</p> <p>Thanks!</p>				
SIGNATURE OF REQUESTER Richardae Taylor, Pharm.D. Regulatory Project Manager 301-594-5793 taylorr@cderr.fda.gov		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
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Richardae Taylor  
9/6/2005 04:40:24 PM

TELECONFERENCE MEETING MINUTES  
NDA 21-514

Date: August 3, 2005  
Location: Conference Room E; WOC2  
Time: 3:00 – 4:00 PM  
Firm: Noven Pharmaceuticals, Inc. / Shire Pharmaceuticals, Inc.  
Drug: methylphenidate transdermal system  
Indication: ADHD  
Meeting Chair: Thomas Laughren, M.D., Division Director, DPP  
Meeting Recorder: Richardae Taylor, Pharm.D., Regulatory Project Manager

**Participants:**

**FDA:**

Dr. Thomas Laughren	Acting Division Director, DPP
Dr. Paul Andreason	Acting Deputy Division Director, DPP
Dr. Robert Levin	Clinical Reviewer
Dr. Thomas Oliver	Chemistry Team Leader
Dr. Sherita McLamore	Chemistry Reviewer
Dr. Richardae Taylor	Regulatory Project Manager

**Noven Pharmaceuticals, Inc. / Shire Pharmaceuticals, Inc.**

Harris Rotman, Ph.D.	Senior Manager, Regulatory Affairs
Charles LaPree	Senior Director, Regulatory Affairs
Will Tilton	Senior Manager, Global Pharmaceutical Technology
Rick Couch, Ph.D.	Senior Vice President, Global Pharmaceutical Technology
Tom Bader	Labeling
Charles Lemler	Materials Manager
Jeff Dow, Esq.	Director, Regulatory Affairs
Tom Obermeier	Director, Supply Chain Management

**Meeting Objective**

Discussion of branded/unbranded labeling requests from sponsor.

**Background:**

Shire/Noven requested a telecon with the Division to discuss their planned branded/unbranded product labeling for methylphenidate transdermal system for the initial launch of the product if approved.

**Discussion:**

During the telecon Shire/Noven explained that they plan upon the approval of methylphenidate transdermal system to launch the product with the following labeling components:

For both the patch backing and tray stickers, Noven/Shire are proposing to always have only the "unbranded" methylphenidate transdermal system name on these items. Their proposal is to have these items remain the same throughout the lifecycle of the product, at time of launch and post-launch. Thus, the ink on the patch backing and tray stickers will remain unchanged for the launch ("unbranded") and "branded" product. Noven/Shire stated that the patch does not have any debossing (submission dated July 29, 2005 referred to a debossed patch backing).

The pouch will change from time of launch to post-launch. Though similar in format and design, the "unbranded" pouches (to be used at time of launch) lack the proposed trade name and logo, the trademark, and the total dose delivered over 9 hours (nominal dose). All other information is identical to the "branded" pouches, and Noven/Shire will switch to the "branded" pouches upon approval.

For the launch product the carton will be marked with the brand name and the patches with the generic name.

The Division told Noven/Shire that it is acceptable for both the patch backing and tray stickers, to always have only the unbranded methylphenidate transdermal system name on these items. In addition, it is acceptable for the pouch that holds the patch to have only the unbranded name for the launch of the product and then post launch the approved brand name will be placed on the pouch.

The Division stated that we would need stability data for the patch. Noven/Shire stated that the current submission, that is under review, contains the information needed to support the ink on the patch.

Noven/Shire asked if the Division could provide final comments regarding all components of labeling months before the due date of the application due to manufacturing times within their company. The Division stated that this is not normal practice and with the consult Divisions also reviewing the labeling that would not be possible.

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Minutes Preparer

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Concurrence, Chair (or designated authority)

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/s/

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Richardae Taylor  
8/12/05 01:42:26 PM  
CSO

Thomas Laughren  
8/12/05 02:47:51 PM  
MEDICAL OFFICER

# MEMORANDUM

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Research and Evaluation  
Office of Drug Evaluation V  
Division of Dermatologic and Dental Drug Products (HFD-540)

Tel 301-827-2020  
FAX 301-827-2075

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**From:** Brenda Carr, M.D. Medical Officer, HFD-540

**Via:** Markham Luke, M.D., Ph.D./Dermatology Team Leader, HFD-540  
Jonathan Wilkin, M.D./Division Director, HFD-540  
Jonca Bull, M.D./Office Director, ODE V

**To:** Russell Katz, M.D./Division Director, HFD-120

**cc:** Mary Jean Kozma-Fornaro/Supervisor, Project Management, HFD-540  
Robert Temple, M.D./Office Director, ODE I

**Consult:** HFD-540 (#585-414672)

**Subject:** Findings from skin sensitization study, N17-020 (IND 54,732)

**Material Reviewed:** The synopsis of skin sensitization study, N 17-020 presented in Appendix 4 of the briefing package for upcoming sponsor meeting (May 26, 2004).

**DATE:** May 21, 2004

**Background:** HFD-120 has a meeting scheduled with Noven Pharmaceuticals, Inc. on May 26, 2004 to discuss development plans for Methylphenidate Transdermal System. On April 25, 2003, the review division issued a Not-Approvable letter citing clinical, chemistry and biopharmaceutics deficiencies. Included in the briefing document for the upcoming meeting is a synopsis of study N17-020, "Skin Sensitization Testing of Noven Methylphenidate Transdermal System." Question #5 in the briefing document is addressed to the Division of Dermatologic and Dental Drug Products and asks:

"Given the results of the skin sensitization study, has the sponsor provided sufficient information to address the Division's concerns regarding potential skin sensitization?"

## Comments:

### Study Design/Procedures

The study evaluated Methylphenidate Transdermal System (MTS), Transdermal System (TS) and saline for the induction of contact sensitization by applications to the skin of healthy adult male and females. The study was evaluator-blind and placebo-controlled with all subjects receiving all test articles. There were nine induction applications to the same site on the back for approximately three weeks. The induction period was followed by a two-week rest period, after which time subjects were challenged with test articles. At challenge, each test article was applied to a naïve site for 48 hours to test for reactions indicative of contact sensitization. The sites were scored approximately 48 and 96 hours after patch application. To confirm sensitization, subjects with positive challenge reactions were re-challenged approximately eight weeks later with test articles applied to a naïve site for 48 hours. Sites were visually assessed up to 96 hours post-removal.

*Comment: As described in the synopsis, the study design appears fairly standard for sensitization testing.*

### Results

Of 194 subjects enrolled, 131 completed all phases of the trial and 63 discontinued from the study prior to the challenge phase for unspecified reasons. Another two subjects were considered evaluable (one didn't receive the 9<sup>th</sup> induction application; one only had a 48-hour evaluation at challenge), making for a total of 133 evaluable subjects. At challenge, MTS was reported to have caused moderate to severe irritation in 76% of subjects at the 48-hour time-point, decreased to 46% at 96 hours.

*Comment: 1) From review of the synopsis, it appears that 133 represents the number of subjects who completed the challenge and re-challenge phases. For a sensitization study, it is generally recommended that enrollment be sufficient to allow for at least 200 evaluable subjects. 2) Previous clinical work had already established the sponsor's product as an irritant.*

The sponsor reports that sensitization was seen in 17 of 133 subjects (12.8%) who completed challenge and re-challenge phases. Additionally, one subject had "the hallmarks of sensitization" at 48 hours, but had no 96-hour evaluation. The sponsor also states that an additional eight subjects classified as having irritancy may have been sensitized to MTS, but re-challenge testing was not done in these subjects. Another three subjects were reported to have results "suggestive" of sensitization. If these additional 12 subjects are taken into consideration, the rate of sensitization becomes approximately 21.8% (29 of 133 subjects).

**Conclusions and recommendations to review division (not intended for sponsor):**

Based on review of the synopsis of study N17-0202, it appears that the sponsor has provided sufficient information to inform labeling regarding the potential for the product to cause skin sensitization. It is noted that the sensitization potential of TS was also evaluated in the study; however, those results were not found in the synopsis. The study also reaffirmed that the sponsor's product is an irritant. No additional studies to assess the issue of skin sensitization are recommended at this time. However, the review division may wish to consider inquiring whether the sponsor has any information regarding the risk of potential sensitization to other dosage forms (e.g. tablets), if skin sensitization develops.

Please do not hesitate to contact the Division of Dermatologic and Dental Drug Products with any additional questions or concerns.

**Response to Question #5:**

Based on review of the information presented in the synopsis of study N17-020 ("Skin Sensitization Testing of Noven Methylphenidate Transdermal System"), the issue of contact sensitization appears to have been adequately assessed. The results in the synopsis indicate that there is significant potential for the sponsor's product to cause contact sensitization: at least 12.8% were confirmed to have been sensitized based on results of re-challenge, and the rate could be as high as 21.8%, if subjects with uncertain outcomes, e.g. "suggestive of sensitization," are taken into consideration. It is recommended that labeling reflect the potential for the product to cause sensitization and describe the results from the skin sensitization study, N17-020. Labeling may be sufficient to address the risk of contact sensitization.

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Brenda Carr  
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MEDICAL OFFICER

Markham Luke  
5/24/04 09:18:28 AM  
MEDICAL OFFICER  
Consult #585 for HFD-120.

Jonathan Wilkin  
5/24/04 01:57:42 PM  
MEDICAL OFFICER

Once cell-mediated allergy is induced, later systemic exposure may produce a systematized type-4 reaction. The skin is more effective in the induction of type-4 reactions than oral exposure. Transdermal MPD may be inappropriate for those who depend on MPD

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

**DATE:** July 22, 2003

**FROM:** Paul J. Andreason, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Consultant's response to sponsor's questions on adequacy of proposed skin sensitization study

**TO:** File, NDA 21-514  
[Note: This memo should be filed with the General Correspondence submission of May 12, 2003 with this NDA.]

In the Division's Not Approved action letter of April 25, 2003 item four stated:

Our Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6- week duration would be helpful in investigating this potential signal.

The sponsor questioned whether or not a currently running skin sensitization study" ...(Draize modified) (-020) in approximately 190 subjects where patches would be worn for 21 days (three patches per week, 48/48/72 hours per patch for 3 weeks). In addition, over 60 patients have worn MethyPatch for more than a year as intended-new patch applied to alternating hips," was sufficient to satisfy the Division's concern.

Brenda Carr, MD from HFD-540 was consulted who provided a written report and telephone follow-up. She stated in the report that the proposed (-020) study might be adequate. In our telephone discussion she stated that she was not sure whether or not the "3-week" skin sensitization study was long enough because after the initial wearing period (in this case 3-weeks) there should be a re-challenge period several weeks later. They do not mention the re-challenge test in their response but she says that the study may be long enough based on the assumption that if it is a "skin sensitization" study then there should be this re-challenge period later on.

Dr Carr stated that the previous study (N17-008) was appropriately long but, from what Dr Carr said about 200 evaluable patients, undersized at the 99 evaluable subjects that study N17-008 produced.

I recommend that:

- The Division verifies what the study design is so we can more fully respond to the company's question about the adequacy of study -020. If in the end, study -020 is adequately designed, then the sponsor also needs to increase the number of subjects in the study so there are at least 200 evaluable patients not just 190 patients enrolled as the summary seems to imply.

- Inform the sponsor that study N17-008 was actually appropriately long enough, but not large enough to provide adequate statistical power with only 99 evaluable subjects.

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/s/

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Paul Andreason  
7/22/03 10:16:44 AM  
MEDICAL OFFICER

# MEMORANDUM

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Research and Evaluation  
Office of Drug Evaluation V  
Division of Dermatologic and Dental Drug Products (HFD-540)

Tel 301-827-2020  
FAX 301-827-2075

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**From:** Brenda Carr, MD/Medical Officer, HFD-540

**Via:** Markham Luke, MD, PhD/Dermatology Team Leader, HFD-540  
Jonathan Wilkin, MD/Division Director, HFD-540

**To:** Russell Katz, MD/Division Director, HFD-120

**Consult# 454; HFD-540 # 312817**

**Subject:** The Sponsor's proposal for additional skin sensitization testing with their product, MethyPatch Transdermal System (NDA 21-514).

**Material Reviewed:** 1) General Correspondence from the Sponsor dated May 12, 2003, (forwarded by facsimile on the same date), in which the Sponsor requests an informal meeting in response to a Not Approvable letter 2) the Sponsor's proposed agenda for the requested meeting, including a list of "issue" questions (also sent May 12<sup>th</sup>) 3) the Not Approvable letter dated April 25, 2003.

**DATE:** June 17, 2003

**Background:** NDA 21-514 was submitted to the Division of Neuropharmacological Drugs (HFD-120) on June 27, 2002 by Noven Pharmaceuticals for their product, Methylphenidate Transdermal System (MTS; ~~Noven~~® system). The product was developed by Noven Pharmaceuticals for the once-daily treatment of Attention Deficit Hyperactivity Disorder (ADHD) by a patch delivery system. In support of the NDA, the Sponsor conducted a combined skin sensitization and irritation study (N17-008), with the complete study report submitted to the NDA. Study N17-008, conducted with MTS patch size 25 cm<sup>2</sup>, revealed the Sponsor's product to be an irritant. Also, in the reviewer's assessment, study N17-008 revealed 3 of 99 evaluable subjects (3%) to show reactions suggestive of sensitization in the challenge phase of the study and the product's role as a potential sensitizer could not be excluded (see HFD-540 consult #360).

Subsequent to the NDA submission, the Sponsor submitted a correspondence to IND 54,732 (date October 21, 2002), in which they indicated that the highest marketed dose would most likely be either the MTS 37.5 cm<sup>2</sup> or the — cm<sup>2</sup> i.e., patch sizes not studied in N17-008. In that IND submission, the Sponsor also indicated that they had initiated a sensitization study with the — cm<sup>2</sup> patch in approximately 200 subjects (see submission for additional detail).

On April 25, 2003, the review division issued a Not-Approvable letter citing numerous clinical, chemistry and biopharmaceutics deficiencies. Pertinent to this consult is what was reported to the Sponsor as Clinical Issue #4:

"Our Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6-week duration would be helpful in investigating this potential signal."

The Sponsor addressed this deficiency in their May 12<sup>th</sup> correspondence as below:

"Since the filing of the original NDA, Noven initiated a new Skin Sensitization trial (Draize modified) (-020) in approximately 190 subjects where patches were worn on the same site for 21 days (3 patches per week, 48/48/72 hours per patch for 3 weeks). In addition, over 60 patients have worn MethyPatch for more than a year as intended-new patch applied daily on alternating hips.

"Does the Agency agree that data from these two studies will address the Agency's concerns?"

**Conclusions:**

1. The study cited in the May 12<sup>th</sup> facsimile may be the sensitization study to which the Sponsor referred (in synopsis form) in the October 21<sup>st</sup>, 2002 submission to IND 54,732 (serial 062). The limited information presented about the Sponsor's new skin sensitization study in the May 12<sup>th</sup> communication permits little comment. It is noted, however, that the treatment period is reported to be 21 days in duration, which may be appropriate for a contact sensitization study. While no information is provided regarding the study duration, this study may not address the request by HFD-120 for a study longer than six weeks in duration. Also, it is recommended that enrollment for a contact sensitization study be sufficient to permit for at least 200 evaluable subjects. Only review of the data from the completed study will allow for a determination of their adequacy.
2. The duration of the previously-conducted combined irritancy/contact sensitization study (N17-008) was appropriate for a study of this sort.

Please consult the Division of Dermatologic and Dental Drug Products as needed regarding the ongoing contact sensitization study. Also, please consult the Division as needed should the Sponsor undertake a contact sensitization study longer than six weeks duration, as requested by the review division.

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/s/

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Brenda Carr  
6/18/03 03:46:45 PM  
MEDICAL OFFICER

Markham Luke  
6/18/03 05:28:40 PM  
MEDICAL OFFICER  
Consult #454 for HFD-120

Jonathan Wilkin  
6/18/03 07:21:34 PM  
MEDICAL OFFICER



NDA 21-514

Noven Pharmaceuticals, Inc.  
Attention: Therese Dixon  
Director, Regulatory Affairs  
11960 Southwest 144<sup>th</sup> Street  
Miami, Florida 33186

Dear Ms. Dixon:

Please refer to your new drug application (NDA) dated June 27, 2002, received June 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MethyPatch® (methylphenidate) Transdermal System.

We acknowledge receipt of your submissions dated October 25, 2002; and February 25, 2003.

We have completed the review of this application and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical Issues

1. Though you have produced one positive study to support the efficacy of MethyPatch, this efficacy was achieved at the expense of excess drug exposure and an unacceptable incidence of significant adverse events, specifically insomnia, anorexia, and significant weight loss in the short-term. These adverse events would be expected to result in possible growth retardation or other serious adverse consequences with more chronic treatment. Importantly, other products approved for once a day dosing in this population are not associated with these risks.
2. The data suggest that patients who suffered from insomnia might benefit from decreasing the wear-time of the patch. Given that large numbers of both stimulant naïve and stimulant experienced patients suffered insomnia, anorexia, and weight loss, it would seem possible that generally decreasing the wear-time might decrease the incidence of these adverse events to acceptable levels. However, this would need to be demonstrated prospectively in another trial that documented that decreased wear-time was both safe and effective.

3. We disagree with your assertion that [redacted] (®) offers a decreased abuse liability. It appears that the methylphenidate in [redacted] (®) may be extracted with common household solvents. This makes it available to be diverted and abused in a non-patch-bound form. Even if the methylphenidate contained in [redacted] (®) could not be extracted, significant amounts of methylphenidate remain in the patch to be diverted and abused. Additional amounts of methylphenidate would be available for diversion if wear-time were decreased.
4. Our Dermatology consultants concluded that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study. A skin exposure study of longer than 6-week duration would be helpful in investigating this potential signal.

In summary, [redacted] (®), as currently constituted and used as currently proposed, significantly overmedicates children at inappropriate times of the day and leads to unacceptable adverse events not associated with other once a day products available for this population. [redacted] (®) also provides a ready source of unaccountable Schedule II controlled substance to be diverted and abused.

The following issues, although not responsible for the Not Approvable action, should still be addressed in any resubmission:

#### Chemistry Issues

1. You indicate that [redacted] has produced ten batches of the drug substance on page 9 of volume 3. Please provide certificates of analyses for those ten batches.
2. Your proposed drug substance specification for the pharmacologically active [redacted] impurity is NMT 1.5%. Please lower the [redacted] specification limit to NMT 0.5% in accordance with the ICH Guidance for Industry: Q3A Impurities in New Drug Substances, or provide data demonstrating that this impurity has been qualified to 1.5%.
3. Your proposed drug substance specification for "other related substances (each)" is NMT 0.5%. Please lower your specification limit to NMT 0.1% in accordance with the ICH Guidance for Industry: Q3A Impurities in New Drug Substances.
4. Please provide a sampling plan for the drug product.
5. The dimensions of the 27.5 mg patch are 1 1/2 X 1 1/2". The dimensions of this patch describe a square. Please update the description of the 27.5 mg to the Unit Shape, Rounded Square.

6. The specification for the [redacted] mg patch is [redacted] mg to [redacted] mg, which corresponds to [redacted]% to [redacted]%. This is not an acceptable specification. The lower specification limit for the drug product assay should be at least 90%. Therefore, we request that you update the specification for the assay for the [redacted] mg patch from [redacted] mg - [redacted] mg to 75.2 mg - 91.9 mg.
7. The specification limits for the related substances ritalinic acid, [redacted] and total impurities are NMT [redacted]%, NMT [redacted]% and NMT [redacted]%, respectively. Under 25°C/60%RH storage conditions, the actual amounts of these individual substances found in the drug product have not exceeded 1.0%, and the total impurities has not exceeded 1.5%. Please tighten these specifications to be more reflective of the data.
8. Please refer to your specification for the rate of dissolution. You have omitted the [redacted]% dissolution rate. Please update your dissolution specification to include the [redacted]% dissolution rate.
9. You indicate that a [redacted] gram load is applied to test the [redacted] strength. Please provide evidence to support that this is a reasonable load in evaluating the [redacted] strength with respect to patient use.
10. You have provided a description of the method used to determine the [redacted]. Because this test does not follow a standard USP methodology, we request that you submit validation data for this method.
11. Provide updated drug product stability.
12. Please indicate which batches were used in the bioequivalence study. Your response should include the dosage, batch number, batch size, manufacturer, drug substance batch number, clinical trial number and certificates of analyses.
13. In the draft labeling, the [redacted] mg/hr, [redacted] mg/hr, [redacted] mg/hr and [redacted] mg/hr patches are associated with color codes A, B, C and D, respectively. However, you do not provide a description of these color codes. Please provide a detailed description of color codes A, B, C and D.
14. In the draft labeling, the [redacted] mg/hr, [redacted] mg/hr, [redacted] mg/hr, and [redacted] mg/hr patches in the pouch (V 5, pages 492-495) and in the individual carton tray sleeves of 30 units (V 5, pages 500-503) the color codes are A, B, C and D respectively. In the draft labeling for the [redacted] mg/hr, [redacted] mg/hr, [redacted] mg/hr and [redacted] mg/hr patches in the pouch tray sleeves of 7 units (V 5, pages 496-499) the color codes are E, F, G and H respectively. Further clarification is needed on these color codes since they appear to be inconsistent.
15. We recommend the following storage statement: "Do not store unpouched. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]."
16. DMF [redacted] ( [redacted] ) is deficient for the [redacted]. The DMF Holder is being notified of this by a separate letter which includes a list of the deficiencies.

Biopharmaceutics Issues

Please adopt the following dissolution method and acceptance criteria:

Apparatus:	USP Drug Release Apparatus 6 (modified cylinder)
Medium:	0.1N HCL
Temperature:	32 ± 0.5° C
Volume:	900 mL
Rotation Speed:	50 rpm
Sampling Times:	0.5 hour      1/2 to 1/2 of Label Claim 1.5 hour      1/2 to 1/2 of Label Claim 3.0 hour      1/2 to 1/2 of Label Claim

\*As per USP 26/NF 21 <724> Drug Release acceptance table 4 for transdermal drug delivery systems

When you respond to the above deficiencies, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

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.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

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

Sincerely,

{See appended electronic signature page}

NDA 21-514

Page 5

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

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Russell Katz

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**MEMORANDUM**

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

**DATE:** April 18, 2003

**FROM:** Paul J. Andreason, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation of Not Approvable action for MethyPatch®

**TO:** File, NDA 21-514  
[Note: This memo should be filed with the June 27, 2002 original submission of this IND.]

**1.0 BACKGROUND**

Noven Pharmaceuticals, Inc. submitted NDA 21-514 - Methylphenidate Transdermal System (MTS; MethyPatch®) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6-12 years. NDA 21-514 is a 505-(b) (2) application that references Novartis Pharmaceutical Corporation's oral Ritalin IR (MPH), a currently approved racemic mixture of the d-threo-methylphenidate and l-threo-methylphenidate enantiomers. MTS also contains *d, l*-methylphenidate (MPH), as the active ingredient, in a multi-polymeric adhesive transdermal patch.

The Sponsor contends that applying the MTS patch to intact skin will provide for the continuous systemic delivery of MPH during the period of patch wear. Their claim is that this will result in "more stable plasma concentrations during a dosing interval than oral administration and contribute to a prolonged and controlled duration of action". The Sponsor states that additional benefits of MTS to oral MPH will be a lower abuse potential, a decreased risk of accidental poisonings, and a use for those unable to swallow pills.

Unfortunately, the data from the pivotal clinical and pharmacokinetic trials show that this formulation is only effective during the school day when children are inappropriately exposed to higher than therapeutic drug levels in the evening. This inappropriately high exposure to drug at an inappropriate time of the day leads to significantly increased problems with insomnia, anorexia, and weight loss. Even though the plasma concentration-time curve shows less variability ("more stable"), the concentrations are too high in the evening in order to achieve a therapeutic level during the school day.

The claim that MTS has a lower abuse potential focuses on the slow onset of effect and long duration of action. This is a widely accepted though imperfect rule of thumb held by the substance abuse treatment community. OxyContin has been recent example of an exception to this rule. This

is not, however, the only factor on which abuse potential depends with MTS. The MTS system requires that there be a significantly greater amount of drug in the patch than is used by the patient during critical times of the day. This left over drug in the used patch represents a significant amount of a Schedule II controlled substance that is technically accounted for, yet that is free to be diverted and abused.

## **2.0 CHEMISTRY**

Chemistry Team reviews were not available at this point in the review cycle.

## **3.0 PHARMACOLOGY**

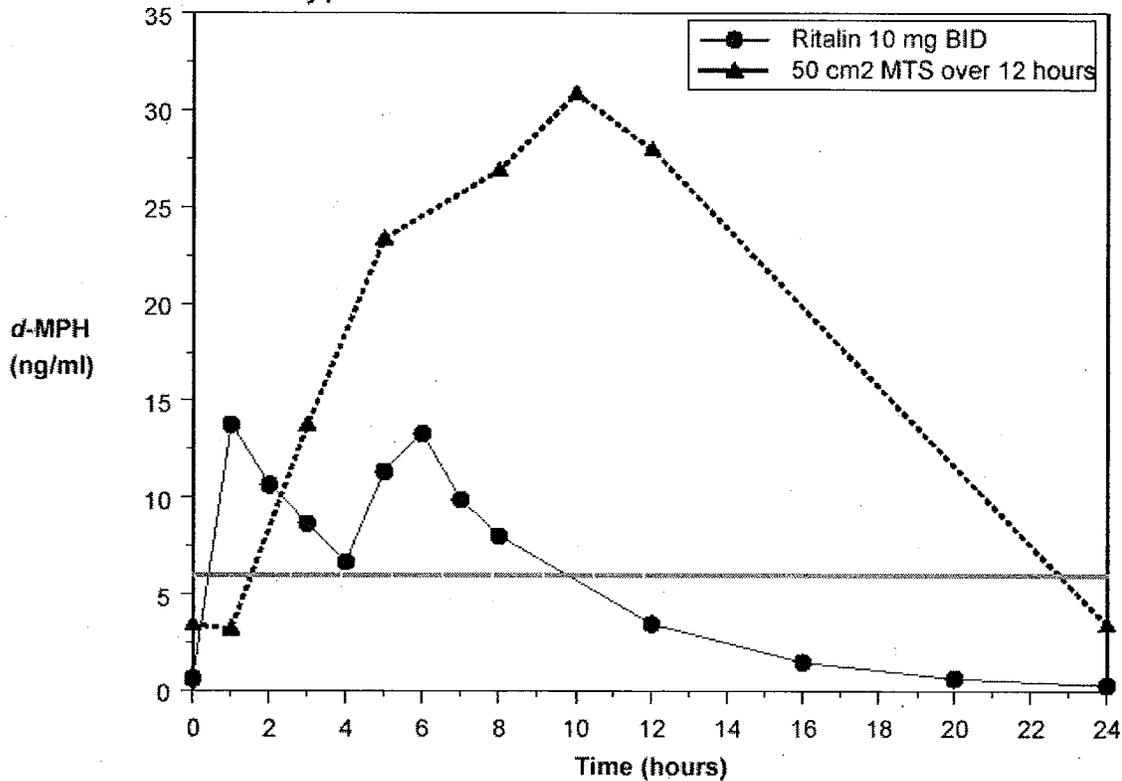
Pharmacology Team reviews were not available at this point in the review cycle. One outstanding concern that they plan to address is that the patch exposes patients to 173 fold higher levels of *l*-methylphenidate than the oral forms. Though *l*-methylphenidate is pharmacodynamically inactive, the Pharmacology Team shall comment on what the potential toxicology concerns of this higher *l*-methylphenidate exposure might be.

## **4.0 BIOPHARMACEUTICS**

Ronald Kavanagh, PhD, did the OCPB primary review. His review makes it clear that in order to achieve what are usually considered therapeutic plasma levels of drug during school times, MTS treated patients are exposed to larger amounts of drug than necessary at times where even the desired daytime effect is not wanted. When adjusted for the dose delivered from the \_\_\_\_\_<sup>®</sup> transdermal system the relative exposures are 3.5 fold higher for d-methylphenidate (d-MPH) and 173 fold higher for l-methylphenidate (*l*-MPH) as compared to oral administration with Ritalin<sup>®</sup>. The following figure illustrates the d-MPH relative exposures:

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### d-MPH Concentration - Time Profiles for Typical Efficacious Doses



Dr Kavanagh goes on to state that by extension there are several implications of \_\_\_\_\_ pharmacokinetics.

a) There is likely going to be a lack of efficacy in the morning with \_\_\_\_\_, unless a sufficiently high dose is used. Thus, clinical studies or studies comparing the time course of \_\_\_\_\_ pharmacokinetics/pharmacodynamic in ADHD (e.g. hourly classroom testing) to oral methylphenidate may be needed. [Study 10 demonstrated Dr. Kavanagh's point. The smaller patch was ineffective by teacher rating but the parents (who made much of their judgement on the time spent with the child after school) felt that there was improvement. Study 18 went on to employ a larger patch that produced efficacy on the teacher rating scale but produced much higher rates of anorexia, insomnia, and weight loss.]

b) There's likely to be side effects in the late afternoon, evening, and possibly at night. Adverse effects that might be expected at these times might include appetite suppression at dinner, and insomnia. [Both Study 10 and 18 demonstrated Dr Kavanagh's point here. Anorexia, insomnia and weight loss are clearly dose dependent and are present at rates that are greater than with oral formulations or equivalent therapeutic strength.]

[Dr. Kavanagh's following three points are valid and need to be addressed by the sponsor.]

c) It's been proposed that tolerance to methylphenidate following oral dosing occurs over the course of the day and the relative drug free period overnight allows a return to baseline. However, the high methylphenidate concentrations that occur at night with \_\_\_\_\_ with measurable concentrations in the morning, may not allow a return to baseline. This might result in less efficacy and/or the need for higher doses.

d) To overcome the early morning lack of efficacy and side effects late in the day clinicians are likely to find that using large doses (i.e. large patches) and removing them after fewer hours may be advantageous. However, this results in used patches containing large amounts of methylphenidate that could be extracted for abuse. [These patches could also be diverted and used intact for weight loss, or several other types of abuse.]

e) The high and prolonged plasma concentrations might predispose patients on \_\_\_\_\_ to depression upon drug withdrawal.

## 5.0 CLINICAL DATA

Glenn Mannheim, MD performed the primary clinical efficacy and safety review.

### 5.1 Efficacy Data

The sponsor conducted two pivotal phase III trials-Study 10 and 18. These were multicenter, randomized, double-blind, placebo-controlled dose titration studies in children with Attention Deficit Hyperactivity Disorder (ADHD) who attended a community class-room setting. It should be noted that the Division only required one positive study for this formulation since the oral formulation was already approved for this indication. The Division policy has been that a new formulation that is not bioequivalent to an already approved formulation may be approved on the basis of pharmacokinetic data and one positive clinical trial. Study 10 failed and from those results, the sponsor concluded that a larger patch was necessary for testing in study 18.

**Study 18** was a multicenter, randomized, double blind, parallel group, placebo controlled trial, dose titration, 6-week trial involving 211 children subjects [MTS: 106, TS (Placebo): 105](males: 150, females: 61), 6-12 years of age (mean age: 8.7 yrs) with a diagnosis of ADHD. At baseline subjects were randomized to either placebo (TS), or, one of two possible starting patches of MTS (12.5 or 18.75 cm<sup>2</sup>) based on weight or, previous oral dose of MPH. The double blind treatment was for four (4) weeks with weekly evaluations of safety and efficacy. Titration occurred up or down at the end of week 1-3 evaluations based on safety reasons or lack of efficacy. However, prior to downward titration, patch wear time was reduced from the recommended wear time of 12 hours to 8.5-9 hours, but not less than 7 hours. The minimum and maximum patch sizes used were 6.25 cm<sup>2</sup> and 50 cm<sup>2</sup>, respectively. At the end of school day each week efficacy evaluations were made.

The primary efficacy variable was the change from baseline in the Teacher's IOWA-Conners Inattention/ Overactivity (Teacher I/O) Rating Scale. In study 18, statistical significance (P < 0.0001) was shown in the MTS group on the Teacher I/O during week 1 of treatment (Visit 3) and continuing through weeks 2-4 (Visits 4, 5 and 6).

Therefore study 18 provided convincing evidence that \_\_\_\_\_ 3 was effective in the treatment of ADHD, but, as I shall argue in the next section of this memo, at a cost to safety that outweighs this benefit.

## 5.2 Safety

In Study 018, the most commonly reported adverse events in the MTS subjects were anorexia (50 %) and insomnia (30 %). Clinically notable body weight decreases ( $\geq 5\%$ ) occurred in 49% of patients in the MTS treatment group vs. 3.8% in the TS group. There were slight increases in the mean pulse rate and blood pressure in the MTS group.

In Study 010, the most commonly reported adverse events in the MTS group were anorexia (17%), insomnia (17%), and headache (13.9%), whereas the most commonly reported events in the TS (placebo) group were cough increased (10.1%), rhinitis (8.3%), and vomiting (7.3%).

The majority of MTS-treated patients reporting anorexia and insomnia were from Study 18. The Sponsor performed a post-hoc analysis to understand the higher frequency of adverse events present in this Study 18. They stated that the anorexia and insomnia were more likely to occur in stimulant-naïve subjects (39% and 59%, respectively) than in stimulant-experienced patients (19% and 40%, respectively) in the MTS group. Additional analyses for these two events indicated that 60% had ongoing anorexia at study end. Ongoing insomnia was still present for 40% at study end. Reducing the patch wear time was effective in ameliorating insomnia. Of 17 patients who had wear time reductions for insomnia, only 6 patients had insomnia at the end of the study. Wear time reduction was not effective in controlling anorexia.

For the placebo TS population, there was a significant mean increase in body weight of 0.5-kg ( $p \leq 0.001$ ).

There were no deaths in the clinical development program. There were no serious adverse events that were likely to be related to study drug.

The Sponsor states that MTS misuse or diversion was not observed during the development program. However, in Study N17-021, there was a substantial number of missing MTS patches for one subject (# 18/16) which the investigator attributed to poor compliance. The Controlled Substance Staff (HFD-009) evaluated the Sponsor's suggestion that MTS had a lower potential of abuse and diversion than the oral MPH product as a result of its sustained-release formulation. The Controlled Substance Staff indicated that MPH from the patch can be easily extracted with common household liquids and organic solvents and be abused in the same manner as oral forms. More importantly, MTS supplies an unaccountable source of drug that need only be diverted from the trash in order to be abused.

Skin irritation was significantly greater in the MTS treated patients over the TS patients. Dr. Mannheim and the Dermatology consultants concur that there is a possible signal for skin sensitization with periods of use longer than the 6-week duration of the study.

## 6.0 WORLD LITERATURE

Though there are many references in the world literature to MPH there are no data to my knowledge on this MTS formulation other than that generated by the sponsor.

### 7.0 FOREIGN REGULATORY ACTIONS

I am not aware of any foreign regulatory actions regarding the use of \_\_\_\_\_ ® in pediatric patients.

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

We decided not to take this NDA to the PDAC.

### 9.0 NON-APPROVAL LETTER

A non-approval letter acknowledging our decision been included with the non-approval package. Since both the clinical reviewer and I agree not to approve this NDA draft labeling is not included with this package.

### 10.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that the Division not approve NDA 21-514 \_\_\_\_\_ for the treatment of ADHD in children ages 6-12 years. Though the sponsor was able to produce one positive study to support the efficacy of \_\_\_\_\_, children were exposed to much more drug for more of the day than with other available oral formulations with a duration of action that covers what the sponsor had hoped to cover with \_\_\_\_\_ as it is currently constituted exposes children to inappropriately high drug levels and at times of the day where they do not benefit from normal levels of drug exposure. This results in significant insomnia, anorexia, and weight loss. In the long run, this will most likely result in growth retardation above what may already be risked with other available stimulant formulations.

In short, \_\_\_\_\_ significantly overmedicates children at inappropriate times of the day and does not appear to offer any benefit over any available oral preparations. MTS also provides a ready source of unaccountable Schedule II controlled substance to be diverted and abused.

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Paul Andreason  
4/18/03 11:55:07 AM  
MEDICAL OFFICER

**MEMORANDUM**

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

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**Date:** April 3, 2003

**To:** Russell Katz, MD, Director  
Division of Neuropharmacologic Drug Products, HFD-120

**Through:** Deborah B. Leiderman, MD, Director  
Michael Klein, PhD, Team Leader  
Controlled Substance Staff, HFD-009

**From:** Ann-Kathryn Maust, MD, Medical Officer  
Controlled Substance Staff, HFD-009

**Subject:** Consultation for NDA 21-514 (methylphenidate transdermal system)  
Abuse Liability Assessment  
Sponsor: Noven Pharmaceuticals, Inc.  
Submission Date: 6/27/02

**Executive Summary**

The Controlled Substance Staff (CSS) has reviewed NDA 21-514 for Methylphenidate Transdermal System (MTS). The review addresses abuse potential, adverse events, chemical extractability, and recommendations related to scheduling, product labeling and information for the patient.

**Conclusions**

The relative abuse potential of MTS is similar to that of other methylphenidate products based upon pharmacokinetic/pharmacodynamic considerations and ease of extractability of active ingredient for the purposes of abuse and diversion. Methylphenidate substance and products are controlled under Schedule II of the Controlled Substances Act (CSA).

1. Relevant Pharmacokinetic Characteristics:

- a. When used as directed, the sustained-release formulation results in a slower rise in plasma concentration and a delayed onset of action relative to oral formulations.
- b. MTS continues to deliver methylphenidate after use if reapplied to skin after removal.

- c. Increased plasma levels of methylphenidate are obtained by application of heat to the patch, applying the patch to the buccal mucosa, to inflamed skin, or using multiple patches simultaneously.
- d. A significantly lower Tmax results from application to the buccal mucosa.
- e. Chewing MTS may lead to release of methylphenidate that can be absorbed through the buccal mucosa, leading to higher methylphenidate plasma levels than transdermal application. To minimize these possible occurrences, the sponsor plans to individually package each MTS in a child-resistant pouch, although they state that they have no experience from their clinical development program with adverse events due to methylphenidate overdose.
- f. Most of the methylphenidate in MTS remains in the patch after use and is discarded. After 8 hours of application, approximately 67 percent of active drug remains in the patch and is available for diversion. Thus, for a typical dose of 55 mg / 25 cm<sup>2</sup> approximately 37 mg would remain. Methylphenidate is easily extracted in a short time period and retrievable in pure form. (See *Appendix*).

## 2. Relevant Pharmacodynamic Characteristics:

- a. MTS application led to "drug liking" in some experienced stimulant abusers (Studies N17-007 and N17-012). (See *Appendix*).
- b. Abuse potential studies showed that individuals who are experienced in the abuse of stimulants liked multiple MTS patches and that "drug liking" was increased by applying heat to MTS or by applying MTS to the buccal mucosa.
- c. Although lacking verification, Patient #18/16 represented a suspected case of diversion. The individual reported losing 13 and throwing away 11 patches. Protocol (Study N17-021) required returning unused product.
- d. Euphoria and hallucinations were reported adverse events during MTS administration in the abuse potential studies and clinical trials.

## 3. Chemical Extraction:

- a. Methylphenidate has been chemically extracted from MTS. Minimal technical expertise and minimal laboratory equipment are needed to isolate and purify methylphenidate for abuse and diversion.
- b. A chemical extraction study demonstrates that significant amounts of methylphenidate and ritalinic acid are extracted from 25 cm<sup>2</sup> MTS in water, isopropanol, acetone, isooctane, and lighter fluid.
- c. A second study demonstrates methylphenidate extraction from 12.5 cm<sup>2</sup> MTS using various commercially available liquors as the extraction solvent. This study

indicates that methylphenidate is extracted from the patch matrix with various alcoholic beverages.

d. The stability trend is related to the acidity (pH). Lower pH (high acidity) results in greater methylphenidate stability and release from the patch. The liquors with higher pH (Rum, Scotch, and Vodka) reach peak extraction at 4-6 hours, then steadily decrease due to methylphenidate degradation in these media.

### **Recommendations**

#### 1. Labeling

Physicians are advised to monitor patients and household members for signs of abuse and diversion including monitoring the quantities of MTS dispensed. Detailed recommendations for the labeling are attached in the *Appendix*.

#### 2. Scheduling

MTS is controlled under Schedule II of the CSA as methylphenidate and all of its products are controlled in Schedule II of the CSA.

#### 3. Patient Package Insert

Instructions on the safe use of MTS by the patient are described in the *Appendix*. Directions on application and disposal are included. Warnings on keeping the drug out of the reach of small children and other family members are also included.

**APPEARS THIS WAY  
ON ORIGINAL**

2 Page(s) Withheld

\_\_\_\_\_ Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

## **II. Abuse Potential Assessment**

### **A. Abuse Potential Studies**

Three clinical pharmacology studies (N17-007, N17-012, and N17-014) and two chemical extraction studies were designed to address MTS abuse potential. The clinical abuse potential studies are described below.

#### ***1. Study N17-007***

Study N17-007 was designed to examine the pharmacokinetics and abuse potential of MTS, subcutaneous (SC) methylphenidate, and phentermine. N17-007 was a two-part study conducted in healthy adult subjects of either sex, aged 31 to 48 years, who were currently abusing stimulants. Part 1 (n = 7) was a single-blind, double-dummy, single dose, dose rising study of MTS and SC methylphenidate that was conducted to determine doses for Part 2. Treatments in Part 1 were placebo (PBO), 25 mg SC methylphenidate, and MTS (1, 2, 3, 4, 6, and 8 patches). Part 2 (n = 20) was a double-blind, triple-dummy, single dose, randomized, crossover comparison of PBO, MTS (3 or 6 patches worn for 24 hours), SC methylphenidate (25 or 50 mg), and oral phentermine (30 mg).

Each MTS patch was 25 cm<sup>2</sup> and contained 55 mg of methylphenidate. Thus, each patch was equivalent to the "20 mg" patch that the sponsor intends to market. The MTS patches were applied to the same side of the scapular region of the back. Subsequent applications were alternated to the opposite side.

The sponsor stated that the primary outcome variable is the production of typical amphetamine-like effects produced by methylphenidate and that the maximum change from baseline and the time of maximum effect would be compared across routes of administration and across doses. These changes and times to maximum effect were to include measures of psychoactivity and euphoria and cardiovascular measures.

#### ***Results***

##### **Euphoria and Hallucinations**

In Part 1, euphoria was reported as an AE with all treatments, except 1 and 3 MTS patches. The highest percentages of euphoria occurred during treatment with 25 mg SC methylphenidate (6 out of 7 subjects or 85.7 %) and 4 MTS patches (4 out of 7 subjects or 57.1 %). Euphoria occurred in 2 out of 7 subjects who received PBO (28.6 %).

In Part 2, euphoria was reported as an AE with all treatments. The highest percentages of euphoria occurred during treatment with 50 mg SC methylphenidate (8 out of 19 subjects or 42.1 %) and 6 MTS patches (6 out of 19 subjects or 31.6 %). Euphoria occurred in 2 out of 19 subjects who received PBO (10.5 %). During treatment with 6 MTS patches, 50 mg SC methylphenidate, and 30 mg oral phentermine, the incidence of hallucinations occurred in one of 20 subjects.

## 2. Study N17-012

Study N17-012 was a two part, double-blind, placebo-controlled, single dose, randomized, crossover study. Part 1 examined the effect of heat on absorption of methylphenidate from MTS. Part 2 evaluated the pharmacokinetics of buccal absorption. Six adult stimulant-abusing volunteers participated in both parts. Effects of MTS were assessed with the Drug Rating Questionnaire-Subject and Observer.

### Part 1 Treatments:

- A: three 25 cm<sup>2</sup> active MTS applied to one arm for 8 hours (heated with heating pad on medium setting for 6 hours) and three 25 cm<sup>2</sup> placebo MTS applied to the other arm for 8 hours.
- B: three 25 cm<sup>2</sup> placebo MTS applied to one arm for 8 hours (heated with heating pad on medium setting for 6 hours) and three 25 cm<sup>2</sup> active MTS applied to other arm for 8 hours.

### Part 2 Treatments:

- A: two 25 cm<sup>2</sup> active MTS—one applied to each side of buccal cavity for 2 hours
- B: two 25 cm<sup>2</sup> placebo MTS—one applied to each side of buccal cavity for 2 hours

### *Pharmacokinetic Results*

Heat increased the C<sub>max</sub> and AUC of methylphenidate. Heat also increased the amount of methylphenidate released from MTS (apparent dose) by 53%. The apparent dose and C<sub>max</sub> were higher following buccal application compared to transdermal application. The mean apparent dose after buccal application of two 25 cm<sup>2</sup> patches for 2 hours was 61.4 mg, compared to 32.0 mg after dermal application (no heat) of three 25 cm<sup>2</sup> patches for 8 hours. The respective mean C<sub>max</sub> values for *d*-methylphenidate collected up to 2 hours after the buccal and 8 hours after the dermal (no heat) exposures were 39.5 ng/mL and 14.6 ng/mL, respectively.

T<sub>max</sub> was reached approximately 4 times faster during buccal administration (1.71 hours) compared to arm administration (7 hours). In a PK study during which adults wore patches on their hips for 16 hours (N17-004), T<sub>max</sub> was reached at 16 hours.

### *Pharmacodynamic Results*

Liking the drug effect, as reported by both subject and observer, was statistically significantly more common when heat was applied. In addition, significantly more subjects experienced drug liking when MTS was applied to the buccal mucosa than when

placebo was applied. The sponsor refers to drug liking as euphoria. No statistically significant disliking of drug occurred during heat application and MTS administration to the buccal mucosa, compared to the no heat condition or to placebo.

Euphoria was reported as an AE in both parts of the study. In Part 1, euphoria occurred in 2 out of 6 subjects (33.3%) when heat was applied to MTS and in 1 out of 6 subjects when heat was not applied to MTS. In Part 2, euphoria occurred in 4 out of 6 subjects (66.7%) who had MTS applied to the buccal mucosa and in zero subjects who had PBO applied to the buccal mucosa.

### **3. N17-014**

Study N17-014 was an open-label study of methylphenidate pharmacokinetics following two 16-hour applications of the same 25 cm<sup>2</sup> MTS patch (containing 55 mg methylphenidate). The subjects were six healthy adult volunteers. On Day 1, each subject had one patch applied to the hip for 16 hours. On Day 2, the patch worn on the previous day was applied to the opposite side of the hip for 16 hours.

#### *Results*

Mean methylphenidate concentrations, C<sub>max</sub>, and AUC were lower after application of the used patch compared with application of the unused patch. The mean apparent dose of methylphenidate delivered during the total 32 hour period was 27.4 mg. Based on relative mean AUC<sub>0-24</sub> values, approximately 60% (16.4 mg) of the methylphenidate dose was delivered during the first 16 hour wear period, and the remainder (11 mg) was delivered during the second wear period. To conclude, methylphenidate was released from patches that were reapplied.

### **B. Clinical Trial Data Relevant to Abuse Potential**

Clinical trial data relevant to abuse potential includes the reports of euphoria, hallucinations, and lost patches that are discussed below.

#### **1. Seven Clinical Safety and Efficacy Studies**

The sponsor stated that during the seven clinical safety and efficacy studies completed in pediatric patients, one of which was long-term, no euphoria and no incidents of MTS abuse or diversion were reported. However, no patients in these studies were over 12 years old, and some of these studies were small.

In Study N17-010, one MTS patient experienced a manic reaction, and two MTS patients experienced hallucinations. The numbers of MTS patients who experienced hallucinations in the rest of the above studies are as follows: N17-011—1 (0.8 %), N17-015—4 (14.8 %), N17-018—1 (0.9 %).

## ***2. ISS Information Relevant to Abuse Potential***

The sponsor stated that they were aware of only one case in which a substantial number of patches were unaccounted for (Study N17-021, Patient #18/16). The investigator attributed the problem to poor compliance and did not suspect misuse or diversion. The CRF shows that the patient was 9 years old and that 13 patches were "lost" and 11 were "thrown away." The patches were lost or thrown away on four different return visit dates. It is not apparent from the information provided why misuse or diversion was not suspected.

The sponsor did not define the word "substantial" in the paragraph above and did not state whether there were other patients who did not return a smaller number of patches. Because methylphenidate is a Schedule II substance, the sponsor is advised to report all incidents of possible loss or theft and any incidents of not returning used or unused patches in the studies as instructed by protocol to the DEA on the DEA's standard "Theft and Loss" form and to the FDA. (CSS sent a memorandum regarding this issue to HFD-120 on 1/29/03.)

## ***3. Summary of Clinical Trial Data Relevant to Abuse Potential***

During MTS administration in the clinical trials, euphoria, manic reaction, and hallucinations occurred, and at least 22 patches were not returned as instructed by protocol. The sponsor has been advised to report all incidents of possible loss or theft and all incidents of not returning used or unused patches. In addition, the sponsor will need to monitor carefully for abuse and diversion if MTS is approved and during ongoing and future clinical trials.

## **III. Adverse Events/Overdose**

The most common AEs in pediatric patients in the two Phase 3 controlled studies (N17-010 and N17-018) were application site reaction, anorexia, insomnia, headache, and abdominal pain. With the exception of application site reaction, these AEs also occur in patients taking oral methylphenidate.

In Study N17-007, stimulant abusers were exposed to eight 25 cm<sup>2</sup> patches (55 mg per patch) for 24 hours and no serious AEs occurred. Mean systolic blood pressure increased by 25 mm Hg and pulse rate increased by as much as 37 bpm.

There is no reported experience with overdose through MTS ingestion.

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/s/

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Corinne Moody  
4/3/03 01:55:28 PM  
CSO

Michael Klein  
4/3/03 01:58:32 PM  
CHEMIST

Deborah Leiderman  
4/3/03 02:49:14 PM  
MEDICAL OFFICER

## REQUEST FOR CONSULTATION

TO (Division/Office): Division of Neuropharmacological Drug Products, HFD-120  
Attention: Robbin M. Nighswander, SCSO

FROM: Controlled Substance Staff, HFD-009  
Corinne P. Moody, Science Policy Analyst

DATE  
03-25-03

IND NO.

NDA NO.  
21-514

TYPE OF DOCUMENT

DATE OF DOCUMENT  
02-13-03

NAME OF DRUG  
See Below

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION  
DATE 04-15-03

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                                | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                             | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE-Abuse Liability Proposal | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                            | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT                     | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION               | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY                          |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

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|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:** We are in the process of providing DEA annual estimates of the medical need for Schedule I and II substances. These estimates are based on a trend analysis of prescription and hospital use of Schedule II substances over the past several years. In addition, we provide DEA with information on anticipated changes that might impact our estimates and that might occur as the result of regulatory or marketing actions for a particular drug. These actions could include the approval of efficacy supplements, labeling changes, problems at manufacturing sites involved in the production of Schedule I and II substances, product discontinuation, development of new dosage forms, etc. Since your Division regulates several drugs included in these schedules, we would appreciate if you could provide us with the following information. (1) A list of NDAs, Efficacy and Manufacturing Supplements approved by your Division for the year 2002, for the following substances - *Schedule I and Schedule II Substances - Amobarbital, D-and DL-Amphetamine, Methylphenidate, Pentobarbital, Secobarbital* (2) A list of INDs that might require the manufacturing of commercial-type batches of products containing substances listed above. (3) Do you know of any regulatory action (new indications, major labeling changes, health care professional letters, etc) taken by your Division that may impact the amount of any of the above mentioned substances' synthesis and distribution?

**NOTE:** This is the same request sent to you by Silvia Calderon in an e-mail dated 03-11-03. Should you have any questions, please contact Corinne Moody at (301) 827-2099.

SIGNATURE OF REQUESTER

Corinne P. Moody, Science Policy Analyst

METHOD OF DELIVERY (Check one):

MAIL

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SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Corinne Moody  
3/25/03 04:15:45 PM

# MEMORANDUM

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Research and Evaluation  
Office of Drug Evaluation V  
Division of Dermatologic and Dental Drug Products (HFD-540)

Tel 301-827-2020  
FAX 301-827-2075

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**From:** Brenda Carr, Medical Officer, HFD-540

**Via:** Markham Luke/Dermatology Team Leader, HFD-540  
Jonathan Wilkin/Division Director, HFD-540

**To:** HFD-120

**Consult:** HFD-540 #360 (0211074)

**Subject:** NDA 21-514

**Material Reviewed:** Sections of Volumes 1, 3 (Chemistry, Manufacturing, and Control) and 41 (Clinical) of the application

**DATE:** March 6, 2003

**Background/Introduction:** Methylphenidate Transdermal System (MTS;  system) was developed by Noven Pharmaceuticals for the once-daily treatment of Attention Deficit Hyperactivity Disorder (ADHD) by a patch delivery system. MTS incorporates Noven's DOT Matrix™ patch technology in which the matrix acts as both the drug reservoir and the adhesive layer. The matrix consists of two adhesives and the active ingredient, *d,l*-methylphenidate, and was designed to release methylphenidate continuously upon application to intact skin.

The Sponsor believes that MTS will offer potential advantages over currently-marketed oral methylphenidate formulations. It is the Sponsor's belief that:

- MTS will provide reliable, effective once-daily treatment for ADHD because of its sustained-release characteristics and mode of administration.
- The wear time can be individually titrated, giving more flexibility in drug exposure to achieve the optimal balance of efficacy and tolerability.

The Sponsor's development plan was expansive. The consult will focus on the dermal safety study (N17-008) and the cutaneous adverse events in the pivotal trials (N17-010 and N17-018). Additionally, the cutaneous adverse events in the completed longterm safety study (N17-021) will be addressed. Finally, brief comment will be made on study N17-017, in which the study product was applied to irritated skin.

### Regulatory History

According to the Sponsor, at the End-of-Phase 2 meeting (February 4, 2000), it was agreed that if a bioavailability study showed comparable plasma methylphenidate levels from MTS for two application sites, a single site could be examined in the controlled clinical studies. In a phase 2 study, N17-005, the pharmacokinetics of methylphenidate in pediatric ADHD subjects wearing MTS on the hip showed higher values for  $C_{max}$  and AUC than for subjects wearing MTS over the scapula. Based on those data, the hip was chosen as the site of application for subsequent controlled trials, including the pivotal trials.

The issue of local reactions to the MTS was discussed with the Agency. According to the Sponsor, the potential for MTS to act as a dermal sensitizer was studied in adult volunteers at the suggestion of the Agency. Additionally, scales for evaluation of skin reactions were employed in the controlled trials in pediatric subjects, as suggested by the Agency.

The Division of Dermatologic and Dental Drug Products was consulted for review of protocol submitted by the Sponsor: "Skin Irritation and Sensitization Testing of Noven™ Methylphenidate Transdermal System" (consult #174; 11006205).

Comments on the protocol included:

1. While sufficient for a cumulative irritancy study, the number of subjects would not be felt adequate for a contact sensitization study. Approximately 200 subjects would be suggested for the latter.
2. Rotation of test articles would not be appropriate in a cumulative irritancy study.
3. It is unclear why the patch testing would be repeated a third time in subjects who have shown two strong positive reactions in the induction/irritation phase (p.8). If the Sponsor is attempting to confirm the initial strong reaction, a single repeat test should suffice. It is unclear what additional information might be gained from a third test and the Sponsor is asked to provide a rationale for this approach.
4. The potential for contact sensitization should be based solely on the outcome at the naïve site rather than being based on the outcome at the original and naïve sites.

**Reviewer's comment:** *It is not clear that any of the comments were considered: the study was initiated on July 27, 2000 and completed on October 1, 2000; consult was dated September 5, 2000.*

### Drug Product

The MTS is described as a translucent unit comprised of three layers:

- 1) a polyester/ethylene vinyl acetate laminate film backing,

- 2) a proprietary adhesive formulation incorporating Noven's DOT Matrix™ transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate (adhesive and drug reservoir) and
- 3) a fluoropolymer-coated polyester protective liner which is attached to the adhesive surface and removed prior to application to the skin.

The active component of the system is methylphenidate (contained in the adhesive layer).

Six systems were used in the clinical trials (below). In the application, the Sponsor states that there are currently no plans to market the \_\_\_\_\_ patch size. Additionally, the \_\_\_\_\_ cm<sup>2</sup> may not be marketed initially, but may be introduced if a consumer need for this dose is identified. Thus, the stated lowest commercially available dose will be the 12.5 cm<sup>2</sup> patch and the highest will be the 37.5 cm<sup>2</sup> patch. The units of measure used throughout the text to describe MTS are: size (cm<sup>2</sup>), dose delivered (mg/hr), and drug content (mg/unit). The table shows the relationship of these units of measure:

Size (cm <sup>2</sup> )	Dose* (mg/hr)	Methylphenidate Content (mg)
6.25	0.45	13.8
12.5	0.9	27.5
18.75	1.35	41.3
25	1.8	55.0
37.5	2.7	82.5
50	3.6	110.0

*\* Nominal in vivo delivery rate per hour in pediatric patients when applied to the hip based on a 12 hour wear period.*

## CLINICAL TRIALS

### N17-008: "Skin Irritation and Sensitization Testing of Noven™ Methylphenidate Transdermal System"

**Investigator:** Lawrence Galitz, M.D.  
South Florida Bioavailability Clinic  
Miami, FL

**Study period:** start date- 07/27/00; end date- 10/01/00

#### **Objectives:**

1. To evaluate the test articles for the induction of contact sensitization by repetitive applications to the skin of healthy human volunteers.
2. To test and compare articles of low irritation potential for human skin irritation elicited by repetitive topical application.

**Study Design:** single-center, randomized, controlled, active/placebo, evaluator-blind, intra-individual comparison study; the study included an induction/irritation period, a rest period, a challenge period, and (for select subjects) a rechallenge period. Approximately 120 subjects were to follow a 21-day exposure period for induction.

**Reviewer's comment:** *While 120 subjects is more than adequate for the irritation objective, a minimum of 200 subjects is suggested for the sensitization objective.*

#### Inclusion Criteria

1. Subject was willing to participate in the study and understood and gave written informed consent.
2. Subject was a normal, healthy, male or female of any race between the age of 18–55 years.
3. Female subjects had to be postmenopausal, physically incapable of childbearing or practicing an acceptable method of birth control (IUD, hormones, diaphragm, and condom with spermicide, or abstinence). If the subject was practicing an acceptable method of birth control, she also had to have maintained her normal menstrual pattern for the three months prior to study entry and have had a negative urine pregnancy test within 14 days of dosing.
4. Subjects had to be judged by the Investigator to be healthy on the basis of pre-study medical history, physical examination, electrocardiogram, and clinical laboratory test results.

**Reviewer's comment:** *The results from the adult subjects can probably be extrapolated to most of the Sponsor's target population, since, according to Hurwitz (Clinical Pediatric Dermatology, 1993), normal adult reactivity is attained by 7 to 8 years of age.*

#### Exclusion Criteria

1. Subject had a history of glaucoma, migraines, cardiovascular, hepatic, renal, gastrointestinal, neurologic, psychiatric, dermatologic, pulmonary, cerebrovascular, hematologic, thromboembolic, immunologic disease, or any other disorder, which required a physician's care.
2. Subject had a history of severe depression, psychoses, anxiety, seizures or Tourette's Syndrome.
3. Subject had a history of sensitivity to methylphenidate.
4. Subject had history of significant skin disorder or presence of scar tissue such as a tattoo, at the potential site of patch application.
5. Subject had a history of allergy to soaps, lotions, cosmetics or adhesives.
6. Subject had a history of significant allergies (including asthma, food or drug allergies).
7. Subject was a former or present narcotic addict, drug abuser or alcoholic.
8. Subject had symptoms of any significant acute illness at the screening visit or prior to start of study.
9. Subject had taken any investigational drug within 30 days or six half-lives of its biologic activity whichever is longer, prior to initial dosing.
10. Subject had a clinically significant abnormal laboratory parameter as defined by the investigator.
11. Subject was pregnant or breastfeeding.

#### Induction Period and Cumulative Irritation Period

The first three weeks of the study served as both the induction period for the contact sensitization objective and the 21-day exposure time for the cumulative irritation

objective.

The protocol called for twenty-one consecutive applications of the test articles to be applied to the same site on the upper back of all subjects for approximately 24 hours. The 4 test articles were:

- 55mg/25 cm<sup>2</sup> MTS (active),
- 0 mg/ 25 cm<sup>2</sup> MTS (placebo),
- 0.1% sodium laurel sulfate (SLS; positive control), and
- physiological saline (negative control).

The Sponsor furnished the MTS test articles; the investigative organization (South Florida Bioavailability Clinic, Inc.) provided the control articles. The control articles were occluded using a nonwoven cotton pad ( ) covered by and secured on all sides by hypoallergenic tape ( ) and were only applied during the induction/irritation period. According to the protocol, (Section 10.0), control articles were only to be applied during the induction/irritation phase.

**Reviewer's comment:** Control articles were also applied during the challenge phase.

Scoring for irritation was done approximately every 24 hours, 30 minutes after patch removal, following which a new patch was applied. Patches were applied and removed by laboratory personnel.

#### Rest Period

Following the induction/irritation period, the study subjects did not receive any application of test article for approximately two weeks.

#### Challenge

Test articles were applied to pre-exposed site and a naïve site to test for reactions indicative of contact sensitization. The sites were scored approximately 24, 48, 72, and 96 hours after patch application (30 minutes, 24, 48, and 72 hours post patch removal). The data from the challenge evaluations formed the basis of the conclusions regarding sensitization.

**Reviewer's comment:** A determination of sensitivity was based on reactions at the naïve site.

#### Rechallenge

Test articles were applied to a naïve site for 24 hours to confirm reactions indicative of contact sensitization.

#### Skin Irritation Assessments

These scales were used during the induction/irritation period. The irritation assessments were conducted daily during induction, approximately 30 minutes following patch removal. The following scales were employed:

a) **Irritation Responses:**

- 0 = No evidence of irritation
- 1 = Minimal erythema, barely perceptible
- 2 = Moderate erythema, readily visible; or minimal edema; or minimal papular response
- 3 = Strong erythema; or erythema and papules
- 4 = Definite edema
- 5 = Erythema, edema and papules
- 6 = Vesicular eruption
- 7 = Strong reaction spreading beyond test site

b) **Superficial Effects**

- A = Slight glazed appearance
- B = Marked glazing
- C = Glazing with peeling and cracking
- F = Glazing with fissures
- G = Film of dried serous exudate covering all or portion of the patch site
- H = Small petechial erosions and/or scabs
- @ = Additional comments as footnote

If any numeric score was appended with a letter grade F, G, or H or any score was 3 or greater, no additional applications of test article were made. For these subjects, a score of 3 was carried forward through the remaining days of the irritation/induction period for statistical analysis. In Section 13.0 of the protocol ("Statistical Analysis"), the stated rationale for this approach is, "An upper limit of 3 is selected for statistical analysis since the intent of this test is to compare treatments that are relatively mild."

**Reviewer's comment:** 1) It is unclear why a seven-point irritation response scale was put forward in the protocol, if the intention was to only score to a maximum of 3 in the analysis. 2) Section 9.5.1.2 of the study report addresses a discrepancy in the irritation scale as described in the protocol (above), and that described on the case report forms and data listings (used in the study). The Sponsor states that the scale in the case report forms and data listings is the "FDA's recommended scoring system for irritation skin reactions" (apparently as described in the Guidance, "Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products" referenced by the Sponsor). However, the protocol was inadvertently not revised to be consistent with the case report form. Instead of the definitions in the protocol (above), the following definitions were applied for an irritation score of 2 or 3 on the case report forms and in the data listings (sample case report form on the p.390 of the protocol):

- 2= Definite erythema, readily visible; or minimal edema or minimal papular response;
- 3= Erythema and papules

The differences in the definitions would appear to have no significant impact on the study results.

### Skin Sensitization Assessments

These scales were used during the challenge period. Reactions were evaluated approximately 30 minutes, 24, 48 and 72 hours post-removal according to the following:

a) **Inflammatory Responses:**

- 0 = No visible reaction
- + = Slight, confluent or patchy erythema
- 1 = Mild erythema (pink)
- 2 = Moderate erythema (definite redness)
- 3 = Strong erythema (very intense redness)

Definition of letter grades appended to a numerical grade:

- E = Edema - swelling, spongy feeling when palpated
- P = Papule - red, solid, pinpoint elevation
- V = Vesicle - small elevation containing fluid
- B = Bulla reaction - fluid-filled lesion (blister)
- S = Spreading - evidence of the reaction beyond the Webril® pad area
- W = Weeping - result of a vesicular or bulla reaction - serous exudate
- I = Induration - solid, elevated, hardened, thickened skin
- \* = Residual reaction to earlier application after absen
- ~ = Response occurs on < 25% of test site

b) **Superficial Effects:**

- g = Glazing
- y = Peeling
- c = Scab, dried film of serous exudate of vesicular or bulla reaction
- d = Hyperpigmentation (reddish-brown discoloration of test site)
- h = Hypopigmentation (loss of visible pigmentation at test site)
- f = Fissuring - grooves in the superficial layers of the skin
- @ = Additional comments appear below or on the following page

Questionable (barely perceptible, minimal or involving less than 25% of the patch site) reactions and the “+” designation were considered inconclusive.

Adherence Scale

Additionally, adherence performance of the active and placebo test articles was graded at each visit. Adherence was assessed at removal according to the following scales:

- 0 = System adhered >90% (“completely on”)
- 1 = System adhered 75% - 90% (“edges lifting off” or “center “raised”)
- 2 = System adhered 50% - 74% (“half-off”)
- 3 = System adhered <50% (“just hanging on”)
- 4 = System became completely detached and was reapplied
- 9 = System not present on skin
- T = Added to an adherence score which required additional taping

**Reviewer's comment:** *It was appropriate to assess adherence since this could impact the quality of the topical safety study results (as well as efficacy in the controlled trials).*

The development of tape dermatitis was considered an adverse event, and, depending on the severity could serve as the basis for discontinuing a subject from the study.

## RESULTS

### Disposition/Demographics

Of 122 subjects enrolled (76 females and 46 males), 116 completed the challenge phase 76 females (mean age: 36.6 years, range: 18-57) and 46 males (mean: 35.1, range: 19-55). There were 114 Whites and 8 Blacks.

Six subjects discontinued the study; none discontinued because of adverse events:

- two subjects discontinued for reasons said to be unrelated to study medication,
- two subjects were lost to follow-up (one failed to present for follow-up; reason not specified for the other subject),
- one subject had a positive pregnancy test on Day 4 of the study,
- one subject moved out of the area.

### Protocol Deviations

The Sponsor describes the following "general" protocol deviations as having occurred during the course of the study (Section 10.2 of the study report):

- Two subjects who discontinued were replaced.
- There were no follow-up scores at the residual sites once the patches were moved due to an irritation score of three or greater.
- One subject was above the inclusion upper age limit of 55 years old.

**Reviewer's comment:** *Protocol Deviations will be further addressed in the discussion of the sensitization results.*

### Irritation results

In Section 11.3.1.2 of the final study report, the Sponsor states that "All subjects had patching discontinued due to irritation scores of 3 (or equivalent) before completing 17 applications with MTS active, placebo, or SLS. Only one subject (No. 27) had all 21 applications of saline."

**Sponsor Text Table 6**

#### **Mean Irritation Scores and Friedman Analysis Results**

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
Code	(n=121)	(n=121)	(n=121)	(n=120)	(n=119)	(n=118)	(n=118)	
A	0.0000	1.5620	1.9835	2.2083	2.4958	2.6864	2.8305	
B	0.0000	0.6198	1.1240	1.6167	2.0840	2.4407	2.8305	
C	0.0000	0.5620	1.1405	1.6000	1.9160	2.1695	2.6949	
D	0.0000	0.3967	0.9917	1.5250	1.7311	2.0339	2.4576	
p-values:	>0.5000	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Treatment	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
Code	(n=115)	(n=116)	(n=116)	(n=116)	(n=114)	(n=113)	(n=112)	(n=112)
A	2.9304	2.9741	2.9741	3.0000	3.0000	3.0000	3.0000	3.0000
B	2.9217	2.9569	2.9655	3.0000	3.0000	3.0000	3.0000	3.0000
C	2.8522	2.9052	2.9052	2.9569	2.9912	3.0000	3.0000	3.0000
D	2.6870	2.7759	2.7672	2.8793	2.9035	2.9469	2.9732	2.9821
p-values:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	0.0286	0.1112
Treatment	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Overall
Code	(n=111)	(n=110)						

A	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	58.5727
B	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	55.7273
C	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	54.8091
D	2.9910	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	53.2545
p-value	0.3930	>0.5000	>0.5000	>0.5000	>0.5000	>0.5000	>0.5000	<0.0001

NOTE: The means shown in the preceding tables were calculated using the transformed irritation scores. The p-values were derived from the Friedman analysis.

KEYS: Treatment Code A (One 25 cm<sup>2</sup> Noven Methylphenidate Transdermal System)  
 Treatment Code B (One 25 cm<sup>2</sup> Placebo Noven Methylphenidate Transdermal System)  
 Treatment Code C (Positive Control: 0.1% Aqueous Sodium Lauryl Sulfate)  
 Treatment Code D (Negative Control: Saline)

**Significant Comparisons: Fisher's LSD test (Sponsor Text Table 7)**

<b>B</b>	Days 2-6		
	<b>Overall</b>		
<b>C</b>	Days 2-8	Day 5-7	
	<b>Overall</b>	<b>Overall</b>	
<b>D</b>	Days 2-14	Days 2-14	Days 2-14
	<b>Overall</b>	<b>Overall</b>	<b>Overall</b>

HTR Codes: A B C  
 KEYS: Treatment Code A (One 25 cm<sup>2</sup> Noven Methylphenidate Transdermal System)  
 Treatment Code B (One 25 cm<sup>2</sup> Placebo Noven Methylphenidate Transdermal System)  
 Treatment Code C (Positive Control: 0.1% Aqueous Sodium Lauryl Sulfate)  
 Treatment Code D (Negative Control: Saline)

**Reviewer's comment:** *The results suggest that, in the initial days, the methylphenidate-containing patch was more irritating than the placebo patch, suggesting that methylphenidate itself might be an irritant. The placebo patch appears to have been slightly more irritating than the controls, suggesting that the adhesive(s) might also contribute to irritancy (not surprisingly). That all sites eventually manifested significant irritancy, suggests the "angry back syndrome", wherein hyperirritability of the skin may make for reactivity to test articles to which there might not otherwise be a reaction. Per the protocol, if any numeric score was 3 ("erythema and papules") or greater or any score was appended with a letter grade F, G, or H ("glazing with fissures", "film of dried serous exudate covering all or portion of the patch site" and "small petechial erosions and/or scabs", respectively), no additional applications of test article were made to that site and a score of 3 was carried forward in the analysis. It is, therefore, unclear how many subjects might have experienced more severe reactions and/or to what extent the severity of any reactions might have continued to increase over time. However, the results clearly indicate that the Sponsor's product is an irritant. This is further supported by fact that only one subject received all 21 irritation/induction applications, which could have implications for the sensitization objective of the study, since the irritation phase was also to serve as the induction phase.*

Sensitization results

The Sponsor reported that 63% of the 116 subjects considered to have completed challenge, exhibited reactions to the active MTS. These reactions were reported primarily as none to mild erythema at the 30 minute evaluation and largely resolved over the course of 24 to 48 hours. These reactions were considered irritant in nature.

As reported by the Sponsor, approximately 37% of the subjects exhibited moderate to strong erythema at the 30 minute evaluation that decreased to slight to no erythema over the course of 24 to 48 hours. In general these responses were greater than those observed in response to the TS placebo, positive and negative control sites. However, since the

reactions were not stronger than the reactions observed during induction and they decreased relatively rapidly, they were considered by the Sponsor to represent irritation but not sensitization.

**Reviewer's comment:** *The reviewer agrees with the general principle that the shorter time course to resolution tends to favor irritancy. However, the appropriateness of comparing the degree of erythema observed during induction with that seen during challenge is in question, since the Sponsor employed different assessment scales in each of these study phases. In the induction phase, erythema was assessed by a scale which included levels that coupled the assessment of erythema with the presence of edema and/or papules. In the challenge phase, erythema was assessed by a scale that measured only erythema. It is not clear why the Sponsor used different scales to assess irritancy and sensitization.*

Of the 116 subjects the Sponsor considered as completing challenge, three subjects were considered by the Sponsor to have exhibited reaction suggestive of sensitization to the Noven MTS active patch:

- Subject No. 17 (declined rechallenge).
- Subject No. 53 (Rechallenge did not confirm sensitization to the Noven MTS active patch in the opinion of the investigator.)
- Subject No. 54 (Rechallenge results were consistent with sensitization to the Noven MTS active patch.)

Therefore, under the conditions of this study, the Sponsor concluded that one subject was confirmed to have been sensitized to the Noven MTS active patch while a second subject was suspected of having been sensitized.

**Reviewer's comment:** *Section 11.2 of the study report ("Measurements of Treatment Compliance") states that, "The removal of any patch other than by laboratory staff was reported as a Protocol Deviation (Appendix VII)." However, Appendix VII does not appear to have been included in the final report (the section labeled "Appendix VII Protocol Deviations" is marked by a blank page).*

*However, review of Listing 12, "Adherence Assessment", contains information that likely would have been included in the missing appendix. From review of Listing 12, it appears that 17 of 116 subjects (15%) had complete detachment of the MTS patch (active) following application of the product for the challenge phase of the study. Of the 17 subjects, 16 presented for the 24-hour challenge assessment with the patch not present on the skin (see "9" on Adherence Scale), and the 17<sup>th</sup> subject had had complete detachment of the patch but reapplied it with tape. (Note: One of these 17 subjects, 76R, had been enrolled as a replacement, in violation of the protocol). Given the patch detachment, it is unclear that these 17 subjects were adequately challenged. Thus, it would appear that only 99 of 116 subjects would be considered evaluable in the challenge phase of the study.*

*It is also noted that 77 of 116 subjects (66%) presented for the challenge visit with some degree of compromise in the adherence of the MTS patch, ranging from "edges lifting off" or "center raised" (1 on Adherence Scale) to "system not present on skin" (9 on scale).*

Based on review of Listing 13 "Topical Assessment" Part 2 ("Challenge and Rechallenge Evaluations"), the reviewer agrees with the Sponsor and considers that only Subjects 17, 53, and 54 showed evidence suggestive of sensitization following challenge. All 3 subjects presented for challenge evaluation with the units "completely on" (Score of 0) and are therefore considered evaluable.

**Subjects Considered by Reviewer to Have Shown Evidence Suggestive of Sensitization on Challenge Testing (Based on review of Listing 13 "Topical Assessment" Part 2)**

	Post-application Assessment Naïve Active Site/Naïve Placebo Site			
	24.5 hrs	48 hrs	72 hrs	96 hrs
Subject 17	2/0	2/0	2/0	2/0
Subject 53	+g/+g	2/0	2/0	2/0
Subject 54	+g/+g	+/0	2/0	2/0

0 = No visible reaction; + = Slight, confluent or patchy erythema; 1 = Mild erythema (pink); 2 = Moderate erythema (definite redness); 3 = Strong erythema (very intense redness); g = Glazing

On rechallenge, Subjects 53 and 54 presented with partially detached patches. Specifically, both had scores of 1 for the MTS patches i.e., "edges lifting off" or center raised" and both subjects had the patches held in place by tape. (Subject 17 was not rechallenged). On rechallenge, Subject 53 showed no reactions at the active or placebo MTS sites (but did manifest moderate to strong erythema with edema at the sodium lauryl sulfate site, which showed slight erythema with glazing at 24.5 hours and no signs at later evaluations e.g. 48 hours). It is unclear whether the challenge results indicate a true negative or false negative due to a compromise in the patch adherence. On rechallenge, in spite of compromised adherence, Subject 54 showed strong erythema and edema which persisted at the naïve site beyond 96 hours.

The outcomes at the placebo sites suggest that if there is a sensitization issue, it would more likely be attributable to the methylphenidate than the adhesives.

### **PIVOTAL STUDIES**

The Sponsor conducted two Phase 3, placebo-controlled, dose-titration studies, N17-010 and N17-018. Both studies were multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible dose titration studies of MTS in pediatric subjects with a primary diagnosis of ADHD. In general, for inclusion the subjects were required to be healthy and between the ages of 6 and 12 years.

Exclusions included:

- Patient had any skin disease, or history of any chronic skin disease, skin cancer (with the exception of localized basal cell carcinoma of the skin which had been fully treated), skin manifestations of allergic disease, or other dermatologic conditions which would interfere with trial assessments or compromise patient safety.
- Patient had sensitive-skin syndrome (this was defined as the development of nonspecific skin irritability reactions to bland materials). In addition, patients who

had sensitivities to the ingredients in soaps, lotions, cosmetics, or adhesives were excluded.

- Patient had clinical signs/symptoms of skin irritation (i.e., pruritus, burning, erythema) or hyper/hypopigmentation at the potential application sites (i.e., scars or tattoos).
- Patient had a documented allergy, hypersensitivity, or "clinically significant" intolerance to methylphenidate (any form) or any components found in Noven's Methlyphenidate Transdermal System.

It noted that Section 5.2.4 of both protocols ("Concomitant Medications") includes the following bolded warning:

**"WARNING:** Since the product being tested in this study is a transdermal formulation, consult the Sponsor or the Sponsor's representative when considering dispensing antibiotics (e.g., tetracycline HCl) with a known side effect of photosensitivity."

***Reviewer's comment:** It is suggested that the exclusion criteria pertaining to pre-existing allergies and skin conditions be reflected in labeling. It is unclear why investigators were warned regarding the dispensing of photosensitizing antibiotics, but it is suggested that this also be reflected in labeling. Also, see earlier reviewer discussion about photo-safety studies.*

Subjects were included in the safety population if they received at least one dose of randomized study medication.

#### **Study 17-010**

In this study, subjects were titrated to maximum effective dose levels using patches of 6.25 cm<sup>2</sup>, 12.5 cm<sup>2</sup>, and 25 cm<sup>2</sup> areas. Patients could be titrated downward if side effects warranted it. Patches were to be worn on the hip during the waking hours (approximately 12 hours per day). A patch was applied in the early morning to a clean, dry, non-oily, and non-irritated site on the subject's hip, alternating right and left side daily and avoiding the waistline area. After one week of treatment, the dose was either maintained or increased by one level. After 2 weeks of treatment, the dose was maintained, increased by one level, or returned to the initial dose. The duration of treatment was 3 weeks.

#### **Study 17-018**

In this study, subjects were titrated to maximum effective dose levels using patches of 12.5 cm<sup>2</sup>, 18.75 cm<sup>2</sup>, 25 cm<sup>2</sup>, 37.5 cm<sup>2</sup>, and 50 cm<sup>2</sup> areas (with 6.25 cm<sup>2</sup> patches available for downward titration if side effects warranted). As with study N17-010, patches were applied in the morning to a non-irritated site on the subject's hip, alternating right and left side daily, with avoidance of the waistline area.

Patches were to be worn on the hip for 12 hours per day (wear time could be reduced to a minimum of 7 hours if adverse effects warranted).

If behavior was not normalized after one week of treatment, the dose was to be doubled to 25 cm<sup>2</sup> or 37.5 cm<sup>2</sup>, unless side effects were prohibitive. As warranted, titration could proceed up to 50 cm<sup>2</sup> by weekly, one-step dose increases. If behavior was normalized, but late-in-the-day side effects were significant, wear time was to be reduced, beginning with a trial of 8.5 to 9 hours per day. Failing this reduction in wear time, the dose could be titrated down once to the next lower dose. Only one dose reduction was allowed during the study. The duration of treatment was 4 weeks.

Pertaining to N17-018, after 2 weeks of treatment (including one dose titration), at the discretion of the investigator, subjects were allowed to withdraw and enroll in Study N17-021, the long-term, open-label safety study, if it was thought that the subject would benefit.

### Accountability

#### **Phase 3 Pediatric Population N17-010 and N17-018 (Modified Text Figure 4, Integrated Summary of Safety)**

N= 406

MTS Treated = 195

Discontinued = 24 (12%)

Due to

Adverse Event = 7

Protocol Deviation = 4

Administrative = 0

Lack of Efficacy = 9

Lost to Follow-Up = 0

Other = 4

Completed = 171 (88%)

Placebo TS Treated = 211

Discontinued = 67 (32%)

Due to

Adverse Event = 5

Protocol Deviation = 3

Administrative = 0

Lack of Efficacy = 54

Lost to Follow-Up = 1

Other = 4

Completed = 144 (68%)

### Demographics

Each patient who enrolled in more than one study was counted only once. Sample sizes of the treatment groups in the various populations may differ slightly from those presented in the Subject Accountability Section (as discussed in Section 3 of the Integrated Summary of Safety). No notable differences between the treatment groups were observed at Baseline.

#### **Demographic and Baseline Characteristics-Phase III Controlled Pediatric Population, n (%) (Modified Text Table 24)**

	MTS(n=201)	Placebo(n=205)
Age (yr)		
Mean	8.6	8.7
s.d.	1.8	1.7
Range	6-12	6-12
Gender, n (%)		
Male	144 (72)	154 (75)
Female	57 (28)	51 (25)
Race, n (%)		
White	145 (72)	144 (70)
Black	27 (13)	37 (18)
Other	29 (14)	24 (12)
Weight (kg)		
N	200	204
Mean	34.0	34.9
s.d.	11.9	11.7
Range	17-93	18-80
< 25 kg, n (%)	48 (24)	45 (22)

25 to 59 kg, n (%)	142 (71)	151 (74)
60 to 80 kg, n (%)	10 (5)	8 (4)
> 80 kg, n (%)	1 (<1)	1 (<1)
Height (cm)		
N	200	204
Mean	134.2	135.1
s.d.	12.9	11.7
Range	99-168	104-170

## Exposure

In the Phase 3 studies, most of the patients received MTS for 21-42 days.

**Cumulative<sup>1</sup> Duration of Exposure to MTS in Days, n (%)**  
(Modified Text Table 26)

Safety Population	1-6	7-20	21-42	43-84	>84	Total
All Pediatric <sup>2</sup>	51(12)	90 (22)	174 (42)	33 (8)	66 (16)	414
Phase III Controlled	5 (2)	36 (18)	157 (78)	4 (2)	0 (0)	202
Long-Term Pediatric	1 (1)	7 (6)	15 (13)	32 (27)	63 (53)	118

<sup>1</sup> Exposure to MTS was summed regardless of dose and number of hours worn.

<sup>2</sup> Some patients may appear in both the Long-Term Pediatric and Phase III Controlled Pediatric Populations; therefore, data are not additive for the Pediatric Population.

**Cumulative<sup>1</sup> Duration of Exposure to MTS by Dose-Phase III Controlled Pediatric Population (n=202), n (%)**  
(Text Table 27)

Duration of Treatment	6.25 cm <sup>2</sup>	12.5 cm <sup>2</sup>	18.75 cm <sup>2</sup>	25 cm <sup>2</sup>	37.5 cm <sup>2</sup>	50 cm <sup>2</sup>
1-6 Days	24 (24)	26 (19)	11 (15)	24 (20)	14 (23)	4 (19)
7-20 Days	76 (75)	106 (78)	52 (70)	81 (68)	44 (71)	17 (81)
21-42 Days	2 (2)	4 (3)	11 (15)	14 (12)	4 (6)	0 (0)
N	102	136	74	119	62	21

<sup>1</sup> Exposure to MTS was summed regardless of dose and number of hours worn.

## CUTANEOUS ADVERSE EVENTS

The denominators in the various populations is based on the contribution of each subject to the denominator of each study treatment that they received.

### Deaths and Serious Adverse Events

No deaths occurred during any of the studies in the MTS clinical development program. There were no skin-related serious adverse events.

### Adverse Events Leading to Discontinuation

Two subjects discontinued study N17-018 (none from 17-010) for skin-related adverse events, one from each treatment group:

- Subject 12/02: This 7-year-old female used the placebo TS patch for 11 days before withdrawing from the study because of skin irritation at the patch site. The subject was assigned to the 18.75 cm<sup>2</sup> patch, and applied the first patch on January 26, 2002. On February 1, 2002, the TS patch was increased to 37.5 cm<sup>2</sup>. The last day of patch

wear was February 5, 2002. At the subject's final clinic visit (February 8, 2002), the investigator noted definite erythema on the subject's right and left hips, with reported itching and moderate discomfort.

**Reviewer's comment:** *The timeframe appears more suggestive of irritation than sensitization.*

- Subject 22/13: This 7-year-old male used the MTS patch for 6 days before withdrawing from the study because of generalized pruritus. The patient was assigned to the 18.75 cm<sup>2</sup> patch, and the first day of application was January 19, 2002. The generalized pruritus began the following day, January 20, 2002. At the subject's final visit (January 25, 2002), the investigator noted the pruritus to be of moderate severity with a probable relationship to study medication. The pruritus resolved following discontinuation of the study medication.

#### Patch Application Site Assessment

Patch application sites were examined for skin reactions and other signs of irritation. The protocols for the phase 3 trials called for these findings to be recorded on dermal irritation scales, but not recorded as adverse events, unless they occurred at sites different from the application site. However, to avoid underreporting the incidence of application site reactions, for purposes of the Integrated Summary of Safety, all data from the dermal irritation scales were merged with the spontaneously reported adverse events, if the investigator had not already reported the event as an adverse event. Additionally, all local site reactions were attributed to study medication.

**Reviewer's comment:** *This appears to be reasonable approach to avoiding underreporting the incidence of application site reactions.*

The current and prior application sites were assessed for skin reactions/irritation at each weekly study visit. The current site was examined through the patch unit i.e. the unit was not removed for this evaluation. Sites were assessed according to the following scale:

- 0 = No evidence of irritation
- 1 = Minimal erythema, barely perceptible
- 2 = Definite erythema with minimal edema or minimal papular response
- 3 = Erythema and papules
- 4 = Definite edema
- 5 = Erythema, edema and papules
- 6 = Vesicular eruption
- 7 = Strong reaction, spreading beyond test site.

**Reviewer's comments:** 1) *This is the same scale employed in the irritation assessments in the dermal safety study N 17-008 (discussed above). It is unclear why examination of the current site of application was conducted by looking through the patch rather than by direct examination. This manner of examination could have potentially compromised the assessment by obscuring and/or distorting physical findings.* 2) *Given that the product is, as acknowledged by the Sponsor, a*

dermal irritant, it would have been informative to have specifically assessed for any pigmentary alterations at the sites of application (e.g., postinflammatory hypo- or hyperpigmentation).

Application site reactions were reported to occur in 178 of 202 (88%) of MTS-treated subjects and 140 of 212 (66%) of placebo TS-treated subjects. All application site reactions were attributed to study medication.

The phase 3 population (n=406) was divided into three racial groups: White, Black, and Other Races. In the MTS-treated subjects, application site reactions occurred in 135 of 145 Whites (93%), 16 of 28 Blacks (57%) and 27 of 29 Other Races (93%). In placebo TS-treated subjects, application site reactions occurred in 106 of 149 Whites (71%), 15 of 37 Blacks (41%) and 19 of 26 Other Races (73%).

**Reviewer's comment:** *The lower incidence of application site reactions in Blacks might be attributable to possible difficulties by some investigators in discerning erythema in darker skin. Erythema assessment might have been further compromised by the examination of the site of current application through the patch.*

In the phase 3 trials, adverse events were also analyzed by age groups: 6-9 years and 10-12 years. Application site reactions in 91% of the 138 MTS-treated subjects in the 6-9 years group and 83% of the 64 MTS-treated subjects in the 10-12 years group.

**Reviewer's comment:** *It is not clear why younger subjects experienced a higher incidence of application site reactions.*

Subjective data were collected for "discomfort" and "pruritus". Subjects were asked, "Are you experiencing any discomfort (as it relates to the MTS)?" Discomfort was then recorded according to the following scale:

- 0 = No discomfort
- 1 = Mild discomfort
- 2 = Moderate, but tolerable discomfort
- 3 = Severe, intolerable discomfort
- 9 = Patch not present (note: this rating did not apply to the prior sites of application)

Subjects who experienced mild, moderate to severe discomfort were further queried: "What kind of overall discomfort did you experience?" On the case report form, the evaluator was to mark whether the discomfort was "itching," "burning" or "other (provide descriptive term for discomfort)".

**Reviewer's comment:** *It is not clear that the wording for the inquiries was appropriate for the age group being studied (6-12 years). For some subjects in this age group, it is likely that the query required some translation for the subject, and/or the response required some interpretation by the evaluator. Such "translation" and/or "interpretation" could have introduced bias.*

Most discomfort ratings (70%-95%) were reported to be of either no or mild discomfort during MTS treatment across the dose groups. The percentages of subjects experiencing

moderate to severe discomfort ranged from 4 to 8% in the 6.25 cm<sup>2</sup> to 25 cm<sup>2</sup> dose groups and was 15% in the 37.5 cm<sup>2</sup> dose group and 20% in 50 cm<sup>2</sup> dose group. The moderate to severe discomfort rating for placebo TS was 7%. For all ratings, 6 to 10 % of all patients had moderate to severe discomfort with the highest patch sizes. No discomfort was reported at the majority of the rating times; moderate or severe discomfort was reported uncommonly and more discomfort was reported by patients wearing the larger patches.

During each week of MTS treatment, most discomfort ratings (83-96%) were reported to as either none or mild in MTS-treated patients across weeks. The percentages of subjects experiencing moderate to severe discomfort ranged from 5% during Week 1 to 9% during Week 4. The moderate to severe discomfort rating for placebo TS-treated subjects was 7%. No or mild discomfort was reported at the majority of the rating times during the 4 weeks of MTS treatment. Moderate to severe discomfort was reported uncommonly and more discomfort was reported during longer exposure to MTS treatment.

**Reviewer's comment:** "Discomfort" appeared to positively correlate with the size of the patch and the duration of exposure.

### Skin Irritation Ratings

**Dermal Irritation Highest Ratings - Phase 3 Population, n (%) (Text Table 38)**

	MTS 6.25 cm <sup>2</sup> (n=102)	MTS 12.5 cm <sup>2</sup> (n=132)	MTS 18.75 cm <sup>2</sup> (n=70)	MTS 25 cm <sup>2</sup> (n=112)	MTS 37.5 cm <sup>2</sup> (n=61)	MTS 50 cm <sup>2</sup> (n=20)	Placebo (n=212)
Unknown	1 (1)	0 (0)	1 (1)	2 (2)	0 (0)	2 (10)	6 (3)
No evidence of irritation	34 (33)	35 (27)	23 (33)	28 (25)	16 (26)	6 (30)	81 (38)
Minimal erythema	40 (39)	49 (37)	19 (27)	38 (34)	21 (34)	4 (20)	84 (40)
Definite erythema	25 (25)	48 (36)	25 (36)	43 (38)	20 (33)	8 (40)	35 (17)
Erythema and papules	2 (2)	0 (0)	1 (1)	1 (1)	2 (3)	0 (0)	5 (2)
Definite edema	0 (0)	0 (0)	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Erythema, edema and papules	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vesicular eruption	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Strong reaction, spreading	0 (0)	0 (0)	0 (0)	0 (0)	1 (2%)	0 (0)	0 (0)

**All Dermal Irritation Ratings For Each Application-Phase 3 Population, n (%) (Text Table 39)**

	MTS 6.25 cm <sup>2</sup> (n=102)	MTS 12.5 cm <sup>2</sup> (n=132)	MTS 18.75 cm <sup>2</sup> (n=70)	MTS 25 cm <sup>2</sup> (n=112)	MTS 37.5 cm <sup>2</sup> (n=61)	MTS 50 cm <sup>2</sup> (n=20)	Placebo (n=212)
No evidence of irritation	119 (53)	154 (47)	100 (49)	116 (39)	90 (49)	24(47)	930 (76)
Minimal erythema	71 (31)	103 (32)	64 (31)	114 (38)	58 (32)	12(24)	243 (20)
Definite erythema	34 (15)	68 (21)	39 (19)	66 (22)	29 (16)	15(29)	46 (4)
Erythema and papules	2 (1)	0 (0)	1 (<1)	1 (<1)	3 (2)	0 (0)	6 (<1)
Definite edema	0 (0)	0 (0)	1 (<1)	0 (0)	1 (1)	0 (0)	0 (0)
Erythema, edema and papules	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vesicular eruption	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Strong reaction, spreading	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)

**Reviewer's comment:** Erythema was the most commonly reported manifestation of irritation in the phase 3 trials

**N17-021**

There were 118 patients treated in this long-term, open-label study of 3 months. (This was not a pivotal study.) Eighty-six (73%) of these 118 treated patients completed the study. Eight (7%) patients discontinued due to lack of efficacy and five (4%) discontinued due to an adverse event. Results from the completed open-label, longterm study (N17 021) are consistent with what was seen in the studies of shorter duration: application site reactions were reported in 108 of 118 subjects (92%).

Three subjects discontinued the longterm study, N 17-021, because of skin-related adverse events (one subject had additional events that contributed to the decision to discontinue the study):

- Subject 0901 ("rash"): This 9-year old male received placebo TS for 4 weeks in study 17-018. He was enrolled in N17 021 on December 7, 2001. The 25 cm<sup>2</sup> MTS patch was applied on December 8, 2001. The patch dose was ultimately increased to and maintained at the 37.5 cm<sup>2</sup> size. On January 27, 2002, the subject developed a "severe rash" at and around the patch on both hips; the rash was considered possibly related to study drug and the medication was permanently discontinued on February 1, 2002. The rash had resolved by March 3, 2002.
- Subject 1010 (Skin sensitivity, hyperactivity and insomnia): This 6-year old male received placebo TS for 3 weeks in 17-018. He was enrolled in 17-021 on February 1, 2002. A 12.5 cm<sup>2</sup> MTS patch was applied on February 2, 2002 and worn for 9 hours. On February 3, 2002, a second patch was applied but removed after 2 hours due to skin sensitivity, hyperactivity and insomnia. All of the events had resolved by the following day and were considered severe and highly probably related to study medication.
- Subject 2004 (Acute contact dermatitis): This 8 year old male received placebo TS for 3.5 weeks in 17-018. The 12.5 cm<sup>2</sup> MTS patch was first applied in Study N17-021 on 01 December 2001. On December 7, 2001, the patch size was doubled to 25 cm<sup>2</sup>. Definite erythema was noted at the current and prior patch sites at this visit. The erythema persisted on December 17, 2001. On December 25, 2001, the last patch was applied and removed 4 hours later. The study medication was permanently withdrawn on December 27, 2001 due to acute contact dermatitis that was considered moderate in intensity and highly probably related to study medication. The rash was treated with an "unknown anti-itch cream." The event had resolved by January 21, 2002.

**Reviewer's comment:** *Based on the assumption that subjects would not have been enrolled into the longterm study had poor local tolerance been evidenced in study N17-018, placebo TS was apparently well-tolerated in N17-018 (subjects who discontinued 17-018 and enrolled into 17-021 discontinued because of lack of efficacy not because of adverse events). Thus, application site reactions in N17-021 would appear to implicate the methylphenidate as the irritant and/or sensitizer for these 3 subjects. The reaction of Subject 0901 suggests sensitivity (because of delayed onset and prolonged duration beyond when the patch was discontinued). The same might be said for Subject 2004 as well.*

## N17-017

In this study, the MTS patch was applied to irritated skin. The results indicated increased systemic drug exposure in this setting and that such application was associated with mild to moderate discomfort. The Sponsor proposes to discourage application to irritated/inflamed in labeling (p. 19 "Background and Overview").

**Reviewer's comment:** *The results are not surprising. Agree with the Sponsor's plans to advise that application to inflamed skin be avoided.*

## Conclusions:

The clinical trials clearly demonstrate that the MTS patch is irritating, and it is suggested that this be reflected in labeling. The results suggest that the adhesive may also cause some irritancy, but not the extent of that observed with the methylphenidate-containing patch.

In the reviewer's assessment, study N17-008 revealed 3 of 99 evaluable subjects (3%) to show reactions suggestive of sensitization in the challenge phase of the study. Generally, a minimum of 200 subjects is suggested to rule out a sensitization rate greater than 1.5%. That a rate of 3% was seen in 99 subjects, suggests that the MTS patch might have some potential to act as a sensitizer. At the very least, seemingly, its role as a sensitizer cannot be excluded. The sensitization issue is further brought into question because, due to irritancy, most subjects may not have been able to be adequately induced because of abbreviated induction periods.

No subjects in the MTS placebo arm had reactions suggestive of sensitization.

Photoirritation and photosensitization studies do not appear to have been conducted by the Sponsor, nor was there any discussion found regarding these studies. Generally, such studies can be waived if no components of the study product absorb in the ultraviolet spectrum. With transdermal patches, a Sponsor might support a request for waiver of photosafety studies, by adequately establishing that their product does not transmit ultraviolet light; however, it is noted that the Sponsor describes their product as "translucent" (Volume 3, p. 7). It is acknowledged that the intended site of application (buttocks), is not generally considered a sun-exposed area. However, scenarios could be envisaged that might result in exposure to sun-exposed skin. Given the irritancy of the product, it is possible that some subjects might remove the MTS unit over the course of the day. Alternatively, the patch could fall off. Both scenarios might allow for the potential mishandling of the patch e.g., exposure of product to a body site for which it is unintended (by misapplication), or to other children for whom it is unintended.

The absorption spectrum for the components of the Sponsor's product could not be located by the reviewer, and a response to an inquiry regarding this issue was pending from the assigned chemist at the time of this writing. It is suggested that the Sponsor

formally address the issues of photoirritation and photosensitization studies either by requesting a waiver (with scientific rationale) or by conducting the studies.

The pattern of irritancy evidenced in the dermal safety study N17-008, was borne out in the pivotal trials i.e., while the placebo patch was irritating, the methylphenidate-containing patch was significantly more so. No new skin-related safety concerns were revealed in the long-term study, N17-021.

It is suggested that the exclusion from the pivotal trials of subjects with pre-existing allergies and skin conditions be reflected in labeling.

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Brenda Carr  
3/12/03 12:28:05 PM  
MEDICAL OFFICER

Markham Luke  
3/12/03 05:28:28 PM  
MEDICAL OFFICER

Jonathan Wilkin  
3/16/03 04:10:32 PM  
MEDICAL OFFICER

**MEMORANDUM**

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

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**Date:** January 29, 2003

**To:** Russell Katz, MD, Director  
Division of Neuropharmacologic Drug Products, HFD-120

**Through:** Deborah B. Leiderman, MD, Director  
Michael Klein, PhD, Team Leader  
Controlled Substance Staff, HFD-009

**From:** Ann-Kathryn Maust, MD, Medical Officer  
Controlled Substance Staff, HFD-009

**Subject:** NDA 21-514 (methylphenidate transdermal system)  
Sponsor: Noven Pharmaceuticals, Inc.  
Submission Date: 6/27/02

This memorandum is a follow-up to discussions between our staffs regarding missing methylphenidate drug product from Study N17-021 for Patient #18/16 (NDA 21-514). According to information provided in the NDA, a substantial number of patches are unaccounted for. As methylphenidate is a Schedule II drug, reporting of incidents of loss or theft to the Drug Enforcement Administration is required.

Please advise the sponsor of the need to file these reports using DEA Standard Form 106. The sponsor also needs to report all incidents of loss or theft and all incidents of not returning used or unused patches as instructed by protocol to the FDA.

cc: NDA 21-514

A.H.-Weikel; R. Katz (HFD-120)

A.K.Maust; M.Klein; D.Leiderman;C.Moody; D.Alpern (HFD-009)

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/s/

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Ann-Kathryn Maust  
1/29/03 12:15:26 PM  
MEDICAL OFFICER

Michael Klein  
1/29/03 02:33:20 PM  
CHEMIST

Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20857

**CLINICAL INSPECTION SUMMARY**

DATE: January 13, 2003

TO: Anna Marie Homonnay-Weikel, R. Ph., Regulatory Project Manager  
Glenn Mannheim, M.D., Medical Officer  
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director  
Good Clinical Practice Branch I & II, HFD-46/47  
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-514

APPLICANT: Noven Pharmaceuticals, Inc.

DRUG: \_\_\_\_\_ (Methylphenidate Transdermal System)

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

CONSULTATION REQUEST DATE: August 14, 2002

ACTION GOAL DATE: April 27, 2003

**I. BACKGROUND:**

The \_\_\_\_\_ contains methylphenidate in an adhesive matrix and is designed to release continuous systemic delivery of methylphenidate, a central nervous system stimulant, during the application to the intact skin. In this application, the sponsor requests the use of \_\_\_\_\_ in Treatment of ADHD in pediatric population. A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and were present before 7 years of age. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental

disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have been present for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; excessive talking; blurting answers; cannot wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

The NDA application was based on the results from protocol N17-018 entitled: "A Multicenter, Double-blind, Placebo-controlled, Safety and Efficacy Study of Methylphenidate Transdermal System in Pediatric Patients with Attention Deficit Hyperactivity Disorder." The study was a multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of Methylphenidate Transdermal System in Pediatric subjects (age 6 to 12 years) with ADHD. The MethyPatch was applied once daily in the morning and was to remain in place for about 12 hours. Adjustment of wear time (approximately 8.5 to 9 hrs, but not less than 7 hrs) was permitted based on the individual needs of the patient. Treatment was initiated with either 12.5 or 18.75 cm<sup>2</sup> patch, depending on body weight or previous dose of methylphenidate. Subjects were titrated to the optimal dose at weekly intervals, depending on clinical response and tolerability. The maximum patch size was 50 cm<sup>2</sup>. Primary efficacy was normalization of behavior as assessed by the teacher scores on the Inattention/Overactivity (I/O) Factor of the IOWA-Conners Rating Scale obtained at the end of the school day on Friday of each week during the double-blind period.

Inspection assignment was issued on September 5, 2002 for 3 sites: Drs Helfing, Lopez and Wynn for protocol N17-018. These sites were the higher enrollers in the study.

## II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION
Dr. Helfing	Salem	OR	09-05-2002	01-07-2003	NAI
Dr. Lopez	Maitland	FL	09-05-2002	12-23-2002	VAI
Dr. Wynn	Milwaukee	WI	09-05-2002	11-13-2002	NAI

### HELFIG, M.D.

At this site, a total of 26 subjects was screened at this site; 4 subjects were screen failures; 22 subjects were randomized; 12 subjects completed the study; 10 subjects discontinued. Reasons for discontinuation included lack of efficacy (6 subjects from placebo group and 1 subject from active MTS group), 1 subject (#1609) from due to adverse event (severe constipation) and 2 subjects withdrew consent.

An audit of 19 records was performed. No major objectionable compliance issue noted. For all subjects, the parent/guardian informed consent and child assent forms were signed. Data appear

acceptable.

LOPEZ, M.D.

Thirty-three subjects were screened at this site; 1 subject was listed as a screen failure; 32 subjects were randomized. From the placebo group, 6 subjects discontinued from the study due to lack of efficacy and 2 subjects discontinued from the active MTS group for similar reason.

An audit of 11 records was performed. Inspection revealed that Dr. Lopez did not obtain the IRB approval for an increase in subject enrollment from 10-25 subjects allowed by the protocol to a total of 33 subjects until the study was completed. There were minor transcription errors for 3 subjects. For all subjects, the parent/guardian informed consent and child assent forms were signed. Data appear acceptable.

WYNN, M.D.

At this site, a total of 15 subjects was screened; 3 subjects were screen failures; 4 subjects from placebo group discontinued because of lack of efficacy; 1 subject (#22/13) from Methylphenidate Transdermal System discontinued due to adverse event (generalized pruritus).

An audit of 9 records was performed. No major objectionable conditions noted. All subjects signed the informed consent. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there was a delay in obtaining IRB approval prior to an increase in subject enrollment at Dr. Lopez's site. Overall, the data from these three sites inspected appear acceptable for use in support of this pending NDA.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

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Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

cc:

NDA 21-514

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/r/s

HFD-47/Khin

HFD-47/Friend

HFD-45/RF

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/s/

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Ni Aye Khin

1/14/03 09:21:47 AM

MEDICAL OFFICER

Original paper version was sent through Dr. A. El-Hage  
who initialed and concurred on 1/13/2003

# Memo

**To:** Russell Katz, MD  
Director, Division of Neuropharmacological Drug Products, HFD-120

**From:** Kevin Dermanoski, RPh  
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

**Through:** Denise Toyer, PharmD  
Team Leader, Division of Medication Errors and Technical Support, HFD-420  
Carol Holquist, RPh  
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

**CC:** Anna Marie Homonnay  
Project Manager, HFD-120

**Date:** October 16, 2002

**Re:** ODS 99-030-1; \_\_\_\_\_ (Methylphenidate Transdermal System); \_\_\_\_\_ mg/hr (10 mg),  
\_\_\_\_\_, mg/hr (15 mg), \_\_\_\_\_ mg/hr (20 mg), and \_\_\_\_\_ mg/hr (30 mg); NDA 21-514

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This memorandum is in response to the August 19, 2002 request from your Division for a re-review of the proprietary name, \_\_\_\_\_. DMETS has not identified any additional proprietary or established names that have the potential for confusion with \_\_\_\_\_, since our initial review, dated October 29, 1999 (ODS consult # 99-030). Therefore, we have no objections to the use of this proprietary name. Draft labels and labeling were provided for review. However, they do not include artwork and font sizes that will be used in the final printed labels and labeling. Therefore, it is not possible to fully assess the safety of the labels and labeling based upon these drafts.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its associated labels and labeling, must be re-reviewed. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established drug names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

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/s/

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Denise Toyer  
10/23/02 09:46:27 AM  
PHARMACIST

Carol Holquist  
10/23/02 01:06:51 PM  
PHARMACIST

Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form

**General Information About the Submission**

<b>NDA Number</b>	21-514	<b>Brand Name</b>	_____
<b>Related IND(s)</b>		<b>Generic Name</b>	Methylphenidate Transdermal System
<b>Related NDA(s)</b>		<b>Pharmacologic Class</b>	CNS Stimulant
<b>OCPB Division (I, II, III)</b>	I HFD-860	<b>Chemical Class</b>	
<b>Medical Division</b>	Neuropharmacology HFD-120	<b>Indication(s)</b>	ADHD
<b>OCPB Reviewer</b>	R. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.	<b>Dosage Form</b>	Adhesive Transdermal System (Patch)
<b>OCPB Team Leader</b>	Raman Baweja, B.S. Pharm., Ph.D.	<b>Strengths</b>	10 mg, 15 mg, 20 mg, 30 mg, _____mg to be delivered over 12 hours 27.5 mg / 12.5 cm <sup>2</sup> _____ mg/18.75 cm <sup>2</sup> 55.0 mg / 25 cm <sup>2</sup> 82.5 mg/ 37.5 cm <sup>2</sup> _____ mg/ _____cm <sup>2</sup>
<b>Dosing Regimen</b>	Applied to the hip once daily upon awakening for 11 – 12 hour		
<b>Date of Submission</b>	June 27, 2002	<b>Route of Administration</b>	Transdermal
<b>Estimated Due Date of OCPB Review</b>	March 1, 2003	<b>Sponsor</b>	Noven
<b>PDUFA Due Date</b>	April 27, 2003	<b>Priority Classification</b>	1S
<b>Division Due Date</b>	March 15, 2003		

**Clinical Pharmacology and Biopharmaceutics Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	X	2		
multiple dose:				
<b>Patients-</b>				
single dose:	X	1		
multiple dose:	X	1		