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PLEASE NOTE: For the purposes of this review (and to be consistent with the sponsor's terminology in the submitted NDA) the following abbreviations are used:

***d*-MPH** = the *d-threo* isomer of methylphenidate (a.k.a. dexmethylphenidate hydrochloride)
***d,l*-MPH** = the racemic mixture of methylphenidate

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Both the four week placebo controlled study and the two week placebo controlled withdrawal study provide evidence that *d*-MPH is an effective medication for treating ADHD in the pediatric population.

The risks of *d*-MPH use present a similar safety profile described in the labeling for *d,l*-MPH. Safety risks identified in the data for *d*-MPH include anorexia with subsequent weight loss (or failure to gain weight as developmentally appropriate), fluctuations in blood pressure and heart rate, abdominal pain, nausea, vomiting and headaches. Also noted in this NDA data base was one case of convulsions in addition to possible onsets of psychotic and other behavioral disturbances.

From a clinical perspective, it is recommended that *d*-MPH be approved for the treatment of ADHD based on both the efficacy and safety data submitted. The pharmacokinetics profile is similar to *d,l*-MPH, and the safety profile in the one comparator study also resembled *d,l*-MPH, which has a long history of being marketed. These findings provide further support to the safety and efficacy profile of *d*-MPH.

B. Recommendation on Phase 4 Studies and Risk Management Steps

It might be helpful for the sponsor to further characterize the issue of weight gain and whether or not administration of *d*-MPH before or after meals affects the issue of anorexia or weight loss. It would also be helpful to get a better picture of how the study drug affects weight changes compared to normal controls, or to assess weight changes in terms of change in percentile of growth curve.

Also of some curiosity is that the subgroup analysis of the adolescent enrolled in this study did not demonstrate a statistically significant difference when comparing either treatment group (*d*-MPH and *d,l*-MPH) with placebo. It is difficult to generalize these findings, as the study was not designed to detect efficacy specifically in this sub-group. Therefore, it might be helpful for the sponsor to conduct studies specifically in adolescents to better address efficacy in this age group.

If the sponsor is considering an indication primarily seen in the adult population, it is recommended that the sponsor better characterize the pharmacokinetic differences between male and female adults.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Dexmethylphenidate hydrochloride (*d*-MPH) is an oral stimulant proposed to treat Attention Deficit/Hyperactivity Disorder (ADHD). *D*-MPH is an isomer of *d,l*-MPH or methylphenidate (a.k.a. Ritalin ®) which is widely used as a first line treatment for ADHD. Data supporting the safety of this NDA was derived from six trials, five of which have been conducted in children. There were 699 "unique patients" exposed to one or more doses of *d*-MPH (including 15 adults and 684 children); the safety data

pool included the pediatric patients only. Open label studies extended exposure up to 6-12 months; 146 patients were exposed to *d*-MPH for at least a year. Only two of the pediatric studies contained a placebo-controlled portion and were considered pivotal studies (Studies 97-M-02 & 97-M-03).

B. Efficacy

Efficacy for the use of *d*-MPH for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) is supported by the two pivotal studies 97-M-02 & 97-M-03. Study 97-M-02 was a 4 week, placebo and comparator (*d,l*-MPH) controlled trial, while Study 97-M-03 included a two week, double-blind, randomized, placebo-controlled, withdrawal phase (Part B).

In Study 97-M-02, the primary efficacy variable was the change at the end of the study compared to baseline on the SNAP-ADHD scale scored by Teachers. There was a statistically significant difference in the primary efficacy variable when comparing the *d*-MPH group with placebo ($p=0.0042$ for OC and $p=0.0015$ for LOCF); the *d,l*-MPH group also showed a statistically significant difference from placebo ($p \leq 0.01$). It was noted in the statistical review by Dr. Koti that the baseline scores (indicating severity at the beginning of the study) may not have been well balanced for this study, because the baseline values of the SNAP-ADHD scoring for the *d*-MPH group compared to the *d,l*-MPH group showed a statistically significant difference; both the *d*-MPH and the *d,l*-MPH groups did not differ from placebo for the baseline scores. Fortunately, the primary efficacy variable was established to compare the *d*-MPH group with placebo, so the baseline imbalances do not cast doubt on the efficacy findings.

Study 97-M-03 included a 2 week placebo controlled, withdrawal phase that was preceded by a 6-week open-label titration phase in which patients were titrated to an efficacious dose of *d*-MPH in the first 4 weeks, and then maintained on that dose for the remaining 2 weeks. The primary efficacy variable was the percent of "Treatment Failures" determined at the last visit of Part B. A statistically significant difference was reported when comparing the *d*-MPH group and the placebo group with a p-value=0.0010. These findings indicate that patients with ADHD had better symptom reduction with the study drug compared to placebo.

In these two pivotal studies, the data support the conclusion that *d*-MPH is a more effective treatment than placebo for the treatment of ADHD. It appears that the treatment effect of *d*-MPH was comparable to a standard first line treatment of ADHD, namely *d,l*-MPH.

C. Safety

The safety data base for this NDA included 684 pediatric patients and 15 adult subjects. There were 426 patients reported to have taken *d*-MPH for at least 6 months (213 patient years), 146 patients exposed for 1 year and 280 patients exposed for $\geq$ 6 months but < 12 months. Although this exposure may be low for a new drug, the study drug's similarity in pharmacokinetics and adverse events profile to the parent drug, *d,l*-MPH, which has a long marketing history, provides some reassurance towards the safe use of *d*-MPH in the treatment of ADHD.

The adverse events profile of *d*-MPH resembles those described in the labeling for *d,l*-MPH. Adverse events that have been clearly defined for this NDA data base by Dr. Sunzel (biopharmaceutics review) include an increase in blood pressure (systolic and diastolic) and heart rate at the tmax (approximately 1 hour).

Also, Dr. Sunzel observed that with higher doses of the study drug, there was a decrease in food intake. This anorexic effect was also identified as a common adverse event for *d*-MPH in safety data base. In the placebo and comparator study, anorexia occurred in 6.3% of *d*-MPH patients compared to 10.9% of patients taking *d,l*-MPH, and 1.2% of placebo patients.

Common adverse events were determined by identifying events which occurred in at least 5% of the *d*-MPH group and at least twice as often in the placebo group. In the placebo controlled studies, the most common adverse events reported for the *d*-MPH safety data base were abdominal pain (15.2%), anorexia (6.3%), nausea (8.9%), vomiting (5.1%), rhinitis (10.1%) and fever (5.1%). Although the mean weight

change over a one year exposure for 54 patients was a gain of 4.3 pounds, the range spanned from a loss of 24 pounds to a gain of 26 pounds. These findings must be thought of in the context that weight gain is expected in this population as normal growth and development. However, it is difficult to interpret an average weight gain when there is much variation of the expected normal for each individual.

There were no discontinuations due to lab abnormalities or associated clinical symptoms. However, in the placebo controlled studies, elevated eosinophils, ALT, bilirubin, calcium, creatinine, and trace ketones (in urine) were observed with more frequency in the *d*-MPH group compared to placebo (see Table 18 below). In the entire NDA data base, there were also liver function study test elevations of clinical significance observed in five patients; however, there were no associated clinical symptoms.

Also of note in this NDA is one report of convulsions in a 9 y.o. female after 3 months of treatment with *d*-MPH. The parent drug, *d,l*-MPH is thought to lower the seizure threshold.

Weight loss and changes in hematological parameters have also been observed in pre-clinical studies. It has also been reported that there is an increase in hepatocellular adenoma in carcinogenicity studies at a dose which the sponsor claims to be 10 times greater than the recommended dose of *d*-MPH.

These safety findings give supporting reasons for blood pressure monitoring and periodic laboratory monitoring. It is also important that weight be monitored closely and assessments made if patients are experiencing anorexia or other gastrointestinal symptoms that may be interfering with the normal weight gain. It would also be prudent to have a warning regarding use in individuals with seizure disorder and the potential to exacerbate psychosis.

D. Dosing

The majority of patients in the NDA data base were administered doses in the range of 5-20 mg/day (dosed at 2.5 to 10 mg bid). The highest single dose administration was 20 mg (in an adult pharmacokinetic study), and the highest known daily dose was 25 mg/day. The proposed labeling recommends dosing of 5-20 mg daily in two divided daily doses. This dosing strength is comparable to half of the dosing strength for methylphenidate, and is supported by efficacy trials using methylphenidate as a comparator arm.

E. Special Populations

There were no notable differences in the pharmacokinetics between boys and girls. However, female adults were shown to have a higher AUC and Cmax than male adults in a single dose pharmacokinetic study, but tmax and $t_{½}$ did not differ amongst the males and females. There were no significant differences of the pharmacokinetic parameters identified between age groups tested, both pediatric and adult. There have been no studies conducted in patients with renal impairment or hepatic insufficiency.

No efficacy studies have been conducted in adults. Also, a subgroup analysis in the 4 week placebo controlled study suggested that *d*-MPH was not as effective in the adolescent age group; however, there were not enough patients in this subgroup to determine the validity of this finding.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

This substance is the *d-threo* isomer of methylphenidate hydrochloride (a.k.a. *d,l-* methylphenidate or Ritalin®). According to the sponsor, the USAN has assigned dexmethylphenidate hydrochloride as the official name. The indication is for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD). Efficacy has been established in patients aged 6-17 years old diagnosed with ADHD. The sponsor is proposing to manufacturer 5 and 10 mg tablets with recommended dosing of twice daily, starting at the initial dose of 5 mg/day (2.5 mg twice daily; approximately 4 hours apart) ranging to a maximum of 20 mg/day (10 mg bid).

B. State of Armamentarium for Indication

Psychostimulants have been used with increasing frequency in the treatment of Attention Deficit/Hyperactivity Disorders (ADHD) over the past thirty years. Various formulations have been marketed for the indication of ADHD using the following three basic compounds: methylphenidate (e.g. Ritalin, Ritalin SR, Metadate ER, Concerta), dextroamphetamine (e.g. Dexedrine, Adderall), and pemoline (Cylert). Pemoline is a Category IV controlled substance, while the methylphenidate and the dextroamphetamine derivatives are a Category II controlled substance.

The sponsor points to one study (Srinivas et al., 1992) in which *d*-MPH was shown to have comparable pharmacokinetics results to *d,l*-MPH. It has been proposed that the *d*-isomer of *d,l*-MPH is the active isomer, while the *l*-enantiomer has minimal pharmacodynamic activity.

C. Important Milestones in Product Development

The sponsor first submitted the related [redacted] on December 16, 1996. An End-of-Phase II meeting was held on January 14, 1998 to discuss the CMC plan and requirements for stability data and in vitro testing (in lieu of bioequivalence testing). A separate End-of-Phase II meeting was also held January 14, 1998 which addressed alternatives for the sponsor to fulfill the preclinical requirements needed before expanding the exposure to patients during the IND phase of this study; it was agreed that the sponsor would exclude females of child bearing potential until the required segment II reproduction studies were completed. It was also agreed that the sponsor needed to submit two pivotal studies, preferably with a *d,l*-MPH comparator arm and a withdrawal phase. A pre-NDA meeting was held on January 6, 2000, and it was agreed that, because this drug was an isomer of *d,l*-MPH which has a long marketed history, and if also the pharmacokinetics were sufficiently similar to *d,l*-MPH, that it may not be necessary to fulfill the ICH requirement of exposure of a new molecular entity. A telecon was held with FDA and the sponsor on July 11, 2000 to address CMC issues including stability and compliance concerns regarding their supplier. Compliance inspections through out the review process have raised concerns regarding the manufacturer and future supplier for this NDA. As of the time of this report, compliance recommended a "withhold" because one site had not completed the required pilot scale batch manufacturing.

D. Other Relevant Information

The sponsor states that all clinical studies for this IND were done under Celgene's sponsorship and are included in the current NDA submission. It is noted that there are currently two individual INDs [redacted] associated with Celgene's IND [redacted] There is also another commercial sponsor investigating the safety and efficacy of *d*-MPH [redacted]

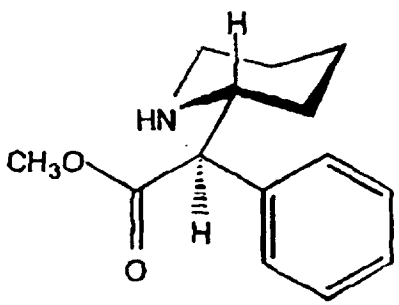
E. Important Issues with Pharmacologically Related Agents

The pharmacokinetic profile of *d*-MPH is very similar to the parent compound *d,l*-MPH. This may suggest that the safety profile developed for *d,l*-MPH over the past 40 years would be similar. It has been well documented that patients suffering from the following conditions should not be administered *d,l*-MPH: agitation, glaucoma, tic, and concomitant use of a monoamine oxidase inhibitors (MAOI). Also of concern with long term use is the associated weight loss (or lack of developmentally appropriate weight gain). These same restrictions should also be described in related products such as *d*-MPH.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The chemical structure for the *d-threo*-enantiomer (*d*-MPH) is:



This substance is the *d-threo* isomer of methylphenidate hydrochloride (a.k.a. *d,l* methylphenidate or Ritalin®). According to the sponsor, the USAN assigned dexmethylphenidate hydrochloride as the official name. The trivial name is *d-threo*-methylphenidate hydrochloride. The sponsor proposes to manufacturer tablets in the strength of 2.5 mg, 5 mg, and 10 mg tablets.

As of the date of this report, one manufacturing site had not completed the required inspection and pilot scale batch manufactoring. The Office of Compliance has recommended a "withhold" status for the NDA until these issues are cleared up.

B. Animal Pharmacology and Toxicology

Methylphenidate (or *d,l*-MPH) is a CNS stimulant thought to have properties of increasing the levels of dopamine by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron. Previous research suggested that the *d*-isomer of *d,l*-MPH was the pharmacologically active agent (Maxwell et al. 1970;Eckerman et al. 1991; and Patrick et al 1987b). In rats, the tmax of *d*-MPH was 30 minutes, which is the same amount of time it takes for the isomer *d*-MPH to reach tmax when *d,l*-MPH is administered (at doses of 1 or 25 mg/kg *d*-MPH or 50 mg/kg *d,l*-MPH). In rats, rabbits, and dogs, the AUC of *d*-MPH was shown to be comparable when doses of *d*-MPH and *d,l*-MPH are equimolar.

In rats, rabbits, and dogs, the plasma half-life of *d*-MPH was between 1-2 hours for both *d*- and *d,l*-MPH. The metabolite, *d*-RA (ritalinic acid) was shown to be longer than for the parent compound with half-lives ranging from 1-3 hours in rats and 4-8 hours in rabbits.

In rat studies, the maximum tolerated dose (MTD) in rats for *d*-MPH was estimated to be 100 mg/kg/day with limiting symptoms of hyperactivity, hypersensitivity, and self mutilation. In dogs, the MTD was estimated to be 10 mg/kg/day with limiting symptoms of hyperactivity, salivation, and increased body temperature.

The NOEL for *d*-MPH was < 20 mg/kg/day in rats and 1/mg/kg/day in dogs, and for *d,l*-MPH was < 40 mg/kg/day in rats and 2 mg/kg/day in dogs. Hematological parameters (including decrease in platelet count, increase in partial thrombin time in males, and increase in eosinophils in females) were observed within 14 days of dosing in rats, but not after 90 days for both *d*-MPH and *d,l*-MPH.

Weight loss was a consistent finding in repeat dosing in dogs.

Reproductive toxicity studies of *d*-MPH show that there is a decrease in maternal body weight, altered food consumption, and increase in duration of gestation. There was no report of developmental effects at maternal doses of up to 20 mg/kg/day of *d*-MPH.

Previously reported as part of the National Toxicology Program (NTP), carcinogenicity studies have shown that *d,l*-MPH demonstrated an increase in hepatocellular adenoma, and in males, an increase in hepatoblastoma. In pharmacokinetic bridging studies, the sponsor proposes that the exposure levels of *d*-MPH with the potential cause this toxicity exceeds the recommended dose by 10 times.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

For complete details, please refer to the Clinical Pharmacology and Biopharmaceutics review.

D-MPH has been shown to be readily absorbed, reaching a maximum concentration within 1 to 1½ hours. The sponsor did not find significant differences in the pharmacokinetics after single or multiple doses. The following sponsor table summarizes the pharmacokinetic properties after a single 10 mg dose and 10 mg twice daily dosing for 7 days:

Table 1 Pharmacokinetic properties as presented in sponsor's proposed label

	Single 10-mg Dose	**10 mg b.i.d. × 7 days**
C_{max} (ng/mL)	21.4 ± 6.5	25.1 ± 10.1
T_{max} (h)	1.1 ± 0.4	1.2 ± 0.4
AUC (ng•h/mL)	82.4 ± 20.6	90.4 ± 24.2
$t_{½}$ (h)	2.3 ± 0.4	2.2 ± 0.4

In adults, food reduced the rate of availability of *d*-MPH increasing the tmax to 2.9 hours compared to 1.5 hours in the fasting state. There was no statistically significant effect of food on *d*-MPH Cmax or AUC. Protein binding has not been assessed for *d*-MPH, but the sponsor points out that *d,l*-methylphenidate is minimally protein bound (<20%). The primary metabolic process of *d*-MPH is by de-esterification to the metabolite *d*-ritalinic acid (a.k.a. *d*-α-phenyl-piperidine acetic acid). This metabolite is thought to be inert. There is very little evidence suggesting that there is interconversion to the *l-threo* enantiomer.

Also of significance is that the pharmacokinetic profile of *d*-MPH appears to be very similar to *d,l*-MPH. It is also noted that the pharmacokinetics do not differ appreciably between girls and boys. However, female adults were shown to have a higher AUC and Cmax than male adults in a single dose pharmacokinetic study, but tmax and $t_{½}$ did not differ amongst the males and females. There did not appear to be significant differences when comparing the pharmacokinetic properties in the fasting and fed states.

B. Pharmacodynamics

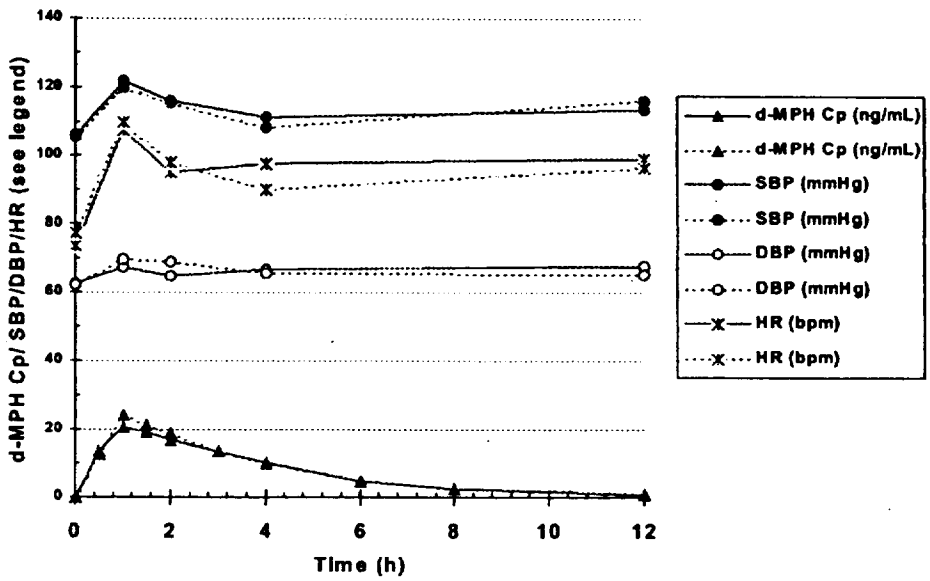
For complete details, please refer to the Clinical Pharmacology and Biopharmaceutics review by Maria Sunzel, Ph.D.

In Study 97-M-01, Dr. Sunzel, FDA biopharmaceutics reviewer, observed that there was a dose-related anorectic effect. Patients taking higher doses (10 or 20 mg) were observed to have up to a 50% reduction of food intake at lunch when compared to placebo. Both *d*-MPH and *d,l*-MPH demonstrated this anorectic effect. These findings suggest that appetite suppression is directly correlated with increasing dose.

D-MPH was observed to have increases in systolic blood pressure (up to 20 mmHg) and heart rate (up to 30 bpm) within four hours of administration, with the peak at tmax. In the follow graph, Dr. Sunzel demonstrated the increases of vital signs in terms of plasma concentration and time:

Figure 1

Vital Signs (n=12) and plasma concentration (n=9) vs. time in children/adolescents. Solid line is after single dose of 10 mg *d*-MPH, and dashed line on day 8 of 10 mg *d*-MPH. Curves show mean values of SBP,HR, DBP and plasma concentration from top to bottom of graph. (Extracted from Dr. Sunzel's review)



IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data in this review are the clinical trials submitted by the sponsor. Also of relevance is the vast literature and experience generated from methylphenidate which has had a marketed history of over 40 years.

B. Tables Listing the Clinical Trials

The following is a table summarizing the studies included in this submission for *d*-MPH:

Table 2 Table of All Studies in NDA 21-278

Study No.	Description	Drug(s) Tested/Regimen	Number of Subjects	Treatment Duration
Clinical Pharmacology Studies				
97-M-01	Single dose, double-blind, placebo and active controlled, crossover study of pk in **children**	Single doses of: *d*-MPH: 2.5, 5, & 10 mg *d,l*-MPH (5,10 & 20 mg)	N=32	Single doses
PK-99-001	Single and multiple dose pk study in **children**	*d*-MPH: 10 mg bid	N=12	6 ½ days
PK-00-001	Single dose, crossover, food effects in **adults**	*d*-MPH: 2-single doses of 20 mg (fasting & fed)	N=15	Single doses
Placebo Controlled Studies				
97-M-02	Double-blind, pbo-controlled, 4 week study with 1 week pbo lead in	*d*-MPH: 5-20 mg/day *d,l*-MPH: 10-40 mg/day	Total: n= 132 *d*-MPH: n=44 *d,l*-MPH: n=46 placebo: n=42	4 weeks with 1 wk pbo lead in
97-M-03	A: Open label B: Withdrawal phase: 2 week placebo controlled C: Open label	A: 5-20 mg/day (titrated to effective dose) B:*d*-MPH 2.5-10 mg bid	N=89	A: 6 weeks:open label B: 2 weeks: withdrawal C: 44 weeks: open label
Open Label Studies				
97-M-04	Open-label, 1 year in **children** with ADHD		N=187	1 year
97-M-05	Open-label, 6 month safety study in **children** with ADHD		N=361	6 month

Please see Appendix A for a full listing of all investigators conducting trials for this NDA.

C. Postmarketing Experience

As of the May 17, 2001 (the safety update), *d*-MPH is not marketed anywhere in the world.

D. Literature Review

The sponsor reviewed and included six publications that discussed *d*-MPH. There was no unexpected information in these articles. A MedLine search did not yield any other relevant articles.

V. Clinical Review Methods

A. How the Review was Conducted

For efficacy, there were only two studies (Study 97-M-02 & Study 97-M-03) with a placebo-controlled portion, and both these studies were reviewed separately for efficacy. Study 97-M-02 offered a 4 week placebo controlled portion assessing change from baseline to the end of the study using the teacher's scoring of the SNAP-ADHD Rating Scale. Study 97-M-03 assessed therapeutic failures in a two week placebo controlled withdrawal trial.

The safety data pooled together all of the studies in the pediatric population with the exception of the clinical pharmacology study PK-99-001, which was reviewed seperately by the clinical pharmacology reviewer. The one adult study PK-00-001 was also evaluated seperately by the clinical pharmacology reviewer. This review includes data from the updated ISS in the safety update of May 17, 2001.

Individual case report forms were reviewed for the following patients: 02/01-02, 02/03-04, 02/04-01, 02/09-06, 02/02-01, 02/02-05, 02/03-11, 02/03-12, 02/07-10, 02/10-07, 02/11-01, 02/01-12, 02/04-14, 03/13-03, 03/32-11, 04/19-01, 04/19-02, 4/29-04, and 04/22-04.

B. Overview of Materials Consulted in Review

The materials used in this review included the following:

Original NDA Submission: October 25, 2000
Safety Update: May 17, 2001
Consultation from Division of Scientific Investigations: June 5, 2001
Consultation from Division of Controlled Substance Staff: June 15, 2001
Statistical Review by Kallapa Koti, Ph.D. (6/25/01)
Office of Clinical Pharmacology and Biopharmaceutics Review by Maria Sunzel, Ph.D. (draft)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Overall, the Division of Scientific Investigations recommended that the sponsor's data was acceptable based on an on-site investigation. However, according to a correspondence dated June 5, 2001, the sponsor was warned not to repeat practices that did not adhere to pertinent federal regulations (e.g. failure to adhere to protocol, inadequate records, and failure to obtain IRB approval of advertisement prior to use).

D. Evaluation of Financial Disclosure

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Vice President of Regulatory Affairs & Project Management at Celgene signed the Form 3454 testifying that, to his knowledge, there was no financial arrangement made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). No disclosures could be collected from three individual investigators/subinvestigators, all of whom the sponsor certifies that they have not entered into any financial arrangement as described in 21 CFR 54.2.

VI. Integrated Review of Efficacy

A. Conclusions and Critical Differences from Sponsor's Proposed Label Claims

The review of the data supports the sponsor's claim that *d*-MPH demonstrated effectiveness in the treatment of ADHD in children aged 6-17 years old in the two pivotal studies when considering the primary efficacy variable, the change from baseline of the teacher SNAP-ADHD score.

What must be kept in mind when evaluating the appropriateness of the sponsor to make comparative claims to *d,l*-MPH is the imbalance of the baseline scores of the comparator *d,l*-MPH with the *d*-MPH in Study 97-M-02. As can be seen in Table 3 below, the baseline scores of the *d*-MPH compared to the *d,l*-MPH group in Study 97-M-02 showed a statistically significant difference suggesting that there was greater pathology at baseline in the *d,l*-MPH group. The mean final scores of the *d,l*-MPH group were higher (more pathology) than the *d*-MPH group, although a statistically significant improvement compared to placebo was established for both groups. Because of the appearance of imbalance in levels of pathology at baseline, it is questionable if the sponsor may accurately make any statements of comparison of *d*-MPH with *d,l*-MPH using this study as supporting evidence.

Table 3 Teacher SNAP-ADHD Scores from Study 97-M-02

	d-MPH	*d,l*-MPH	placebo
Baseline	1.41±0.73	1.78 ±0.72	1.614±0.68
Final	0.77±0.66	1.11±0.89	1.46 ±0.77

Data extracted from Statistical Review by Dr. Koti

Because of this discrepancy, it is questionable if the sponsor should be allowed to include findings from the *d,l*-MPH group as they have in figure 1 of the original labeling proposal.

In the sponsor's revised draft labeling (submitted 7/6/01), the sponsor claims that Study 97-M-02 provides evidence that "the duration of activity was statistically significantly longer in children treated with [redacted] than in children treated with *d,l*-threo-Methylphenidate HCl." This statement is misleading for several reasons. According to the protocol, the assessments that parents made were at the time periods of 3PM (a composite of the day) and 6PM (a composite of the afternoon) on weekends only. This method of recording does not lend itself to interpretations of improvement with time, as these were recorded during the week end days only and were not done on an hourly basis to allow for direct comparison. Duration of activity was not a specified efficacy variable, nor was the study designed appropriately to reflect such a finding.

The sponsor also adds in the last paragraph of the **CLINICAL STUDIES** section: "This was confirmed by an objective math test." It could be inferred that "it" is referring to the duration of activity. Again, not only was the math testing a secondary efficacy variable, but also, the study was not designed to be assessing changes over each hour to reflect a accurate reading of duration of activity.

Also, in the sponsor's revised draft labeling (submitted 7/6/01), there is a figure which reflects only the final scores of the instrument used in the primary efficacy variable, the teacher SNAP-ADHD scores. The actual primary efficacy variable was the change from baseline to end score. If the sponsor is interested in showing the final scores, it would be more reflective of the data if the baseline scores were also shown.

B. General Approach to Review of the Efficacy of the Drug

Of the six studies conducted by Celgene, only Studies 97-M-02 & 97-M-03 contained a placebo controlled portion that provided data interpretable for efficacy findings. Study 97-M-02 was a 4 week placebo controlled portion allowing for a comparison of change from baseline to the end of the study using a scale of severity of illness (the **Teacher's** scoring of the SNAP-ADHD Rating Scale). Meanwhile, Study 97-M-03 assessed therapeutic failures in a two-week placebo controlled withdrawal trial using the CGI-I to determine treatment failure.

This review will refer to the statistical review of Kallapa Koti, Ph.D., FDA statistician.

C. Detailed Review of Trials

1. Study 97-M-02

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the safety and efficacy of *d*-MPH in treating pediatric patients diagnosed with ADHD.

Population

Patients chosen for this study were aged 6-17 and diagnosed with ADHD according the DSM-IV criteria. The sponsor included all three ADHD subtypes in this study (i.e. predominantly inattentive, predominantly hyperactive/impulsive, or combined). Patients were allowed to have the following co-morbid diagnoses: oppositional-defiant disorder, conduct disorder, learning disorder, elimination disorders, adjustment disorder, sleep disorders not requiring medication, communication disorder including speech/language delays, impulse control disorders not requiring medication, symptoms of anxiety not requiring medication, and symptoms of depression not requiring medication. Excluded from the study were females who have undergone menses.

Design

This was a 12 site, randomized, double blind, four-week, placebo and comparator (*d,l*-MPH) controlled trial, preceded by a one week single-blind placebo lead in. Patients were randomized to one of the following treatment groups: 1) *d*-MPH in dose ranges of 2.5 mg bid to 10 mg bid, 2) *d,l*-MPH in dose ranges of 5 mg bid to 20 mg bid, and 3) placebo. Assessment for dose titration was to be done weekly and was based on therapeutic response; if a therapeutic response was not observed, then the dose was doubled weekly until a therapeutic response was observed. Dosing was to be at 7-8AM and at 11:30AM – 12:30PM. Forbidden concomitant medications included antidepressants, neuroleptics/antipsychotics, mood stabilizers, anticonvulsants, beta-blockers, alpha-2-agonists, other CNS stimulants, thyroid medications, chronic oral steroids, and sedatives/hypnotics.

Screening included a history and physical, routine labs, and urinalysis. Vital signs were monitored weekly throughout the study, and a physical, labs and urinalysis were repeated at the end of the study. Please see Appendix C for the Sponsor's schedule of events.

Analysis Plan

The primary efficacy variable is the change from baseline to last visit in the **Teacher's** scoring of the SNAP-ADHD Rating Scale (see Appendix B for a copy of the SNAP). Teachers were instructed to complete the SNAP-ADHD Rating Scale twice weekly during the school week; the two scores would be averaged to establish the scoring for that week of treatment. Other secondary measure of efficacy included changes from baseline in: 1) both the 3PM and the 6 PM Parent SNAP-ADHD ratings (parents were instructed to complete the SNAP-ADHD twice on Saturday and twice on Sunday at 3 PM, or 2 hours post dosing, and at 6 PM), 2) the CGI-I, 3) the percent of Therapeutic Responders defined as obtaining a score of either 1 (very much improved) or 2 (Much improved) on the CGI-I at last visit compared to baseline, and 4) Math test scores.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 174 patients screened, 132 patients were randomized into the double-blind treatment. Reasons for ineligibility included parental/guardian refusal, concurrent psychiatric disorder, failure to meet criteria for ADHD, and body weight not within 30% of age normal; one patient was discontinued at the end of the placebo lead in. Of the 132 patients in the intent-to-treat population, 13 (10%) discontinued and 119 (90%) completed the study. Reasons for early withdrawal included: protocol violation (2 of 44 *d*-MPH patients, 1 of 46 dl-MPH, and 2 of 42 placebo patients), adverse events (2 of 46 dl-MPH patients and 2 of 42 placebo patients), therapeutic failure (2 of 42 placebo patients), and lost to follow up (3 of 46 dl-MPH patients). A total of 119 (*d*-MPH: 42; dl-MPH: 40; placebo: 37) patients completed the study.

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 116 boys (87.9%) and 16 girls (12.1%). The population consisted of 103 (78%) Caucasians, 18 (13.6%) African-American, 4 (3.0%) Hispanic, 1 (0.8%) Asian, and 6 "other" (including multiracial or American Indian). The sponsor did not find a statistically significant difference in demographics between treatment groups at baseline.

There was no statistical difference in the subtypes of ADHD (Inattentive, Hyperactive/Impulsive/ and Combined) between the treatment groups; although, the *d*-MPH group did have a higher percentage of inattentive subtype.

The following table, prepared by Dr. Koti, FDA statistician , presents the baseline scores of each group:

Table 4 Baseline SNAP scores from Study 97-M-02 (extracted from Dr. Koti's review)

	d-MPH	*d,l*-MPH	Placebo
N	42	41	41
Mean ± SD	1.4± 0.7	1.8± 0.7	1.6± 0.7
Range			

Dr. Koti determined that the baseline values of the *d*-MPH and *d,l*-MPH groups were not comparable and had a statistically significant difference. These findings may suggest that there was a greater severity of illness in the *d,l*-MPH group at baseline. It is also noted that the patients in the *d,l*-MPH group had a severity of illness (as measured by the CGI-S) that was statistically higher than the placebo group at baseline; the sponsor reasoned that the *d,l*-MPH group was not the primary treatment group comparison being made, so they did not adjust the analysis based on this finding. Neither the *d*-MPH nor the *d,l*-MPH groups showed a statistically significant difference at baseline compared to placebo.

Looking at a subgroup analysis of the adolescent age group only (aged 12-19), Dr. Koti observed that there was no statistical difference when comparing the score of the 39 (of 119) adolescents amongst the three treatment groups (including no difference between the study drug and placebo as well as no difference between the *d,l*-MPH group compared to placebo). However, represents too small a sample to make any conclusions regarding efficacy in this age group.

Dosing was based on individual titration to a dose that the principle investigator determined to be a therapeutic response. The majority of patients had a dose escalation at least once during the study. The sponsor notes protocol violations of dose increases despite a therapeutic response in 19 patients (10 patients in *d*-MPH group; 8 in dl-MPH group; 1 in placebo group). The following table summarizes the dosing patterns of participants in the study:

Table 5 Doses Administered in Study 97-M-02

	D-MPH (BID)			*DL*-MPH (BID)			PLACEBO
	2.5 mg	5 mg	10 mg	5 mg	10 mg	20 mg	
Week 1 N=132	44 (100%)	0	0	46 (100%)	0	0	42
Week 2 N=129	4 (9.3)	39 (90.7)	0	8 (17.8)	37 (82.2)	0	41
Week 3 N=125	2 (4.9)	9 (22.0)	30 (73.2)	6 (14.0)	10 (23.3)	27 (62.8)	41
Week 4 N=119	2 (5.0)	4 (10.0)	34 (85.0)	7 (16.7)	6 (14.3)	29 (69.0)	37

Concomitant Medications

Concomitant medications included acetaminophen (18 patients or 13.6%), ibuprofen (12 patients or 9.1%), aspirin (9 patients or 6.8%), loratidine (7 patients or 5.3%), and diphenhydramine (3 patients or 2.3%). Of note was one patient who took a single dose of Adderall prior to the final visit (Patient 01-10 randomized to *d*-MPH) and who was included in the study analysis. There was no notable difference between treatment groups in terms of concomitant medications.

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference ($p<0.0001$ for LOCF, and $p=0.0004$ for OC) when comparing mean change from baseline to Week 4 on the Teacher SNAP-ADHD in the *d*-MPH and the placebo groups. The sponsor reports a statistically significant difference when comparing the primary efficacy variable for *d,l*-MPH with the placebo group ($p=0.0042$ for OC and $p=0.0015$ for the LOCF). In his efficacy review, Dr. Koti calculated that in observed cases data, there was a statistically significant difference comparing the *d*-MPH group and placebo with a p-

value< 0.010. Dr. Koti also concluded that the *d*-MPH groups and the *d,l*-MPH group's change from baseline did not differ statistically. The following table from Dr. Koti's review, summarizes the efficacy findings:

Table 6 Teacher SNAP-ADHD scores for study 97-M-02 (from Dr. Koti's review)

	Study 97-M-02 (Double-blind)		
	d-MPH	*d,l*-MPH	**Placebo**
Baseline (Visit 3)			
N	42	41	41
Mean ± SD	1.4± 0.7	1.8± 0.7	1.6± 0.7
Range	[redacted]		
Final Visit [1]			
N	39	37	36
Mean ± SD	0.8 ±0.7	0.9± 0.8	1.4± 0.8
Range	[redacted]		

For a secondary efficacy variable, the sponsor examined the percent of therapeutic responders [therapeutic responders defined as a score of either 1 (very much improved) or 2 (Much improved) on the CGI-I at last visit compared to baseline]. After doing an analysis of the percent of therapeutic response, Dr. Koti concluded that there was a statistically significant difference in the percent of therapeutic responders comparing the treatment groups to placebo:

Table 7 Secondary efficacy measure – Percent of Therapeutic Response for Study 97-M-02 (Table from Dr. Koti's review)

Treatment	No Response	Response	Total
Placebo	34	8	42
d-MPH, 2.5-10mg bid	15	29	44
dl-MPH, 5-20mg bid	25	21	46
Total	74	58	132

Conclusions

The results of Study 97-M-02, a pivotal study, provides evidence that *d*-MPH is effective in the treatment of children diagnosed with ADHD. It is unclear from this study if efficacy has been shown to be effective in the age group of 12-19 years old.

2. Study 97-M-03

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the safety and efficacy of *d*-MPH in treating pediatric patients diagnosed with ADHD.

Population

The population description is the same as for Study 97-M-02 (see above).

Design

The design of this study includes 3 parts: 1) Part A is a 6-week open-label titration phase in which patients will be titrated to an efficacious dose of *d*-MPH in the first 4 weeks, and then maintained on that dose for the remaining 2 weeks, followed by, 2) Part B, a two week, double-blind, randomized, placebo-controlled, withdrawal phase, and then, 3) Part C, an open label treatment phase of 18 weeks in which all patients received *d*-MPH. The study was conducted at 7 sites.

During Part A, patients were to be titrated from 2.5 mg *d*-MPH bid to 10 mg bid unless they were previously treated with *d,l*-MPH. If previously treated with *d,l*-MPH, patients started on half the dose of the racemic mixture (e.g. 5 mg *d*-MPH for those treated with 10 mg *dl*-MPH). Titration upward depended on a weekly assessment of therapeutic response. A therapeutic response is defined by a score of either 1 (very much improved) or 2 (much improved) on the investigator's CGI-I and the study medication is well tolerated.

During Part B, patients were randomized (and double blind) to either the *d*-MPH group (at the same dose taken at the end of Part A) or the placebo group.

During Part C, the 18 week open label extension phase, patients were given the same dose they received in the final week of Part A.

Screening for the study included a history and physical, routine labs, urinalysis. Vitals were monitored weekly, and a physical, routine labs, urinalysis were repeated at the end of Weeks 18 and 27.

Analysis Plan

The primary efficacy variable is the percent of Treatment Failures determined at the last visit of the withdrawal phase of Part B. A Treatment Failure is defined as a score of either 7 (Very much worse) or 6 (much worse) on the CGI-I during the withdrawal phase. Secondary efficacy variables include the change from beginning to final visit of Part B (the withdrawal phase) in the CGI-I score, the Teacher SNAP-ADHD scores, the 3 PM Parent SNAP ADHD scores, the 6 PM parent SNAP ADHD scores, and the average Math Test scores.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the117 patients screened, 89 patients were enrolled into Part A (6 weeks open label treatment of *d*-MPH), and 76 (85.4%) completed Part A. Reasons for withdrawal included adverse events, treatment failure, lost to follow-up, consent withdrawn, and protocol violation.

There were 75 patients continued onto Part B (2 week placebo controlled withdrawal phase). The one patient who did not continue on experienced adverse events (headaches, insomnia, and rash). Of the 75 patients, 35 were randomized to the *d*-MPH group and 40 to the placebo group; each group had one withdrawal with a completion rate of 97.1% (n=34) for the *d*-MPH group, and 97.5% (n=39) for the placebo group.

Of the 75 patients entered into Part C, 53 (70.7%) completed the study. Reasons for withdrawal for the 22 (29.3%) patients included therapeutic failure (7 patients), protocol violations (6 patients), noncompliance (5 patients), and refusal of blood draws (1 patient).

Demographics /Group Comparability

The majority of the patients in Part B of this study were Caucasian males comprised of 72 boys (80.9%) and 17 girls (19.1%). The population consisted of 68 (76.4%) Caucasians, 13(14.6%) African-American,

and 8 (9.0%) Hispanic. It is unclear if the sponsor conducted an analysis of the between treatment groups for demographics. Both treatment groups in Part B appeared to have comparable demographics.

The majority of patients were started on the dose of 2.5 mg bid *d*-MPH (77 or 86.5 %), and the majority were taking 10 mg bid *d*-MPH at the end of the titration phase, Part A (55 or 73.3%). The following sponsor table summarizes the dosing during this study:

Table 8
Summary of Doses Study Medication Dispensed by Visit (sponsor table from Study Report; table 19)

Dose Dispensed by Visit	N	*d*-MPH dose taken b.i.d.		
		2.5 mg	5 mg	10 mg
Open-label Titration (Part A)				
Baseline (Visit 2)	89	77 (86.5%)	10 (11.2%)	2 (2.2%)
Week 1 (Visit 3)	87	3 (3.4%)	73 (83.9%)	11 (12.6%)
Week 2 (Visit 4)	84	3 (3.6%)	22 (26.2%)	59 (70.2%)
Week 3 (Visit 5)	77	2 (2.6%)	14 (18.2%)	61 (79.2%)
Week 4 (Visit 6)	77	1 (1.3%)	17 (22.1%)	59 (76.6%)
Week 5 (Visit 7)	75	1 (1.3%)	19 (25.3%)	55 (73.3%)
Double-blind Withdrawal (Part B)				
Baseline (Visit 8)	34 *d*-MPH	0	10 (29.4%)	24 (70.6%)
	40 placebo	1 (2.5%)	7 (17.5%)	32 (80.0%)
Week 1 (Visit 9)	35 *d*-MPH	0	11 (31.4%)	24 (68.6%)
	39 placebo	1 (2.6%)	7 (17.9%)	31 (79.5%)
Open-label Continuation (Part C)				
Week 8[2] (Visit 10)	75	1 (1.3%)	19 (25.3%)	55 (73.3%)
Week 9[2] (Visit 11)	75	1 (1.3%)	15 (20%)	59 (78.7%)
Week 11[2] (Visit 12)	66	1 (1.5%)	11 (16.7%)	54 (81.8%)
Week 26[2] (Visit 13)	63	2 (3.2%)	11 (17.5%)	50 (79.4%)
Week 38[2] (Visit 14)	54	3 (5.6%)	8 (14.8%)	43 (79.6%)

Concomitant Medications

Concomitant medications during Part B included sympathomimetic medications (n=3 for *d*-MPH and n=3 for placebo) and verapamil (one patient being treated for hypertension).

Efficacy Results

For the purposes of establishing efficacy, only Part B was placebo controlled, and, therefore, is interpretable. Therefore, the discussion will be limited to the analysis of Part B. For the primary efficacy variable of treatment failure for Part B, the sponsor reported a statistically significant difference observed between the *d*-MPH group and the placebo group (p=0.0010 with the Mantel-Haenszel test with and without stratification). Treatment failure are defined as a CGI-I score of either "much worse" or "very worse, and 6 of 35 patients in the *d*-MPH group and 24 of 39 (61.5%) randomized to placebo were considered treatment failures. For Part B, statistical significance is also observed in the change from baseline in the mean Teacher SNAP-ADHD (p=0.028), in the average 3 PM Parent SNAP-ADHD scores (p=0.0026), the 6 PM Parent SNAP-ADHD scores (p=0.0381), and the Math Test Score (p=0.024).

In his re-analysis of the percent of treatment failures, Dr. Koti reported that there was a statistically significant difference seen in the proportions of treatment failures when comparing placebo and *d*-MPH, confirming a p-value =0.001. The following table, extracted from Dr. Koti's review summarizes the percent of treatment failure:

Table 9
Primary efficacy measure- Percent of Treatment Failure (LOCF)
Study 97-M-03 (extracted from Dr. Koti's review)

Treatment	Not Failure (%)	Failure (%)	Total
Placebo	15 (37.5)	25 (62.5)	40
d-MPH	29 (82.9)	6 (17.1)	35
Total	44	31	75

Dr. Koti confirmed that there was a statistical significance demonstrated comparing the change of the scoring of the Teacher SNAP-ADHD from the beginning of Part B to the end of Part B. Although this was a secondary efficacy variable, a p-value=0.0007 demonstrates a statistically significant difference comparing the study drug to placebo.

Conclusions

The results from study 97-M-03 support the claim that *d*-MPH is effective in the treatment of ADHD.

D. Efficacy Conclusions

Both studies 97-M-02 and 97-M-03 support claims that *d*-MPH is effective in the treatment of ADHD.

VII. Integrated Review of Safety

A. Description of Patient Exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)

In this NDA data base, 699 "unique patients" were exposed to one or more doses of *d*-MPH. This includes 15 adults and a total of 684 pediatric patients. Only data from the pediatric population was considered in the integrated safety database that was accumulated from the six studies in the pediatric population. The sponsor points out that some tables may present a total of 689, because five patients were counted twice. In the two double blind placebo controlled studies (97-M-02 & 97-M-03), there were 79 unique patients exposed to *d*-MPH.

As can be seen from the sponsor's table below, the mean age for patients exposed to *d*-MPH in this safety data base was 9.7 ± 2.5 years within the range of 5 to 17 years. The majority of patients were male and Caucasian. Studies were conducted in the U.S.

Table 10
Overview of Demographics: All Subjects (from sponsor's ISS)

Characteristics	Overall *d*-MPH (N = 689)	Clinical Pharmacology (N = 44)	Placebo Controlled Studies		
			d-MPH (N = 79)	*d,l*-MPH (N = 46)	Placebo (N = 82)
Age					
Mean (SD)	9.7 (2.5)	-	-	-	-
Range	5 – 17	7 – 16	6 – 16	6 – 17	6 – 16
Gender					
Male	569 (82.6%)	40 (90.9%)	71 (89.9%)	40 (87.0%)	66 (80.5%)
Female	120 (17.4%)	4 (9.1%)	8 (10.1%)	6 (13.0%)	16 (19.5%)
Ethnicity					
Caucasian	554 (80.4%)	33 (75.0%)	63 (79.7%)	34 (73.9%)	64 (78.0%)
African-American	77 (11.2%)	3 (6.8%)	10 (12.7%)	6 (13.0%)	12 (14.6%)
Other	58 (8.3%)	8 (18.2%)	6 (17.6%)	6 (13.1%)	6 (17.3%)

The placebo controlled studies were primary conducted in Caucasian males with a mean age of approximately 10 years old. The demographics for the placebo controlled studies are summarized in the following table developed by Dr. Koti, FDA statistician:

Table 11: Demographics for the Placebo Controlled Studies (from Dr. Koti's review)

Baseline	Study 97-M-02			Study 97-M-03	
Characteristic	*d*-MPH	*d,l*-MPH	Placebo	*d*-MPH	Placebo
Age (years)					
Mean ± SD	10.0 ± 2.5	9.8 ± 2.8	9.6 ± 2.7	10.1± 2.9	9.9± 2.7
Median	9.5	9.0	9.0	10	9.5
Range	6 – 16	6 – 17	6 - 16	6 – 16	6 - 16
Sex n (%)					
Male	41 (93.2)	40 (87.0)	35 (83.3)	5 (14.3)	9 (22.5)
Female	3 (6.8)	6 (13.0)	7 (16.7)	30 (85.7)	31 (77.5)
Ethnicity n (%)					
Caucasian	35 (79.5)	34 (73.9)	34 (81.0)	28 (80)	30 (75)
African American	5 (11.4)	6 (13.0)	7 (16.7)	5 (14.3)	5 (12.5)
Asian	0 (0.0)	1 (2.2)	0 (0.0)	0	0
Hispanic	2 (4.5)	1 (2.2)	1 (2.4)	0	0
Other	2 (4.5)	4 (8.7)	0 (0.0)	2 (5.7)	5 (12.5)

Three of the six pediatric studies (97-M-03, 97-M-04, 97-M-05) were open label extensions offering exposure to *d*-MPH for time periods beyond 6 and 12 months. There were 426 patients reported to have taken *d*-MPH for at least 6 months (213 patient years) , 146 patients exposed for 1 year (146 patient years), and 280 patients exposed for ≥ 6 months but < 12 months (unable to calculate exact patients years from this report). These durations of exposure include unscheduled gaps of time.

The majority of patients in the NDA data base were administered doses in the range of 5-20 mg/day (dosed at 2.5 to 10 mg bid). The highest single dose administration was 20 mg (in an adult pharmacokinetic study), and the highest known daily dose was 25 mg/day.

B. Background and Methodology

In the original submission, the sponsor stated that all the safety and efficacy studies supporting the NDA were completed prior to the submission date of October, 2000 with only three single investigator-studies ongoing. A safety update was submitted on May 21, 2001 which included updated information on these 3 ongoing single-investigator studies with a cut off of February 2001.

There were three clinical pharmacology studies: two conducted in children (97-M-01 & PK-99-001)and one in adults (PK-00-001). Study 97-M-01 examined 3 doses of *d*-MPH (2.5, 5, & 10 mg), 3 doses of *d,l*-MPH (and placebo. Study PK-99-001 was a single and multiple dose pharmacokinetic study. Study PK-00-001 examines the effects of food on the pharmacokinetics in a singe dose fasting and fed trial in adults. Please refer to the review from the Division of Biopharmaceutics for detailed reviews of these studies.

The pooled safety data described in the ISS includes data from 684 unique pediatric patients and includes only one of the clinical pharmacology studies (PK-99-001). In the ISS, the sponsor states that clinical laboratory and physical examination information from Study 97-M-01, a pharmacokinetic pediatric trial, was not pooled into the integrated safety data base, because the alternating administration of the study drug with *d,l*-MPH made it difficult to attribute an event to which drug, thus confounding the data. Study PK-00-001, a pharmacokinetic study that included 15 adults, is also not pooled into the safety data base. Studies 97-M-01 and PK-00-001 were reviewed in depth by Dr. Sunzel (FDA biopharmaceutics reviewer) and pertinent findings are included in this review.

The sponsor has defined baseline values as those collected prior to starting study drug in the first study enrolled. If a patient enrolled into an extension study, the first baseline value from the first study is considered baseline for the extension study.

C. Deaths/Other serious adverse events

There were no deaths in this NDA data base.

Other serious adverse events occurred in seven patients. The following table summarizes these events:

Table 12
Summary of nonfatal serious adverse events occurring in patients taking *d*-MPH.

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
05/24-50	9/F	20	115	New onset of seizure. D/ced study
04/24-38	9/M	10	??	Abdominal pain admitted for 1 day (treatment unclear) continued with study medication
4/22-03	7/M	5	9	Crying spells, aggression, hyperactivity and hearing voices. He also put a belt around his neck (he had previously put a belt around his neck prior to taking medication). Was admitted and d/ced medications.
04/23-31	12/M	20	≈305	Violent aggressive behavior & suicidal/homicidal thoughts. Was hospitalized and medication changed to Adderall 5 mg/day.
04/22-16	10/F	20	≈320	Dehydration treated with IV fluids. Withdrew from study 13 days later as parent couldn't bring child for appointments
05/Patient 20-10	8/M	5	2	Bi-frontal headaches, worsening in severity. D/ced study drug 13 days later & was diagnosed with Lyme disease, treated and re-entered study
03/12-08	14/M	20	63	Orbital contusion from baseball accident
05/27-08	9/M	15	181	Incident occurred 21 days after d/c. Hospitalized for homicidal ideation.

It is difficult to determine the causality of these events; however, seizure and abdominal pain are known events to be associated with use of the related stimulant *d,l*-MPH.

D. Assessment of Dropouts

1. Overall pattern of dropouts

Of the 684 patients exposed to *d*-MPH, 230 (34%) patients dropped out prior to completing the study. The most common reasons for withdrawal were lack of efficacy (9.0%), adverse events (7.3%) and protocol violations (7.5%) as can be seen in the sponsor's table below:

Table 13
Summary of Dropouts (from sponsor's ISS)

Discontinuation	Overall *d*-MPH	Clinical Pharmacology	Placebo Controlled Studies		
			d-MPH	*d,l*-MPH	Placebo
Exposed	689	43	79	46	82
Completed	454 (65.9%)	42 (97.7%)	76 (96.2%)	40 (87.0%)	76 (92.7%)
Discontinued		1 (2.3%)	3 (3.8%)	6 (13.0%)	6 (7.3%)
Reason for Discontinuation					
Adverse Event	50 (7.3%)	0	0	1 (2.2%)	2 (2.4%)
Lack of Efficacy	62 (9.0%)	0	0	0	3 (3.7%)
Withdrawn Consent	10(1.5%)	1 (2.3%)	0	0	0
Protocol Violation	52 (7.5%)	0	3 (3.8%)	1 (2.2%)	2 (2.4%)
Lost to Follow-up	44 (6.4%)	0	0	3 (6.5%)	0
Other	12 (1.7%)	0	0	1 (2.2%)	0

As can be seen above, in the placebo controlled studies, the completion rate was lowest for the *d,l*-MPH and highest for the *d*-MPH group. There does not appear to be a consistent trend to explain these findings as the majority of patients in the *d,l*-MPH group discontinued because they were lost to follow up.

In the total safety pooling for *d*-MPH, the most frequent reason for dropouts was lack of efficacy.

2. Adverse Events Associated with Dropouts

In the placebo controlled portion of Studies 97-M-02 or 97-M-03, there were no patients randomized to the *d*-MPH group who discontinued due to an adverse event. However, four patients randomized to the *d,l*-MPH and placebo groups discontinued for the following reasons: severe anxiety/palpitations/tachycardia (randomized to *d,l*-MPH), gastrointestinal symptoms (*d,l*-MPH), insomnia/anxiety/uncontrollable crying (placebo) and sedation (placebo).

The adverse events leading to withdrawal within the entire safety data base of *d*-MPH have previously been described in the labeling for *d,l*-MPH. The following modified sponsor table summarizes all patients taking *d*-MPH who withdrew due to an adverse event:

Table 14 Patients taking *d*-MPH who discontinued due to an adverse event

Patient Number	Age, Gender	Days on *d*-MPH	Dose of *d*-MPH (bid)	Adverse event (COSTART)

Patient Number	Age, Gender	Days on *d*-MPH	Dose of *d*-MPH (bid)	Adverse event (COSTART)
Neurologic/Psychiatric				
05/24-50	9, F	120	10 mg	Convulsion, gait abnormal, incontinence, vomiting confusion
04/19-11	8, M	243	10 mg	Tic-like movement of head (twitching)
04/19-12	8, M	267	10 mg	Tic-like movement with mouth and forehead (twitching)
04/23-19	6, M	21	5 mg	Excessive eye blinking (twitching)
03/13-08	12, M	14	5 mg	Severe rambling speech (personality disorder)
04/20-01	8, M	148	2.5 mg	More emotional
04/21-05	16, M	15	2.5 mg	Marked sadness (depression)
04/22-01	9, M	5	10 mg	"Feeling funny" (depersonalization)
03/33-09	10, M	21	2.5	Labile mood
04/22-03	7, M	10	2.5 mg	Admitted to hospital due to auditory hallucinations, and agitated behavior; also reported on the same day: crying spells and blank expression (Hallucinations, emotional lability, agitation, apathy)
04/25-14	9, M	210	5 mg	depression
04/19-09	9, M	28	5 mg	Dizziness (dizziness)
05/11-24	8, M	31	10 mg	Wet his pants, unprovoked sobbing perseverant speech
04/31-08	12, F	200	10 mg	Patient was becoming more "giggly"
05/23-58	8, M	141	10 mg	Behaviour problems and depression
05/17-15	15, M	113	7.5 mg	Nervous (nervousness), sweating (sweating)
				Felt high, fidgety, nail biting
03/33-03	10, F	11	5 mg	Moderate headaches (headache)
04/23-16	11, M	24	10 mg	Headaches, mood swings, depression (depression)
04/23-31	12, M	327	10 mg	Was hospitalized due to aggressive behavior and suicidal/homicidal thoughts (depression requiring counseling was reported on the same day) (Hostility, depression, psychotic depression)
04/24-23	7, M	331	5 mg	Increased aggressiveness (hostility)
03/33-30	8, M	14	5	Sleep-terrors and sleep walking (sleep disorder)
03/32-08	10, M	135	10 mg	Insomnia (insomnia)
05/17-17	11, M	57	5 mg	Mild insomnia, stomachache, decreased appetite
05/19-16	8, M	137	10 mg	Not been sleeping
05/09-04	10, M	155	5 mg	More active in the evening (hyperkinesia)
04/19-13	11, M	63	5 mg	Lethargy (somnolence)
04/19-15	8, F	85	10 mg	Listlessness (malaise)

Patient Number	Age, Gender	Days on *d*-MPH	Dose of *d*-MPH (bid)	Adverse event (COSTART)
Weight Change				
03/13-03	14, M	180	10 mg	Loss of appetite (anorexia)
03/32-11	7, F	168	10 mg	Weight loss; 3 lbs in 11 months
04/23-26	11, M	106	10 mg	Weight loss: 4 lbs. in 3 months
04/23-11	11, M	247	10 mg	Weight gain (weight gain)
05/09-12	8, M	187	10 mg	Appetite loss continues Wetting on himself (incontinence)
05/10-08	9, M	94	10 mg	Diminished appetite
05/11-34	6, F	14	5 mg	Loss of appetite; loss of sleep
Cardiac				
04/19-03	11, M	50	5 mg	Palm sweating, dizziness, general malaise, heart flutter (Sweating, dizziness, malaise, palpitation)
03/29-02	9, M	182	10 mg	Agitation, tachycardia, headache (agitation, tachycardia, headache)
04/19-02	6, F	15	5 mg	Chest pounding/heart racing (palpitation)
04/19-04	11, M	78	5 mg	Chest pain, tachycardia, dizziness (chest pain, tachycardia, dizziness)
05/17-04	11, F	2	2.5 mg	Chest hurt, rapid heart rate, headache, nauseous, skin clammy to touch[2], up all night[2]; subsequently, the event was attributed to "Strep. throat".
04/22-04	16, M	16	5 mg	Irregular pulse (arrhythmia)
05/11-09	11, F	78	10 mg	Heart racing (tachycardia)
Gastrointestinal				
04/19-01	10, M	44	10 mg	Abdominal pain and tenderness (abdominal pain)
Other				
05/17-15	15, M	113	7.5 mg	Nervous (nervousness), sweating (sweating)
				Felt high, fidgety, nail biting
04/25-05	10, F	101	2.5 mg	Presence of white/gray hairs on head (hair discoloration)

E. Other safety findings

1. Adverse Event Incidence

When the sponsor pooled all studies together, it was found that of the 689 (which includes 5 patients counted twice) patients who were given the study drug, 558 (81%) experienced at least one treatment-emergent adverse event. The most common adverse events reported for the *d*-MPH safety data base occurring in ≥ 5% were headache (24%), abdominal pain (14%), accidental injury (19.5%), viral infection (17%), anorexia (14.4%), vomiting (7.9%), nausea (6.6%) and insomnia (8%). The incidents of adverse events ≥ 5% are listed in the sponsor's following table:

Table 15
Incidence of Adverse Experiences by Body System
Reported in ≥ 5.0% of All ADHD Patients Exposed to *d*-MPH

Body System/ Preferred Term	***d*-MPH (N = 689)**	***>= 6 months* (N = 421)**
Body as a Whole	**407 (59.2%)**	**85 (20.2%)**
Abdominal pain	96 (14.0%)	6 (1.4%)
Accidental injury	134 (19.5%)	22 (5.2%)
Fever	73 (10.6%)	15 (3.6%)
Flu syndrome	35 (5.1%)	10 (2.4%)
Headache	165 (24.0%)	11 (2.6%)
Viral infection	117 (17.0%)	16 (3.8%)
Digestive System	**229 (33.3%)**	**22 (5.2%)**
Anorexia	99 (14.4%)	3 (0.7%)
Nausea	45 (6.6%)	3 (0.7%)
Vomiting	54 (7.9%)	8 (1.9%)
Hematologic and Lymphatic	**46 (6.7%)**	**9 (2.1%)**
Lymphadenopathy	23 (3.3%)	2 (0.5%)
Metabolic and Nutritional	**60 (8.7%)**	**15 (3.6%)**
Weight loss	25 (3.6%)	4 (1.0%)
Nervous System	**236 (34.4%)**	**39 (9.3%)**
Insomnia	55 (8.0%)	6 (1.4%)
Nervousness	39 (5.7%)	4 (1.0%)
Respiratory System	**216 (31.4%)**	**33 (7.8%)**
Cough increased	75 (10.9%)	10 (2.4%)
Pharyngitis	78 (11.3%)	11 (2.6%)
Rhinitis	95 (13.8%)	14 (3.3%)
Skin and Appendages	**95 (13.8%)**	**15 (3.6%)**
Contact dermatitis	15 (2.2%)	2 (0.5%)
Rash	30 (4.4%)	3 (0.7%)
Special Senses	**77 (11.2%)**	**12 (2.9%)**
Conjunctivitis	25 (3.6%)	3 (0.7%)
Otitis media	37 (5.4%)	5 (1.2%)

Although it may appear that the incidence of events lessened with time, it is possible that patients withdrew because the event may have been burdensome.

In order to better characterize the safety of this drug, it would be most helpful to examine the adverse events profile generated in studies 97-M-02 and 97-M-03, the two placebo controlled studies in this NDA data base. The most common adverse events for the *d*-MPH group (i.e. occurring in at least 5% of the *d*-MPH group and twice as much as in the placebo group) include abdominal pain (15.2%), anorexia (6.3%), nausea (8.9%), vomiting (5.1%), rhinitis (10.1%) and fever (5.1%). It is noted that abdominal pain occurred more frequently in the *d*-MPH (15.2%) compared to the *d,l*-MPH group (4.3%); otherwise, the adverse events for the *d*-MPH group occurred with a similar incidence or less frequently than in the *d,l*-MPH group. The following sponsor table summarizes the incidence of adverse events in the placebo controlled studies (Study 97-M-02 and 97-M-03) with the comparator of *d,l*-MPH (in Study 97-M-02 only) that occurred in at least 1% of the patients:

Table 16: Treatment-emergent Adverse Events Occurring in ≥1% or more patients in the Double-blind Treatment in Studies 97-M-02 and 97-M-03

Body System / Adverse Event (COSTART)	Number of Unique Patients (%)		
	d-MPH (N = 79)	*d,l*-MPH (N = 46)	Placebo (N = 82)
Body as a Whole	**28 (35.4%)**	**20 (43.5%)**	**27 (32.9%)**
Abdominal pain	12 (15.2%)	2 (4.3%)	5 (6.1%)
Accidental injury	4 (5.1%)	4 (8.7%)	5 (6.1%)
Chest pain	2 (2.5%)	0	0
Fever	4 (5.1%)	3 (6.5%)	1 (1.2%)
Flu syndrome	2 (2.5%)	0	3 (3.7%)
Headache	10 (12.7%)	11 (23.9%)	7 (8.5%)
Pain	4 (5.1%)	1 (2.2%)	3 (3.7%)
Viral infection	2 (2.5%)	4 (8.7%)	5 (6.1%)
Digestive System	**19 (24.1%)**	**10 (21.7%)**	**7 (8.5%)**
Anorexia	5 (6.3%)	5 (10.9%)	1 (1.2%)
Diarrhea	3 (3.8%)	1 (2.2%)	1 (1.2%)
Gastroenteritis	0	0	2 (2.4%)
Nausea	7 (8.9%)	6 (13.0%)	1 (1.2%)
Vomiting	4 (5.1%)	3 (6.5%)	3 (3.7%)
Metabolic and Nutritional System	**3 (3.8%)**	**1 (2.2%)**	**0**
Ketosis (ketones in urine)	2 (2.5%)	0	0
Musculoskeletal System	**0**	**1 (2.2%)**	**2 (2.4%)**
Myalgia	0	1 (2.2%)	2 (2.4%)
Nervous System	**11 (13.9%)**	**12 (26.1%)**	**7 (8.5%)**
Emotional lability	3 (3.8%)	2 (4.3%)	1 (1.2%)
Insomnia	2 (2.5%)	2 (4.3%)	3 (3.7%)
Nervousness	2 (2.5%)	1 (2.2%)	1 (1.2%)
Personality disorder	2 (2.5%)	1 (2.2%)	0
Somnolence	3 (3.8%)	2 (4.3%)	2 (2.4%)
Respiratory System	**15 (19.0%)**	**8 (17.4%)**	**11 (13.4%)**
Cough increased	2 (2.5%)	2 (4.3%)	1 (1.2%)
Epistaxis	3 (3.8%)	1 (2.2%)	1 (1.2%)
Pharyngitis	2 (2.5%)	2 (4.3%)	2 (2.4%)
Rhinitis	8 (10.1%)	2 (4.3%)	6 (7.3%)
Skin and Appendages	**3 (3.8%)**	**2 (4.3%)**	**5 (6.1%)**
Eczema	2 (2.5%)	0	0
Herpes Simplex	0	0	2 (2.4%)
Special Senses	**2 (2.5%)**	**1 (2.2%)**	**2 (2.4%)**
Ear pain	0	0	2 (2.4%)

In the safety update, the sponsor included preliminary data from ongoing studies. This data did not include any unexpected adverse events.

2. Adverse events upon withdrawal of treatment

Study 97-M-03 included a 2-week double blind withdrawal phase (Part B) which may offer insight into events associated with withdrawal of treatment. In the placebo group (i.e. patients withdrawn from *d*-MPH treatment at the end of Part A of Study 97-M-03), insomnia, headaches and rhinitis occurred with greater frequency than in the *d*-MPH group as can be seen in the following sponsor table:

Table 17
Treatment-emergent Adverse Events during Double-blind Withdrawal (Part B) Reported in 2 or More Patients

Body System / Adverse Event (COSTART)	*d*-MPH (N = 35)	Placebo (N = 40)
Patients with Events	**16 (45.7%)**	**15 (37.5%)**
Body as a Whole		
Abdominal pain	3 (8.6%)	0
Chest pain	2 (5.7%)	0
Headache	2 (5.7%)	3 (7.5%)
Pain	0	2 (5.0%)
Nervous System		
Insomnia	0	2 (5%)
Respiratory System		
Cough increased	2 (5.7%)	0
Rhinitis	0	2 (5.0%)

The sample is too small to make definitive conclusions regarding withdrawal effects, but insomnia, headaches and rhinitis have been associated with withdrawal effects from some medications.

3. Laboratory Findings

Post baseline laboratory values were collected from the *d*-MPH group of one pharmacokinetic study (Study PK-99-001) and the four clinical studies (97-M-02, 97-M-03, 97-M-04, 97-M-05). Study 97-M-02 was the only study with a placebo arm in which laboratory testing was performed. The following laboratory values were assessed: **Biochemistry:** AST, ALT, Alkaline Phosphate, Bilirubin, Creatinine, blood urea nitrogen (BUN); **Hematology:** Hemoglobin, Hematocrit, WBC, Eosinophils, Platelet Count; **Urinalysis:** Glucose, Protein.

The sponsor did not provide percentages of outliers, but did provide line listings of labs that were determined to be clinically significant by their criteria. It is noted that there were no patients reported in this NDA data base to have discontinued due to adverse events related to laboratory findings.

This section of the review will concentrate on the clinical laboratory values collected from the placebo controlled Study 97-M-02, to allow for comparison to be made to the placebo group. Although it is difficult to eliminate the confounding variable of time period, outliers from longer term studies will be mentioned for completeness.

The central tendency reported for the laboratory findings in the placebo controlled Study 97-M-02 did not show any abnormalities indicative of a trend towards liver, renal or metabolic complications. There were no incidences of clinically significant values identified in the placebo controlled Study 97-M-02. Based on the information in the ISS, the following table describes the percent of outliers in Study 97-M-02:

Table 18 Summary of out-of-reference range post-treatment laboratory test results that reached clinical significance

	Number (%) of Subjects With Within-Range Baseline Values & Out-of-Range Post-Treatment Values		
	d-MPH n=42	*d,l*-MPH n=42	Placebo n=42
Hematology			
Hemoglobin			
WBC			

	Number (%) of Subjects With Within-Range Baseline Values & Out-of-Range Post-Treatment Values		
	d-MPH n=42	*d,l*-MPH n=42	Placebo n=42
Platelet Count			
Eosinophils			
Neutrophils			
Biochemistry			
AST			
ALT			
Total Bilirubin			
Alkaline Phosphatase			
Glucose			
Calcium			
creatinine			
BUN			
Urinalysis			
Specific Gravity			
Total protein			
Albuminuria			
Trace ketones			

Although no patients were reported as having clinical symptoms such as jaundice, significant increases in liver function studies (≥ 3 times the upper limit of normal) occurred in patients being treated with *d*-MPH in the longer term studies. The following sponsor table summarizes the patients whose liver function tests met criteria for possible clinical significance after exposure to *d*-MPH:

Table 19 *d*-MPH-treated Patients with On-Treatment Liver Function Test That Met Criteria for Possible Clinical Significance **(modified from sponsor table)

Study No. / Patient ID	Laboratory Test	Age / Sex	Baseline	Result	Dose (mg b.i.d.)	Observation Time	Outcome
02/07-22	ALT NL:5-30	12 / M	41.0 IU/L*	198 IU/L	10	Month 6	No Follow up
	AST NL:0-37	12 / M	22.0 IU/L	153 IU/L	10	Month 6	No Follow up
03/32-04	ALT	9 / M	13.0 IU/L	85 IU/L	2.5	Month 1	Patient DC
04/24-25	ALT	8/ M	30.0 IU/L	107 IU/L	5	Month 12	Resolved
05/03-23	Total Bilirubin 0.0-0.9	12 / M	1.4 mg/dL*	2.1 mg/dL	2.5	Month 6	Resolved
05/17-09	ALT	10 / M	66.0 IU/L*	94 IU/L	10	Month 3	Resolved

*Abnormal baseline value.

**Clinical significance AP, AST, and ALT ≥ 3 times the upper limit of normal; total bilirubin ≥ 2.0 *mg/dL*.

The only patients reported to have an elevated bilirubin had a baseline value that was out of the reference range of normal at baseline. It is noted there were no cases reported which had a combination of elevated ALT/AST and elevated bilirubin.

4. Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse, temperature, and body weight were collected in all studies at baseline and at each visit. Height was only recorded at screening.

In order to establish a comparator control, it is helpful to look in more depth at Study 97-M-02, the placebo controlled pivotal study. As can be seen in the following sponsor table, the mean systolic and diastolic changes do not differ appreciably between the placebo, *d,l*-MPH, and *d*-MPH groups:

Table 20
Mean Baseline Systolic and Diastolic Blood Pressures and Changes from Baseline for study 97-M-02

Treatment Group		Baseline	Weeks on Double-Blind Treatment			
			Week 1	Week 2	Week 3	Week 4
Systolic Blood Pressure						
***d*-MPH**	N	44	43	40	39	42
	Mean ± SD	104.8 ± 12.7	-1.3 ± 9.4	-0.5 ± 10.9	1.3 ± 9.1	1.9 ± 8.7
	Range	[redacted]				
***d,l*-MPH**	N	46	45	42	38	41
	Mean ± SD	104.6 ± 13.9	0.8 ± 10.8	-1.1 ± 10.6	2.6 ± 13.2	2.5 ± 13.9
	Range	[redacted]				
Placebo	N	42	41	39	40	36
	Mean ± SD	101.6 ± 13.5	0.2 ± 10.8	0.6 ± 10.1	1.8 ± 11.3	0.7 ± 8.4
	Range	[redacted]				
Diastolic Blood Pressure						
***d*-MPH**	N	44	43	40	39	42
	Mean ± SD	64.0 ± 7.5	0.3 ± 8.9	0.5 ± 8.3	1.0 ± 8.5	2.8 ± 8.5
	Range	[redacted]				
***d,l*-MPH**	N	46	45	42	38	41
	Mean ± SD	63.8 ± 9.0	-0.1 ± 8.7	0.0 ± 7.0	2.3 ± 8.9	2.5 ± 9.7
	Range	[redacted]				
Placebo	N	42	41	39	40	36
	Mean ± SD	62.3 ± 7.8	0.8 ± 8.8	0.1 ± 9.8	1.1 ± 9.8	1.0 ± 8.7
	Range	[redacted]				

In Study 97-M-02, clinically significant low systolic blood pressure recording were observed in one patient randomized to *d*-MPH (Patient 08-02) and four patients randomized to *d,l*-MPH (Patients 04-07, 08-09, 10-07and 33-23) with ranges between [redacted] (changes from baseline ranged from [redacted] Individual changes were not listed in the ISS or study report.

Diastolic changes that were clinically significant (based on the cut-off values) were observed in one patient randomized to *d*-MPH (Patient 01-10), two patients randomized to *d,l*-MPH (Patients 03-03 and 03-05), and one placebo-treated patient (Patient 33-15). The sponsor listed values ranging from [redacted] with decrease of [redacted] from baseline for these diastolic changes. However, none of these patients were reported to have associated clinical symptoms, nor were these findings reported as adverse events. Individual values were not listed in the ISS or the study report; however, the sponsor attributes these changes to a poorly fitting blood pressure cuff, such as using an adult sized cuff on pediatric patients. There were no reports of hypotension or hypertension.

Mean pulse changes were comparable for all the treatment groups in Study 97-M-02 in Week 1. For the remainder of the study there was an increase in pulse of 2-3 bpm observed in the *d*-MPH and *d,l*-MPH groups compared to placebo. The following sponsor table summarizes the heart rate findings:

Table 21
Mean Baseline Pulse and Change from Baseline for Study 97-M-02

Treatment Group		Baseline	Weeks on Double-Blind Treatment			
			Week 1	Week 2	Week 3	Week 4
d-MPH	N	44	43	40	39	42
	Mean ± SD	82.9 ± 11.1	-0.4 ± 11.5	2.4 ±11.0	3.2 ± 12.7	2.2 ± 13.9
	Range	[redacted]				
d,l-MPH	N	46	45	42	38	41
	Mean ± SD	84.6 ± 11.9	-0.6 ± 11.0	2.2 ± 13.8	3.4 ± 12.8	3.1 ± 14.3
	Range	[redacted]				
Placebo	N	42	40	39	40	36
	Mean ± SD	84.7 ± 10.8	-3.9 ± 11.2	-2.6 ± 12.7	1.1 ± 12.7	-2.8 ± 12.1
	Range	[redacted]				

In Study 97-M-02, there was one patient randomized to *d,l*-MPH who was discontinued due to palpitations, anxiety and tachycardia(02/02-05); however, the magnitude of the tachycardia was not described in the CRF.

In the biopharmaceutics review of Study PK-99-001, Dr. Sunzel, FDA biopharmaceutics reviewer, described a 9 y.o. female (Subject 12) who had an increase in systolic blood pressure on day 8 at 1 hour post dosing that was increased up to 159/78 from 117/55 pre-dose.

Please refer to Section III B above which summarizes Dr. Sunzel's finding from study PK-001-001 in which an increase in heart rate (up to 30 bpm) and an increase in systolic blood pressure (up to 20 mmHg) within the first 4 hours of study drug administration was observed. This trend was also seen in Study PK-99-001 where there is a peak change in heart rate and blood pressure at tmax of *d*-MPH (tmax ≅ 1.5 hrs). Please refer to Dr. Sunzel's review for more details.

Body weight was measured weekly during the placebo controlled Study 97-M-02. The mean weights at baseline for all groups were comparable. Weight changes during this four week study showed slight variations with the *d*-MPH and the *d,l*-MPH group showing an overall loss (-.01 and –1.5 respectively) and the placebo group showing a mean increase of 1 pound. The following sponsor table summarizes the data from this study:

Table 22
Mean Baseline Body Weight (Pounds) and Changes from Baseline

Treatment Group		Baseline	Weeks on Double-Blind Treatment			
			Week 1	Week 2	Week 3	Week 4
d-MPH	N	44	43	40	39	42
	Mean ± SD	83.7 ± 27.7	0.0 ± 2.3	-0.1 ± 1.8	-0.7 ± 2.2	-0.1 ± 2.8
	Range	[redacted]				
d,l-MPH	N	46	45	41	38	41
	Mean ± SD	82.6 ± 33.7	-0.5 ± 1.8	-0.9 ± 2.5	-1.1 ± 1.7	-1.5 ± 3.3
	Range	[redacted]				
Placebo	N	42	41	39	40	37
	Mean ± SD	81.7 ± 32.1	-0.4 ± 3.7	0.7 ± 2.4	0.7 ± 2.3	1.0 ± 2.9
	Range	[redacted]				

In Study 97-M-02, clinically significant weight losses were found in 4 patients randomized to *d*-MPH (ranges of [redacted] decrease from baseline), 6 patients randomized to *d,l*-MPH (5-10.5% weight loss) and 2 patients randomized to placebo (14-17.8% weight loss).

Although most of Study 97-M-03 was open label, it's duration of 52 weeks offers insight into the effects of the study drug's long term use. Within 6 months, the mean weight change observed was –0.8 ± 3.1 lbs, and, at one year, the mean change was 4.3 ± 8.3 lbs. There were reports of 9 individual patients having clinically significant weight losses ranging up to a maximum of 17 % of body weight over 15 weeks of taking the study drug. The following sponsor table summarizes the weight changes in patients from study 97-M-03:

Table 23
Summary of Weight Changes in Patients Treated With *d*-MPH

Parameter (unit)	Statistic	Visit 2	6 Weeks (Visit 8)	1 Year (Visit 15)
			Change from Visit 2	Change from Visit 2
Weights (lb.)	N	86	72	54
	Mean ± SD	88 ± 34.2	-0.8 ± 3.1	4.3 ± 8.3
	Range			

Temperature

In the entire NDA data base, there were 6 patients reported who had temperature increases with a maximum elevation to102.7 °. None of these were reported to be an adverse event.

Electrocardiograms

No electrocardiograms were obtained during the development of this drug.

5. Withdrawal reactions and abuse potential

The sponsor did not report or characterize any withdrawal reactions. As discussed in the consult from the Division of Controlled Substances (6/15/01), during the withdrawal phase of Study 97-M-03, there were 6 patients taking placebo who reported adverse events (including "flu syndrome," headache, myalgia, pharyngitis, nasal discharge and sneezing) during the first 3 days after discontinuing the study drug. Although the investigators determined that these were not drug related events, the consult concluded that that no formal measure of withdrawal were used and it appeared that at least one patient experienced a withdrawal symptoms (i.e. "flu syndrome").

It was recommended that *d*-MPH be scheduled as a Class II, because it is the active enantiomer of *d,l*-MPH which is scheduled as Class II. It is also noted that the sponsor has not performed human abuse potential studies with *d*-MPH.

6. Human Reproduction Data

There was no information in this NDA regarding human reproduction data.

7. Overdose experience

There were no overdoses reported in this NDA data base.

F. Adequacy of Safety Testing (Adequacy of patient exposure and assessments)

It is recognized that the pharmacokinetic profile and the safety profile of *d*-MPH presented in this NDA are similar to *d,l*-methylphenidate, which has a long history of being marketed. Because of these similarities, the exposure for *d*-MPH could be considered adequate. It is noted that non-Caucasians and females were under-represented in this NDA data base.

G. Summarize Critical Safety Findings and Limitations of Data

All of the safety concerns that have arisen in this NDA data base have also been described in the labeling for the parent drug *d,l*-MPH. However, the proposed labeling submitted by the sponsor states in the warnings and contraindications sections that "racemic methylphenidate" is contraindicated or that "racemic methylphenidate" may cause behavior disturbance or seizures rather than referring to *d*-MPH. This poses a dilemma for the labeling, because the inference is that these are not necessarily warnings for *d*-MPH. Although causality was not well established, there was one case of seizure disorder, and several cases of behavioral disturbance observed in this NDA data base. Because of the similarities of the isomer and racemic methylphenidate (similar structure and pharmacokinetics), it is recommended that the contraindications and warnings remain the same except where there is evidence to support otherwise.

Because there were a few outliers identified with elevated liver function studies, it may be prudent to also include that liver function studies be assessed periodically.

VIII. Dosing, Regimen, and Administration Issues

The majority of patients in the NDA data base were administered doses in the range of 5-20 mg/day (dosed at 2.5 to 10 mg bid). The highest single dose administration was 20 mg (in an adult pharmacokinetic study), and the highest known daily dose was 25 mg/day. The proposed labeling recommends dosing of 5-20 mg daily in two divided daily doses. This dosing strength is comparable (and equimolar) to half of the dosing strength for methylphenidate, and is supported by efficacy trials using methylphenidate as a comparator arm.

Also, because the pharmacokinetic properties have not differed appreciably in the fasting or fed state, *d*-MPH is labeled to be administered with or without food.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor compared pharmacokinetic properties in males and females and did not find an appreciable difference. However, Dr. Sunzel noted an increase in AUC and Cmax in adult females compared to adult males in a single dose pharmacokinetic study; it is unclear how significant this finding is clinically, because the $t_{½}$ and tmax are comparable for both genders. Boys and girls were found to have similar pharmacokinetic properties in a study of 5 boys and 4 girls after a single dose of 10 mg *d*-MPH. If the sponsor is going to extend their claims to indications primarily found in the adult population, it would be helpful to obtain a clearer characterization of the gender differences in pharmacokinetic parameters. It is also noted that the majority of patients in this NDA data base are males, but the current viewpoint is that more boys than girls are diagnosed and treated with ADHD.

B. Evaluation Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There were no significant pharmacokinetic differences observed in children ages 6-17 and healthy adults after single doses of *d*-MPH. The sponsor did not have sufficient exposure to characterize ethnic variations.

Looking at a subgroup analysis of the adolescent age group only (aged 12-19) for the four week placebo controlled Study 97-M-02, Dr. Koti observed that there was no statistical difference when comparing the scores of the 39 (of 119) adolescents amongst the three treatment groups (including no difference between the study drug and placebo as well as between *d,l*-MPH and placebo). However, this was too small a sample to make any conclusions regarding efficacy in this age subgroup.

C. Evaluation of Pediatric Program

The target population for this study drug was primarily the pediatric population diagnosed with ADHD. The sponsor has conducted both efficacy studies in the pediatric population.

D. Comments on Data Available or Needed in Other Population (Renal, Hepatic Compromised Patients, or Use in Pregnancy)

The sponsor has not tested this drug in patients with renal or hepatic compromise. The safety of use in pregnancy has also not been assessed.

X. Conclusions and Recommendations

A. Conclusions

Efficacy

The formulation of *d*-MPH has been shown to be effective in the treatment of ADHD in the pediatric population. There is some suggestion that the *d*-MPH may not have been as effective for the subgroup of adolescents, but the study was not designed nor powered to assess the difference in this subgroup. It is also noted that within this same adolescent subgroup, d,l-MPH was not shown to be significantly different than placebo. It would be helpful if the sponsor conducted further studies to assess the differences in age group responses. However, efficacy was established in the study population overall which included boys and girls aged 6 to 17 years old.

Safety

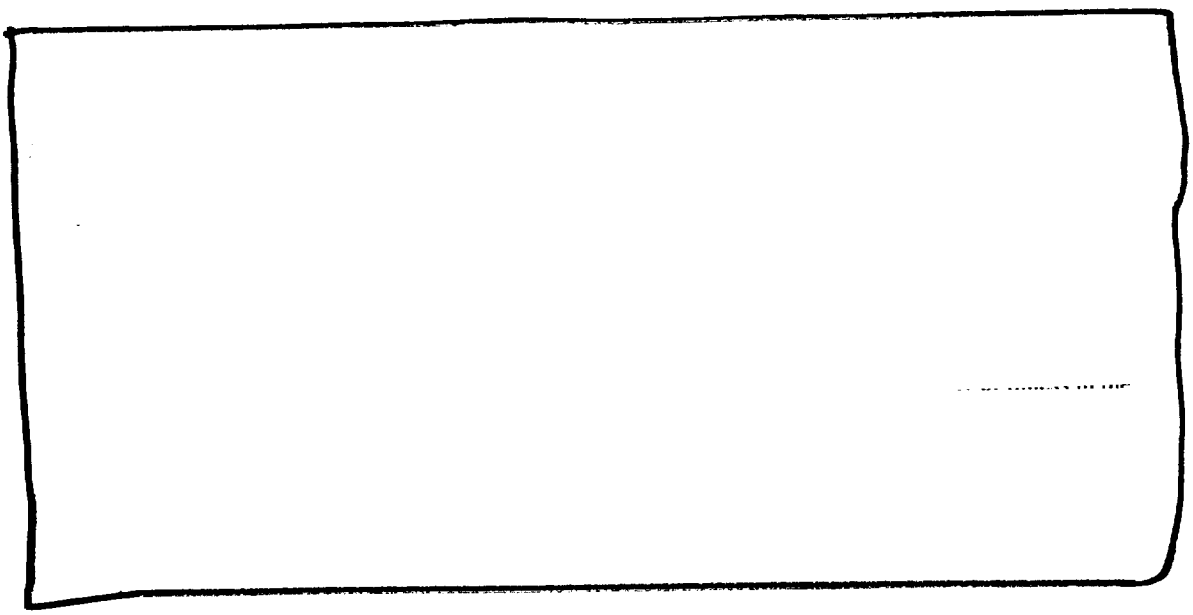
The safety findings in this review were consistent with findings previously reported in the literature and labeling of currently marketed racemic methylphenidate formulations. There are no safety findings which would impede the marketing of this formulation of the isomer *d*-MPH.

One issue that is of concern is the effect of anorexia and subsequent weight loss. The sponsor analyzed their long term data for weight as the mean weight gain/loss. It may be more helpful to use a method that reflects a composite of individual weight changes during the study so that expected developmental weight changes are taken into account. One suggested method is to look at the change in percentile in growth charts and then calculate a mean change for the data base. Otherwise, in the manner that the sponsor presented the weight change data, it is not interpretable; this data does not take into account what would be an expected developmental weight gain.

Labeling

1. Under **Special Populations** in the Gender section

As described in Dr. Sunzel's biopharmaceutics review, in a single dose study in adults, females were shown to have elevated Cmax and AUC values compared to males, whereas the tmax and $t_{½}$ were comparable for males and females.



3. In the **CONTRAINDICATIONS** and **WARNINGS** section:

All of the safety concerns that have arisen in this NDA data base have also been identified in the labeling for the parent drug *d,l*-MPH. However, the sponsor has proposed to mention only "racemic methylphenidate" in the contraindications (of agitation, hypersensitivity, glaucoma, tics, MAOI use) and the warnings (psychosis, seizures and visual disturbance). This posses a dilemma for the labeling, because the inference is that these are not necessarily warnings or contraindications for *d*-MPH. Although causality was not well established, there was one case of seizure disorder, and several cases of behavioral disturbance observed in this NDA data base for *d*-MPH. Because of the similarities of the isomer compared to the racemic methylphenidate (i.e. similar structure and pharmacokinetics), it is recommended that the contraindications and warnings remain the same for both until the sponsor can demonstrate otherwise.

4. Under **WARNINGS** in the section of Hypertension and Other Cardiovascular Conditions

In previous labeling for this section, sponsors have described the data for pulse and blood pressure in the placebo controlled studies. In this labeling version (7/6/01) the sponsor has chosen to describe the mean changes of pulse and blood pressure for in the entire safety data base. Of most concern in this section is the statement "The small mean increases in blood pressure are not clinically significant," which could be misinterpreted and falsely reassuring.

5. In the Drug Interactions Section

The sponsor has omitted the following paragraph, and it is recommended that it be added to the labeling:

"Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated."

6. In the **Adverse Findings in Clinical Trials with** [redacted] section:

In discussing adverse events associated with discontinuation of treatment, the sponsor states that there were no withdrawals from the *d*-MPH group in the placebo-controlled trials. However, they go onto restate this

information in Table 2 (line 332) which provides little new information and exaggerates the 2 withdrawals from the *dl*-MPH and the placebo group by counting each symptom from the same patient as a separate event. It is recommended that this table be deleted as it presents redundant information.

In Table 3 (Line 347), it would be more consistent with previous labels for this class of drugs to include only events which have occurred in at least 1% of cases and with an incidence greater than placebo. Also of concern is that the sponsor has included findings of the comparator group, *d,l*-MPH; the study was not designed to detect differences between these two groups.

7. In the **DOSAGE AND ADMINISTRATION** Section

In line 413, the sponsor states that "dosage should be individualized according to the needs and responses of the patient." This statement precedes the detailed dosing information and does not refer to the instructions below. It is recommended that the sponsor clarify this statement by adding the maximum dosage recommended. Also for "Patients Currently Using Methylphenidate" the sponsor has omitted mentioning a maximum dose of 20 mg/day.

B. Recommendations

It is recommended that this NDA receive an "approvable" action. Of concern is that the sponsor has not had an inspection at their new manufacturing site, [redacted] Consequently, data required to set dissolution specification is not yet available.

It is also recommended that the sponsor better define the weight changes with longer term use. One suggestion is that they could composite individual changes in percentile from growth charts, which take into account developmentally appropriate weight gains.

If the sponsor is considering an indication in the adult population, it is recommended that the sponsor better characterize the pharmacokinetic differences between male and female adults.

Appendix A: Sponsor's List of Investigators

Principal Investigator	Site Address	Study Number(s)
Daniel Adler, MD	Neurology Group of Bergen County, PA 1200 East Ridgewood Avenue 2nd Floor – East Wing Ridgewood, NJ 07450	97-M-04 97-M-05
L. Eugene Arnold, MD and Michael Aman, PhD	Ohio State University Nisonger Center 1581 Dodd Drive Columbus, OH 43210	97-M-03
Timothy Bohan, PhD, MD (formerly with Michael Lesem, MD)	Therapeutic Research, Inc. 1213 Hermann Drive, Suite 715 Houston, TX 77004 Formerly: Claghorn-Lesem Research Clinic, Inc. 6750 West Loop South, Suite 1050 Bellaire, TX 77401	97-M-03
Bruce Bogdanoff, MD	Neurological Associates of Delaware Valley Crozer-Chester Medical Center Ambulatory Care Pavilion, Suite 533 One Medical Center Boulevard Upland, PA 19013	97-M-04 97-M-05
David W. Brown, MD	4411 Medical Parkway Austin, TX 78756	97-M-05
Caryn L. Carlson, PhD	University of Texas at Austin Department of Psychology 330 Mezes Hall Austin, TX 78712	97-M-05
Charles D. Casat, MD	Behavioral Health Center 501 Billingsly Road Charlotte, NC 28211	97-M-02 97-M-05
C. Keith Conners, PhD	Duke University Medical Center First Union Tower, Office Wing B, Suite 230 2220 West Main Street Durham, NC 27705	97-M-02 97-M-05
Daniel Coury, MD	Children's Hospital 700 Children's Drive Columbus, OH 43205	97-M-02 97-M-05
Josephine Elia, MD	Children's Hospital of Philadelphia 34th Street & Civic Center Boulevard Main Building Room 3636 Philadelphia, PA 19104-4399	97-M-02 97-M-05
David Feifel, MD. PhD	UCSD Medical Center Department of Psychiatry 200 West Arbor Drive San Diego, CA 92103-8620	97-M-02 97-M-05
L. Matthew Frank, MD	Neuro-developmental Center 850 South Hampton Avenue, 3rd Floor Norfolk, VA 23510	97-M-04 97-M-05
Clifford Goldman, MD	ClinSearch, Inc. 1 Prospect Street Summit, NJ 07901	97-M-04 97-M-05

Principal Investigator	Site Address	Study Number(s)
James T. Grimm, MD (formerly Nicholas Telew, MD)	Oregon Center for Clinical Investigations, Inc. 132 East Broadway Street, Suite 332 Eugene, OR 97401	97-M-05
James A. Hedrick, MD, FAAP	Kentucky Pediatric/Adult Research 201 South 5th Street, Suite 3 Bardstown, KY 40004	97-M-04 97-M-05
Sharon L. Hirsch, MD	Children's Memorial Hospital 2300 Children's Plaza, Box 10 Chicago, IL 60614	97-M-01 97-M-05
Allan P. Ingenito, MD	Minneapolis Clinic of Neurology, Ltd. 209 Mercy Health Center 3960 Coon Rapids Boulevard Coon Rapids, MN 55433-2577	97-M-05
Diane Johnson, PhD	Duke University Medical Center First Union Tower, Office Wing B, Suite 230 Durham, NC 27705	97-M-03
William J. Keating, MD	Scotland Family Medicine Clinical Trials 3730 Scotland Road Scotland, PA 17254	97-M-04
James C. Kisicki, MD	MDS Harris P.O. Box 80837 621 Rose Street Lincoln, NE 68501	*d*-MPH PK-00-001
Martin W. Kremenitzer, MD	Associated Neurologists, P.C. 69 Sand Pit Road Danbury, CT 06810	97-M-05
Alan J. Levine, MD	Denver Center for Medical Research 4704 Harlan Street, Suite 430 Denver, CO 80212	97-M-03
Kara S. Lewis, MD	Barrow Neurological Group Research Corporation 500 W. Thomas Road, Suite 300 Phoenix, AZ 85013	97-M-05
Brian J. McConville, MD	University of Cincinnati College of Medicine *Department of Psychiatry* 231 Bethesda Avenue Cincinnati, OH 45267	97-M-02 97-M-05
Donna Palumbo, PhD	University of Rochester Department of Neurology – Box 673 601 Elmwood Avenue Room 5 - 5237 Rochester, NY 14642	97-M-02 97-M-05
Steven R. Pliszka, MD	University of Texas HSCSA Department of Psychiatry 7703 Floyd Curl Drive San Antonio, TX 78284	97-M-02 97-M-05

Principal Investigator	Site Address, Telephone and Facsimile Numbers	Study Number(s)
Declan Quinn, BCh, MB, FRCP(C)	Department of Psychiatry University of Saskatchewan Royal University Hospital Room 241 Ellis Hall 103 Hospital Drive Saskatoon, Saskatchewan CANADA S7N 0W3	97-M-01 97-M-05
Ralph W. Richter, MD	Clinical Pharmaceutical Trials, Inc. 1705 E. 19th Street – Suite 406 Tulsa, OK 74104	97-M-02 97-M-05
R. Bart Sangal, MD	Clinical Neurophysiology Services, PC Beaumont Hospital Office Buildings 44199 Dequindre, Suite 311 Troy, MI 48098	97-M-02 97-M-03 97-M-05
James Swanson, PhD*	UCI Child Development Center 19722 MacArthur Boulevard Irvine, CA 92612	97-M-01 97-M-02 97-M-05
Nicholas W. Telew, MD	Oregon Center for Clinical Investigations 132 East Broadway Street, Suite 332 Eugene, OR 97401	97-M-02
Harvey A. Tilker, PhD	Four Rivers Clinical Research, Inc. 81 Lakeview Drive Paducah, KY 42001	97-M-04 97-M-05
Margaret Weiss, MD, PhD	British Columbia's Children's and Women's Health Center Department of Psychiatry Out-Patient Clinic C4-4480 Oak Street Vancouver, BC V6H 3V4 Canada	97-M-05
Scott A. West, MD	Psychiatric Institute of Florida 77 West Underwood Street, 3rd Floor Orlando, FL 32806	97-M-03
Sharon Wigal, PhD*	UCI Child Development Center 19722 MacArthur Boulevard Irvine, CA 92612	d-MPH-PK-99-001 97-M-01* 97-M-03
Daniel R. Wynn, MD	Consultants in Neurology, Ltd. 1535 Lake Cook Road, Suite 601 Northbrook, IL 60062	97-M-04 97-M-05

* Sharon Wigal, PhD is a co-Investigator on Study 97-M-01.

Appendix B : SNAP-ADHD Teacher Rating Scale

Instructions: Below are a number of behavioral symptoms present among children with ADHD. For each item, circle the column which best describes this child's behavior today. Please respond to all items.

	Not at all	Just a Little	Quite a Bit	Very Much
1. Often fails to give close attention to details or makes careless mistakes in schoolwork or tasks	0	1	2	3
2. Often has difficulty sustaining attention in tasks or play activities	0	1	2	3
3. Often does not seem to listen when spoken to directly	0	1	2	3
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties	0	1	2	3
5. Often has difficulty organizing tasks and activities	0	1	2	3
6. Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort	0	1	2	3
7. Often loses things necessary for activities (e.g., toys, school assignments, pencils, or books)	0	1	2	3
8. Often is distracted by extraneous stimuli	0	1	2	3
9. Often is forgetful in daily activities	0	1	2	3
10. Often fidgets with hands or feet or squirms in seat	0	1	2	3
11. Often leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
12. Often runs about or climbs excessively in situations in which it is inappropriate	0	1	2	3
13. Often has difficulty playing or engaging in leisure activities quietly	0	1	2	3
14. Often is "on the go" or often acts as if "driven by a motor"	0	1	2	3
15. Often talks excessively	0	1	2	3
16. Often blurts out answers before questions have been completed	0	1	2	3
17. Often has difficulty awaiting turn	0	1	2	3
18. Often interrupts or intrudes on others (e.g., butts into conversations/games)	0	1	2	3

Appendix C: Sponsor's Schedule of Events for Study 97-M-02

Study Procedure	Screening (Visit 1)	1-Week Single-blind Placebo (Visit 2)	4-Week Double-blind Treatment				
			Baseline (Visit 3)	Week 1 (Visit 4)	Week 2 (Visit 5)	Week 3 (Visit 6)	Week 4 (Visit 7)
Medical / Medication History	♦						
Physical Examination	♦						♦
Vital Signs	♦	♦	♦	♦	♦	♦	♦
Hematology/Chemistry	♦						♦
Urinalysis	♦						♦
Concomitant Medications	♦	♦	♦	♦	♦	♦	♦
Teacher-SNAP-ADHD			♦[1]	♦[1]	♦[1]	♦[1]	♦[1]
Parent-SNAP-ADHD			♦[2]	♦[2]	♦[2]	♦[2]	♦[2]
CGI-I			♦[3]	♦	♦	♦	♦
CGI-S		♦	♦[3]				
Math Test (Home)			♦[2]	♦	♦	♦	♦
Math Test (Clinic)			♦[3]	♦	♦	♦	♦
Adverse Events / Concurrent Illness	♦	♦	♦	♦	♦	♦	♦
Study Medication		♦	♦	♦	♦	♦	
Study Termination							♦

[1] To be recorded twice weekly by the teacher at school in the afternoon, during the week preceding the listed clinic visit.

[2] SNAP-ADHD to be recorded twice daily on the weekends by the parent and any day the child was not in school, and the Math Test once daily during the week preceding the clinic visit.

NDA 21-278 ADDENDUM; (New drug product manufacturing site & Dissolution specifications)
dexmethylphenidate HCl
M Sunzel

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

ADDENDUM to main review dated July 30, 2001:

1. **New manufacturing site - [redacted] (Biopharmaceutical aspects)**

2. ***In Vitro* Dissolution Specifications**

d-threo-methylphenidate HCl (dexmethylphenidate HCl); [redacted]
2.5 mg, 5 mg and 10 mg tablets

Indication:	Attention Deficit/Hyperactivity Disorder (ADHD)
Sponsor:	Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059
Submission Date:	July 31, 2001
Reviewer:	Maria Sunzel, Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

Division of Pharmaceutical Evaluation 1 (HFD-860)

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NDA 21-278 ADDENDUM; (New drug product manufacturing site & Dissolution specifications)
dexmethylphenidate HCl
M Sunzel

1. RECOMMENDATION

From a biopharmaceutical perspective, the new drug product manufacturing site and the *in vitro* dissolution method proposed by the sponsor are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The OCPB recommends a revision of the *in vitro* dissolution specifications to Q = [redacted] in 30 min, which also leads to a change in sampling time to 30 min. Please forward the revisions to the sponsor.

This NDA, from a clinical pharmacology and biopharmaceutical point of view, is acceptable to the OCPB, if the sponsor accepts the recommended revisions of the *in vitro* dissolution specifications.

2. EXECUTIVE SUMMARY

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product filed in the original NDA [redacted] was being changed to [redacted] Therefore, comparative *in vitro* dissolution profiles for all dosage strengths were requested for the tablets produced at the old and new sites. The sponsor submitted the requested data on July 31, 2001.

This addendum to the main CPB review dated July 30, 2001 is a review of the dissolution data comparing the to-be-marketed dexmethylphenidate (*d-threo*-methylphenidate) HCl immediate release (IR) tablets manufactured at the old and new production sites. Based on this data, final dissolution specifications for all three strengths (2.5, 5 and 10 mg) of dexmethylphenidate tablets [redacted] will be set.

The *in vitro* dissolution method selected by the sponsor is acceptable. However, the dissolution specifications should be changed to Q = [redacted] in 30 minutes (see below).

[redacted]

FDA's recommended specification: Q = [redacted] dissolved in **30 min**
(change from sponsor's proposal of Q not less than [redacted] in 45 min)

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3. *IN VITRO* DISSOLUTION

3.1. Formulation

The sponsor intends to market three strengths of an immediate release (IR) tablet formulation, namely 2.5 mg, 5 mg and 10 mg.

The to-be-marketed IR tablets contain 2.5 mg, 5 mg, and 10 mg of *d*-MPH, respectively. The proposed commercial tablets contain D&C Yellow lake #10 (5 mg) and FD&C blue no 1 #5516 aluminum lake (2.5 mg), while the 10 mg tablet strength does not contain dye.

The compositions of the to-be-marketed IR tablets have been provided in the main review (dated 07/30/01), and are also provided in Appendix 1, Table A-5, in this addendum.

3.2. Dissolution method

3.2.1 Background

The sponsor has chosen the USP method (USP 24 NF 19) for *d,l*-MPH hydrochloride IR tablets as the *in vitro* dissolution method for the final drug product

The proposed *in vitro* dissolution method and specifications are as follows:

Sponsor's proposed specification: Q not less than dissolved in 45 min

New manufacturing site and dissolution profile comparisons:
In addition to the data presented in this additional review, the main review of this NDA (dated 7/30/01) contains data evaluating the *in vitro* dissolution method, under different conditions (clinical trial formulations, influence of pH and a comparison between drug substance from two different manufacturers). The data that was included in the main review was found to be acceptable, where similar *in vitro* dissolution profiles were demonstrated in the tested conditions. Therefore, the selected dissolution method is considered acceptable. However, the specifications need to be changed (see below for details).

In March 2001, the sponsor notified the FDA that the manufacturing site for the drug product filed in the original NDA was being changed to Therefore, comparative *in vitro* dissolution profiles for all dosage strengths were requested for the tablets produced at the old and new sites (since in addition to the site change, there were minor changes with respect to equipment etc.).

In accordance with this previous agreement, the sponsor has now submitted an investigational report entitled "Similarity between dexmethylphenidate hydrochloride tablets manufactured at to those manufactured at This review consists of an evaluation of the comparative *in vitro* dissolution profiles between the two manufacturing sites and dissolution specifications for the final drug products, manufactured by

3.2.2 Methods

The sponsor compared the *in vitro* dissolution profiles of the to-be-marketed formulations (2.5 mg, 5 mg, & 10 mg tablets) manufactured at the old and new sites in 4 different media

[redacted] volume of media and temperature were according to the proposed method. For further details, see Appendix 1.

3.2.3 Results

The *in vitro* dissolution profiles in water [redacted] of the tablets manufactured at the two different sites are depicted in Figure 1. Corresponding figures for the additional tested media are included in Appendix 1. The mean values of the three tablet strengths, including similarity factors between the tablets produced at the two sites are shown in Table 1.

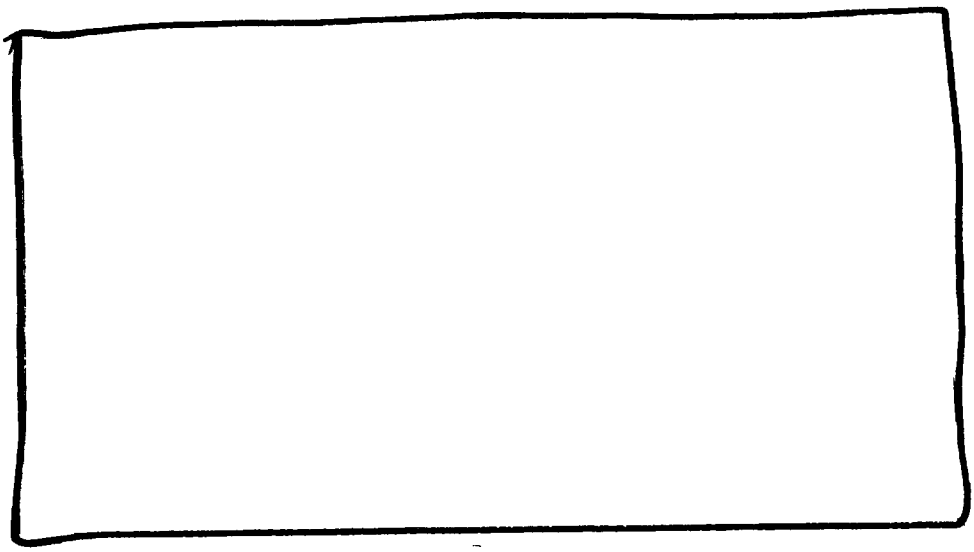
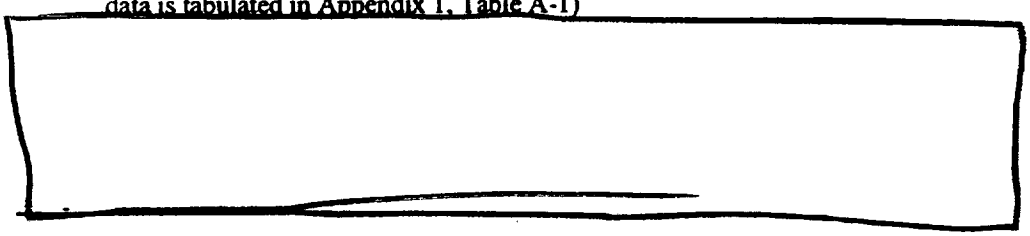


FIGURE 1. Proposed *in vitro* dissolution method ([redacted] *In vitro* dissolution (% dissolved) vs. time profiles for the old ([redacted] and new [redacted] lines) manufacturing sites for all to-be-marketed tablet strengths. Mean values of 12 units/point. (Individual data is tabulated in Appendix 1, Table A-1)

TABLE 1. *In vitro* dissolution (%; mean ± SD in compendial medium: water) and similarity factor (f_2) of the proposed commercial formulations of *d*-MPH tablets manufactured at two different sites; n=12 tablets/strength; [redacted] is the chosen manufacturer. (Individual data is tabulated in Appendix 1, Table A-1)



The mean values of the different tablet strengths for the additional tested media, including similarity factors between the tablets produced at the two sites are shown in Tables 2-4.

[redacted]

Comment: The f_2 comparison is not particularly useful, as the sponsor also points out. Already at 15 min approximately [redacted] has been dissolved, suggesting that an earlier time point could have been included (See FDA Guidance "*Immediate release solid oral dosage forms SUPAC: CMC, In vitro dissolution and in vivo bioequivalence documentation*", dated November, 1995). However, a dissolution of about [redacted] in 30 min in water, and [redacted] in 15 min in [redacted] indicate rapid dissolution (according to FDA's BCS Guidance, August 2000).

Although some differences were noted at the 15 min time point for the tablets manufactured at the two sites, dissolution is essentially rapid with [redacted] dissolved in 30 min in all media. In addition, t_{max} was achieved in 1-1.5 h *in vivo*. Based upon this information, and that f_2 was >50 in all cases, the dissolution profiles are considered similar, and the [redacted] site is acceptable.

3.2.4 Conclusion

The *in vitro* dissolution profiles of the tablets manufactured at [redacted] (old site) and [redacted] (new site) are similar in the tested media. However, due to the rapid dissolution of these immediate release tablet formulations (2.5 mg, 5 mg and 10 mg strengths), the specifications should be set to Q = [redacted] dissolved in 30 min, instead of 45 min. The method description should also be changed to 'Sampling time: 30 min'.

4. SIGNATURES

Maria Sunzel, Ph.D. _____

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

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

c.c.: NDA 21-278, HFD-120 (Katz, Laughren, Glass), HFD-860 (Mehta, Sahajwalla, Uppoor, Sunzel)

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ON ORIGINAL

7 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.