CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW

CLINICAL REVIEW

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Therapeutic Class	Stimulant
Applicant	Novartis
Priority Designation	S
Formulation	Extended Release Capsules
Dosing Regimen	5, 10, 20, [redacted] capsules once daily
Indication	Attention Deficit and Hyperactivity Disorder
Intended Population	Children, Adolescents and Adults

1 EXECUTIVE SUMMARY 4

1.1 RECOMMENDATION ON REGULATORY ACTION 4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 4
1.2.1 Risk Management Activity 4
1.2.2 Phase 4 Commitments 4
1.3.2 Efficacy 5
1.3.3 Safety 6
1.3.4 Dosing Regimen and Administration 7
1.3.5 Drug-Drug Interactions 7
1.3.6 Special Populations 7

2 INTRODUCTION AND BACKGROUND 8

2.1 PRODUCT INFORMATION 8
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 8
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 8
2.5 PRESUBMISSION REGULATORY ACTIVITY 9

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 9

3.1 CMC 9
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 9

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 9

4.1 SOURCES OF CLINICAL DATA 9
4.2 TABLE OF CLINICAL STUDIES 9
4.4 DATA QUALITY AND INTEGRITY 10
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 11

5 CLINICAL PHARMACOLOGY 11

5.1 PHARMACOKINETICS 11
5.2 PHARMACODYNAMICS 11
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 12

6 INTEGRATED REVIEW OF EFFICACY 12

6.1 INDICATION 12
6.1.1 Methods 12
6.1.2 General Discussion of Endpoints 13
6.1.3 Study Design 13
6.1.4 Efficacy Findings 14
6.1.5 Clinical Microbiology 17
6.1.6 Efficacy Conclusions 17

7 INTEGRATED REVIEW OF SAFETY 17

7.1 METHODS AND FINDINGS 17
7.1.1 Deaths 18
7.1.2 Other Serious Adverse Events 18
7.1.3 Dropouts and Other Significant Adverse Events 19
7.1.4 Other Search Strategies 20
7.1.5 Common Adverse Events 20
7.1.6 Less Common Adverse Events 21
7.1.7 Laboratory Findings 22
7.1.8 Vital Signs 23
7.1.9 Electrocardiograms (ECGs) 24
7.1.10 Immunogenicity 24
7.1.11 Human Carcinogenicity 25

7.1.12 Special Safety Studies 25
7.1.13 Withdrawal Phenomena and/or Abuse Potential 25
7.1.14 Human Reproduction and Pregnancy Data 25
7.1.15 Assessment of Effect on Growth 25
7.1.16 Overdose Experience 26
7.1.17 Postmarketing Experience 26
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 26
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 26
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 30
7.2.3 Adequacy of Overall Clinical Experience 30
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 30
7.2.5 Adequacy of Routine Clinical Testing 30
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 30
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 31
7.2.8 Assessment of Quality and Completeness of Data 31
7.2.9 Additional Submissions, Including Safety Update 31
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 31

8 ADDITIONAL CLINICAL ISSUES 32

8.1 DOSING REGIMEN AND ADMINISTRATION 32
8.2 DRUG-DRUG INTERACTIONS 32
8.3 SPECIAL POPULATIONS 32
8.4 PEDIATRICS 33
8.5 ADVISORY COMMITTEE MEETING 33
8.6 LITERATURE REVIEW 33
8.7 POSTMARKETING RISK MANAGEMENT PLAN 33

9 OVERALL ASSESSMENT 33

9.1 CONCLUSIONS 33
9.2 RECOMMENDATION ON REGULATORY ACTION 34
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 34
9.3.1 Risk Management Activity 34
9.3.2 Required Phase 4 Commitments 34
9.4 LABELING REVIEW 34
9.5 COMMENTS TO APPLICANT 35

10 APPENDICES 36

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 36
10.1.1 Study 2301 36
10.1.2 Study 2302 40
10.1.3 Study US08 44
10.2 LINE-BY-LINE LABELING REVIEW 47
10.3 SUPPORTING TABLES 49

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that this NDA receive an approvable action. The sponsor has been able to establish efficacy in one study in the pediatric population and one study in the adult population for the treatment of ADHD. The safety profile, as presented thus far, resembles other currently marketed stimulant mediations that are also used to treat ADHD.

Missing from the data submitted with this NDA are z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean) for the pediatric patients; this does not allow for an accurate assessment of difficulties with growth with the use of Focalin XR. Also missing from the submitted data are the details of QT and QTc intervals on the ECGs in the adult patients studied.

It is recommended that the sponsor supply the data omitted in this NDA submission (discussed above) to allow a more accurate labeling of this medication.

It is concerning that the sponsor did not conduct any studies longer than 7 weeks in the pediatric population; especially in light of the fact that ADHD is a disorder that is commonly treated with medication for many years. It is also disappointing that the sponsor only exposed seven adolescents to Focalin XR thus far in the drug's development. Also of concern is that the sponsor has not conducted any post-baseline ECGs in the pediatric population.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

For all stimulant drug products there have been concerns regarding the paucity of long term safety data, especially in light of the fact that these drugs may be used for years in children and adults. There has been concern and discussion within the Office of Drug Safety to have better safety monitoring and testing for the long term effects of stimulants on cardiovascular (i.e. hypertension, myocardial infarction, arrhythmia, cardiomyopathy, and sudden death), cerebrovascular (stroke), cancer (hepatoblastoma), and neuropsychiatric (psychosis, hallucinations, seizures) events.

1.2.2 Phase 4 Commitments

It is recommended that the sponsor study the safety and efficacy of Focalin XR in the adolescent population. This NDA contains data from only 7 patients in this age group. It is noted that the study that included these subjects was not powered to detect efficacy in this population;

however, the efficacy results did not appear statistically significant in the same sample studied. It is also noted that for the immediate release Focalin (NDA 21278), there was the same difficulty of efficacy not being established in the adolescent population of 39 patients; that sample was also too small, and that study also was not powered to make any conclusions regarding efficacy in the adolescent population.

It is also recommended that the sponsor conduct ECGs in the pediatric population as there were no post-baseline ECGs conducted. There also were no ECGs conducted in any population for the original NDA for Focalin immediate release.

Lastly, (but, perhaps the most important concern), the sponsor did not conduct any studies longer than 7 weeks in the pediatric population; this is a serious deficiency in light of the fact that ADHD is a disorder that is commonly treated with medication for many years. It is recommended that the sponsor conduct long term studies in the pediatric population (at least 1 year) to obtain an adequate safety profile.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Focalin ™ XR is a long acting formulation of dextro-methlyphenidate which has been marketed as Focalin ™ since 2001. Focalin XR utilizes a time released mechanism referred to as SODAS ™ (Spheroidal Oral Drug Absorption System), a similar technology as used in Ritalin LA extended release capsules (marketed since 2002).

This application for Focalin XR proposes to support the efficacy and safety in both the pediatric and adult ADHD population. The pivotal efficacy studies include one study in the pediatric population (2301) and one in the adult population (2302) . In addition to the pivotal studies, the sponsor submitted another short term pediatric study (US08), and a longer term adult study (2302E).

In the 7 week pediatric study 2301, there were 103 patients enrolled of which 53 were exposed to Focalin XR (dosing 5-30 mg). In the pediatric study 2301, the mean exposure to study drug was 47.1 days (range of 12-56 days) for the Focalin XR group and 43.1 days (range of 4-58 days) for the placebo group. There were 36 patients (of 53 or 67.9%) with an exposure of at least 49 days in the Focalin XR group. In the adult safety data base (including both studies 2302 and 2302E), there were 204 patient exposed to Focalin LA of which 101 adult patients were exposed for ≥ 6 months.

1.3.2 Efficacy

The sponsor conducted two pivotal placebo controlled studies to support the efficacy of Focalin XR for the treatment in ADHD in both the pediatric and adult population, namely Studies 2301 and 2302.

Study 2301 is a 7 week, multi-center, randomized, double-blind, placebo controlled study in 103 children and adolescents diagnosed with ADHD. The primary efficacy endpoint is the change from baseline to endpoint of the Conners ADHD/DSM-IV Scales for teachers (CADS-T). The study utilizes a flexible dosing schedule (5, 10, 20, or 30 mg/day) based on efficacy and tolerability. The results of this study demonstrate a statistically significant result ($p<0.001$) using the CADS-T DSM-IV total subscale score; the mean changes from baseline to final visit were 16.3 for Focalin XR group compared to 5.7 for the placebo group. However, when a subgroup analysis for age is performed, a statistically significant result is observed for children aged 6-12 ($p<.001$), but not for the adolescent patients aged 13 to 17 ($p=0.361$). It is difficult to make firm conclusions regarding the efficacy data in adolescents, because there were only 7 adolescents in this study exposed to Focalin XR, an insufficient number to assess the effectiveness of this drug in the treatment for ADHD.

Study 2302 is a 5 week, multi-center, randomized, double-blind, placebo controlled study in 221 adults diagnosed with ADHD. The primary efficacy endpoint is the change from baseline to endpoint of the DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS). This is a fixed dose study with dosing groups of Focalin XR 20, 30, and 40 mg. The sponsor demonstrates a statistically significant difference when comparing the change from baseline scores in the DSM-IV ADHD RS total score for all Focalin XR treatment groups with placebo (Focalin XR 20 mg: $p=0.006$; Focalin XR 30 mg: $p=0.012$; Focalin XR 40 mg: $p<0.001$). The sponsor designated the primary efficacy variables to be only the 30 and 40 mg groups, but all Focalin XR groups (Focalin XR 20, 30 and 40 mg) are shown to be efficacious as compared to placebo.

1.3.3 Safety

In their safety analysis, the sponsor identifies the two distinct populations of pediatrics and of adults. For the pediatric population, the sponsor focused primarily on the pivotal study 2301 (7 week pediatric placebo controlled study with n=53 on study drug), and did not combine the safety analyses for Study 2301 and Study US08 (a 2 week pediatric, cross-over study with only 6 days on study drug). A major concern for the drug development program for Focalin XR thus far is that there were only 7 adolescents exposed to Focalin XR, and there are no longer term studies in the pediatric population; the safety data base for the pediatric population is based solely on a maximum exposure time of 49 days. Also of note is that no post-baseline ECGs have been performed in the pediatric population.

To support safety claims for the adult population, the sponsor focuses on the pivotal Study 2302 (5 week placebo controlled adult study) and the combined data from Study 2302 and 2302E (24 week extension study of 2302). In the pooled safety data base including Studies 2302 and 2302E, there are 204 adult patients exposed to Focalin XR; the mean duration of exposure for the adult safety data base was 4.8 months (range: 9.0 months to 0.1 months). There are 101 adult patients exposed to Focalin XR for $\geq$ 6 months.

In both the pediatric and adult population, there is evidence that Focalin XR increases the mean change from baseline of sitting pulse, and of sitting diastolic and systolic blood pressure. Orthostatic changes were not assessed in the studies submitted.

It is difficult to determine the true effect that Focalin XR had on growth in the pediatric population, because the sponsor did not assess this data in terms of z-scores scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean), and there were no longer term extension studies. The sponsor reports that a decrease of $\geq$ 7% body weight was observed in 6 (of 47) pediatric patients treated with Focalin XR (range 1.9 to 5.4 kg) and no placebo patients. For the adult population, the sponsor reports that "clinically notable" weight loss was reported in 6 adult patients treated with Focalin XR (range 5.7 to 9.6 kg) and one placebo patient (21.4 kg).

It is not possible to ascertain the QT and QTc intervals in the adult population tested as the sponsor has not provided this data in this submission. There were no post-baseline ECGs conducted in the pediatric population.

1.3.4 Dosing Regimen and Administration

The pediatric, placebo-controlled study 2301 utilizes a flexible dosing of Focalin XR 5-30 mg/day with a mean final dose of 24 mg/day. The majority of patients were maintained on doses of 20 mg/day or 30 mg/day. The sponsor proposes a starting dose for pediatric patients of 5 mg/day with a recommended maximum dose of Focalin XR [redacted] mg/day. This proposal is consistent with the findings from the clinical trial.

The adult placebo-controlled study 2302 is a fixed dose study with dose groups including Focalin XR 20 mg/day, 30 mg/day, and 40 mg/day. The results of the study show a statistically significant difference when comparing all Focalin XR groups to placebo. It is noted that the primary efficacy variable focused on the Focalin 30 mg/day and 40 mg/day groups. The sponsor proposes a starting dose for adult patient of 10 mg/day up to a maximum of [redacted] mg/day. This proposal is consistent with the findings from the clinical trial.

1.3.5 Drug-Drug Interactions

There were no drug-drug interactions studies reviewed for this NDA.

1.3.6 Special Populations

There were no special populations studies reviewed for this NDA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Focalin ™ XR is the extended release formulation of dextro-methylphenidate (marketed as Focalin ™), which is thought to be the active enatiomer of methylphenidate. Focalin immediate release, marketed since 2001, is a Category II stimulant drug labeled for the indication of ADHD, and had been tested in the pediatric population only. The proposed indication for Focalin XR is for the treatment of ADHD in the pediatric and adult population. The proposal is for Focalin XR to be administered once daily in the morning at recommended maximum doses of [redacted] mg in the pediatric population, and [redacted] mg in the adult population.

2.2 Currently Available Treatment for Indications

Psychostimulants have been used with increasing frequency in the treatment of Attention Deficit/Hyperactivity Disorders (ADHD) over the past thirty years. Various formulations are currently marketed for the indication of ADHD using the following four basic compounds: methylphenidate (e.g. Ritalin, Ritalin SR, Metadate ER, Concerta), dextromethylphenidate (Focalin), dextroamphetamine (e.g. Dexedrine, Adderall), and pemoline. Pemoline is a Category IV controlled substance (note: the originator drug for pemoline, Cylert, has recently been withdrawn from the market), while the methylphenidate and the dextroamphetamine derivatives are a Category II controlled substance. More recently, atomoxetine, a norepinephrine reuptake inhibitor, has been marketed and labeled as a non-stimulant ADHD drug and is not scheduled as a controlled substance.

The following are marketed extended release forms of stimulants to treat ADHD: Ritalin LA, Ritalin SR, Concerta Extended Release, Adderall XR, Metadate CD, and Metadate ER. Atomoxetine is also labeled for once a day dosing.

The proposed form of Focalin XR utilizes the SODAS ™ (Spheroidal Oral Drug Absorption System) technology similar to the one used for Ritalin LA extended release capsules.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for Focalin XR is d-methylphenidate which is currently marketed as the immediate release form of Focalin ™. Focalin ™ was marketed in 2001.

2.4 Important Issues With Pharmacologically Related Products

Stimulant medications are known to increase blood pressure and heart rate. There has been concern that these effects may have long term repercussions of other cardiovascular and cerebrovascular events. Recently, there have been concerns regarding chromosomal aberrations in children exposed to methylphenidate, as well as animal studies correlating hepatoblastomas with methylphenidate use.

2.5 Presubmission Regulatory Activity

The immediate release form of Focalin was approved for marketing in November 2001. A Pre-IND meeting (IND 63,885) was held May 2, 2002 during which it was agreed that the sponsor would not be required to do additional preclinical work, and the sponsor was encouraged to do a fixed dose study in the pediatric population; it was agreed that the a single study in adults would be sufficient for an adult ADHD claim. A pre-NDA meeting was held on November 13, 2003 during which format and statistical issues were discussed; it was also discussed that a pediatric written request would not be issued for this NDA.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The Chemistry review recommends approval of this NDA from the CMC perspective. Based on the stability data, it is recommended that an 18 month expiry be granted for Focalin XR capsules.

For further detail of FDA Chemistry Review, please refer to Review of Chemistry, Manufactory, and Controls by Chhagan G. Tele, Ph.D (4/15/05).

3.2 Animal Pharmacology/Toxicology

No animal studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical 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.

4.2 Table of Clinical Studies

The following sponsor table summarizes the studies submitted for review in this submission:

Table 4.2 Summary of Clinical Trials for Focalin XR (adapted from Sponsor Table 1-1 in Section 2.7.4 Summary of Clinical Safety)

Study No.	Study Objective, Population	Patients	Treatment Duration	Medication dose/day	Type of Control
Controlled efficacy trials					
[2301]	efficacy/safety study in pediatric population, 6-17 years of age	Planned:100 Randomized: 103	7 weeks	5-30 mg Focalin LA Flexible dosing	Placebo
[US08]	duration of effect in pediatric population, 6-12 years of age	Planned: 54 Randomized: 54	2 weeks	Focalin LA 20 mg	Placebo
[2302]	efficacy/safety study in adult population	Planned: 220 Randomized: 221	5 weeks	Starting dose:10 mg Focalin LA Maintenance dose: 20, 30 or 40 mg/day Focalin LA	Placebo
Extension studies					
[2302E1]	long-term efficacy/safety in Adult population	Planned: 165 Entered:170	24 weeks	Starting dose:10 mg Focalin LA Maintenance dose: 20, 30 or 40 mg/day Focalin LA	None

4.3 Review Strategy

For the purpose of evaluating efficacy, there were two placebo controlled studies reviewed, one 7 week study in the pediatric population (Study 2301), and one 5 week study in the adult population (2302). For additional safety data the sponsor included pediatric study US08 (a two week placebo controlled study) and the six month extension study in adults (2302E). No longer-term extension studies conducted in the pediatric population were submitted for review.

4.4 Data Quality and Integrity

There were four sites inspected by FDA Division of Scientific Investigations. It was concluded that there was sufficient documentation to assure that all audited patients existed, all patients received the assigned study medication, and that primary efficacy endpoints followed the specified protocol. It was also concluded that that all enrolled patients at the audited centers fulfilled the eligibility criteria, and that no underreporting of adverse events were noted. All sites audited were considered acceptable to support this NDA. Details of some concern included reasons for withdrawal in which one patient (#00012 of Protocol 2302) was non-compliant but was listed as "withdrew consent" and another patient (#00016 of Protocol 2302) experienced multiple adverse events (racing thoughts, paranoia, irritability, nervous and jittery, etc) was listed as "withdrew consent." Please see DSI report (3/24/05) for further details.

4.5 Compliance with Good Clinical Practices

Please see the DSI report (3/24/05) regarding details of findings; none of which are thought to have compromised the integrity of the data submitted.

4.6 Financial Disclosures

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Vice President of Neuroscience 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 (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The sponsor submitted in their summary of financial disclosures that Dr. [redacted] received "> $25,000" as an "honoraria (total compensation)." The site where Dr. [redacted] participated was investigated for data integrity by DSI, and no significant findings were discovered that would significantly alter efficacy findings for this NDA.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Focalin XR is readily absorbed with the peak plasma concentration achieved in the fasted stated at 1 -1 ½ hours post-dosing. Given the OROS mechanism, there is a bi-modal plasma concentration with two distinct peaks four hours apart (based on studies in healthy adults) with a lower second Cmax. The sponsor describes the pharmacokinetics of Focalin XR as similar to 2 tablets of Focalin immediate release dosed 4 hours apart, with a larger individual tmax range with Focalin XR, and less peak and trough fluctuations with the Focalin XR formulation.

Please refer to the biopharmaceutic review for further details (unavailable at the time of this review).

5.2 Pharmacodynamics

The sponsor states that there were no pharmacodynamic measurements performed in the three Clinical Pharmacology studies submitted with Focalin XR.

For Focalin immediate release there were dose-related anorectic effects observed; 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 suggested that appetite suppression is directly correlated with increasing dose.

D-MPH immediate release was also 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.

For further detail, please refer to the Biopharmaceutics review for this NDA (not available at the time of this review).

5.3 Exposure-Response Relationships

See Section 5.2 above for discussion.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication for this NDA is Attention Deficit and Hyperactivity Disorder (ADHD). This is a disorder that has been traditionally studied and diagnosed primarily in children, but more recently, has been recognized in the adult population (with requirements that symptoms first occurred prior to age 7). As stated in the labeling, ADHD as defined in DSM-IV, implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

6.1.1 Methods

For the purposes of efficacy, the pivotal studies reviewed were **Study 2301** (7 week placebo controlled study in **pediatric** patients diagnosed with ADHD) and **Study 2302** (5 week placebo

controlled study in **adults** with ADHD. The sponsor also submitted Study US08 (a placebo controlled two week cross over study in pediatric patients). Study US08 was not considered a pivotal study by the sponsor and the only dose tested was Focalin XR 20 mg; for these reasons, US08 did not obtain an FDA statistics review and is not discussed in this efficacy section (Note: for completion, the Appendix 10.1.3 of this review describes Study US 08, but the statistical results discussed are from the sponsor's submission and have not been confirmed by FDA statisticians).

6.1.2 General Discussion of Endpoints

For the pivotal **pediatric** study, Study 2301, the primary efficacy variable is the change from baseline to endpoint of the Conners ADHD/DSM-IV Scales for teachers (CADS-T). Based on the diagnostic criteria of ADHD according to the DSM-IV, this scale includes the ADHD Index (12 items) and DSM-IV total subscale (18 items). The Subscale is divided into DSM-IV Inattentive Subscale (9 items) and the DSM-IV Hyperactive-Impulsive subscale (9 items). Although not validated for sensitivity to drug effects, this scale is widely used to assess improvement in ADHD symptoms in the pediatric population.

For purposes of efficacy in the pediatric population, it is very relevant for the teacher to be scoring the primary efficacy variable, because it is during the school hours that children diagnosed with ADHD appear to suffer in a manner that does not allow them to remain in their current schooling situation.

For the pivotal **adult** study, Study 2302, the primary efficacy variable is the change from baseline to endpoint of the DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS). The DSM IV ADHD RS directly reflects the DSM-IV checklist by using an 18 item symptom scoring. This is a clinician recoded instrument based on patient reports of the past week. The following summary scores can be derived: Inattention sub-score, Hyperactivity/Impulsivity sub-score, and a total score. This instrument was originally designed for the pediatric population, but the sponsor modified wording to be better suited to assessing adult symptomatology.

6.1.3 Study Design

Study 2301 is a 7 week randomized, multi-center, placebo controlled study conducted in 103 **pediatric** patients (ages 6-17 y.o.) diagnosed with ADHD. Patients were dosed according to a flexible dosing schedules (5, 10, 20 or 30 mg/day) allowing for up to 5 weeks to be titrated to an optimal dose (in increments of 5 mg/day/week for Weeks 1-4 and increments of 5 or 10 mg/day for Week 5). Following the titration period, patients were required to have at least a two week maintenance period of the optimal dose. Doses were administered each morning.

Although it is optimal for pivotal studies to be fixed dose (as discussed with the sponsor in the pre-IND meeting of May 2, 2002), the sponsor rationalizes that a flexible dosing is more

indicative of how patients are dosed in clinical practice. A flexible dose design limits the amount of tolerability data provided, as well as skews any dose response data.

Another limitation to this pediatric design is that patients are required to be at their optimal dose for only 2 weeks; however, the current thinking is that this should be a sufficient enough time to observe ADHD efficacy results using a stimulant medication.

Study 2302 is a multi-centered, placebo controlled, 5 week, randomized, double blind, fixed dose study in 295 **adult** patients aged 18-60. At baseline, patients were randomized to one of four groups: Focalin XR [20 mg, 30 mg, or 40 mg] or placebo. Dosing was titrated in increments of 10 mg/week, so that by Week 4, all patients were taking their assigned dosing. Doses were administered each morning.

Although this is the first stimulant to be labeled for adult use, the sponsor was only required to do one pivotal study (not two) as agreed in the pre-IND meeting of May 2, 2002.

6.1.4 Efficacy Findings

6.1.4.1 Pediatric Study 2301 (For more detail, please refer to FDA Statistical Review by Yeh-Fong Chen, Ph.D. and Appendix 10.1.1 of this review)

A total of 85 (of 103) patients completed the study (Focalin XR: n=48; placebo: n=37). The discontinuation rate is higher in placebo group (26%) compared to the Focalin XR group (9.4%); the placebo group has a higher rate of "lost to follow-up" (placebo: 12%, Focalin XR: 3.8%), and "unsatisfactory therapeutic effect (placebo: 8%, Focalin XR: 3.8%). It is noted that there were no patients in the Focalin group who discontinued due to an adverse event (Please see Appendix 10.1.1 for a detailed review of 2301).

The majority of the patients in this study are Caucasian males with a mean age of 10.0 years old (range of 6.0 to 17.0). The population consists of 66 males (64.1%) and 22 females (41.5%) of which there were 62 (60.2%) Caucasians, 24 (23.3%) African-Americans, 17 (16.5 %) categorized by the sponsor as "Other." Although there do not appear to be any statistically significant differences in demographics between treatment groups at baseline, there is a clear majority of males in the placebo group (70% male vs. 30 % female) compared to the treatment group (58.5 % males vs. 41.5 % female).

There are two subgroups identified: 1) 90 **children** aged 6-12 y.o. (88% completed), of which 45 patients were randomized to Focalin XR treatment and 2) 17 **adolescents**, aged >12-<18 y.o. (76% completed) of which only 7 patients were randomized to Focalin XR treatment.

The mean final dose is Focalin XR 24 mg/day. As can be seen from the table below (Table 6.1.4.1a), the majority of patients were maintained on doses of 20 mg/day (28.8%) or 30 mg/day (53.8%).

Table 6.1.4.1a Level of final Dose by Treatment Groups for Intent to Treat Population
(Table excerpt from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

Level of Final Dose	Focalin LA N=52 n (%)
5 mg/day	1 (1.9)
10 mg/day	3 (5.8)
15 mg/day	5 (9.6)
20 mg/day	15 (28.8)
30 mg/day	28 (53.8)
Mean (SD)	24.0 (7.14)

The sponsor demonstrated a statistically significant result ($p<0.001$) using the CADS-T DSM-IV total subscale score; the mean changes from baseline to final visit were 16.3 for Focalin XR group compared to 5.7 for the placebo group. These results were confirmed by Dr. Chen's statistical review.

From the table below (Table 6.1.4.1b), it can be seen that a statistically significant result is observed for children aged 6-12 ($p<.001$), but not for the adolescent patients aged 13 to 17 ($p=0.361$). Although the data for adolescents does not demonstrate a statistical significance, the numerical trend of change from baseline does demonstrate a greater improvement for Focalin XR compared to placebo (mean change of 9.6 vs. 3.3, respectively). It is also noted that these results are based on a very small population (n=7 adolescents exposed to Focalin XR), and that this study is not powered to detect a difference in this subgroup population.

From her statistical review, Dr. Chen concluded that both male and female patients showed a statistically significant treatment effect in favor of Focalin XR.

Table 6.1.4.1b Analysis of Change from Baseline in the CADS-T Total Subscale Score from Age Subgroups for Study 2301
(Table from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

Age: 6-12 years		Focalin LA N = 45	Placebo N = 35
Baseline (Visit 2)	Mean (SD)	34.0 (9.04)	35.0 (9.15)
Final Visit (Visit 9)	Mean (SD)	17.1 (12.74)	28.5 (14.84)
Change from Baseline*	Mean (SD)	16.9 (15.97)	6.5 (13.03)
	Adjusted Mean Change	17.5	6
	P-Value	<0.001	
Age: >12 - <18 years		Focalin LA N = 7	Placebo N = 10
Baseline (Visit 2)	Mean (SD)	29.0 (9.57)	34.4 (13.23)
Final Visit (Visit 9)	Mean (SD)	19.7 (10.73)	30.7 (18.92)
Change from Baseline*	Mean (SD)	9.3 (9.12)	3.7 (14.15)
	Adjusted Mean Change	9.6	3.3
	P-Value	0.361	

6.1.4.2 Adult Study 2302 (For more detail, please refer to FDA Statistical Review by Yeh-Fong Chen, Ph.D. and Appendix 10.1.2 of this review)

A total of 184 (of 221) patients completed the study (Focalin XR: n=141 or 83.9%; placebo: n=43 or 81.1%). Adverse events are the most common reason for discontinuation (Focalin XR: n=10.7%, placebo: 7.5%). As pointed out by Dr. Chen, the Focalin XR 30 mg group has a higher rate of discontinuation for adverse event (12.7%) and withdrawal of consent (3.6%), compared to the 20 mg (12.7%, 0) and 40 mg (9.1%, 0) groups. No Focalin XR patient discontinued due to unsatisfactory results.

The majority of the patients in this study are Caucasian males with a mean age of 38.7 years old (range of 18 to 62). The population consisted of 127 males (57.5%) and 94 females (42.5%) of which there were 189 (85.5%) Caucasians, 10 (4.5%) African-Americans, 7 (3.2 %) "Oriental," and 15 (6.8%) categorized by the sponsor as "Other." FDA statistician Dr. Chen states that the Focalin XR 20 mg group had a statistically significantly higher proportion of Caucasians (100%) compared to Focalin XR 30 mg, 40 mg and placebo groups (87.3%, 68.2% and 75.5%, respectively); otherwise, there does not appear to be any statistically significant differences in demographics between treatment groups at baseline.

The sponsor demonstrates a statistically significant difference when comparing the change from baseline scores in the DSM-IV ADHD RS total score of all Focalin XR treatment groups with placebo (Focalin XR 20 mg: p=0.006; Focalin XR 30 mg: p=0.012; Focalin XR 40 mg: p<0.001). Dr. Chen confirmed these results, and points out that the sponsor's primary efficacy variable was based on only the comparison of the Focalin XR 30 and 40 mg groups to placebo.
Table 6.1.4.2 Change from baseline in the DSM-IV ADHD RS Total Score by Treatment/LOCF (ITT Population for Study 2302)

(Table from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

		Focalin LA 20 mg (N=57)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=54)	Placebo (N=53)
Visit 2 (Baseline)	Mean	36.8	36.9	36.9	37.5
	SD	7.20	8.07	8.25	7.82
Final DB Visit	Mean	23.1	23.5	20.0	29.6
	SD	11.65	11.80	11.50	13.58
Change from Baseline	Mean	13.7	13.4	16.9	7.9
	SD	10.69	10.81	13.34	11.20
Adjusted Mean Change		13.3	12.9	16.5	7.6
P-Value		0.006	0.012	<0.001	

Dr. Chen was able to confirm that both males and females demonstrated a statistically significant treatment effect in favor of Focalin XR. Also, an analysis looking at age subgrouping of patients ≤ 40 years old and patients >40 to 60 years old demonstrated that both the younger and older patients showed statistically significant treatment effect in favor of Focalin XR.

6.1.5 Clinical Microbiology

There were no microbiology studies submitted with this NDA.

6.1.6 Efficacy Conclusions

Study 2301 demonstrates that Focalin XR is effective for the treatment of ADHD in the pediatric population. It is unclear from this study if efficacy has been demonstrated for the adolescent age group (13-17 y.o.).

Study 2302 demonstrates that Focalin XR is effective for the treatment of ADHD in the adult population (maximum age tested was 60 years old).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review is based primarily on the sponsor's Safety Summary and accompanying Study Reports submitted by the sponsor in 7/28/04.

For the pediatric population, the main focus of the review was on the pediatric study 2301, a 7 week placebo controlled study. The pediatric study US08 only offers safety data based on a maximum of 6 days of exposure to Focalin 20 mg/day; if significant events occurred, they are mentioned in this review. Otherwise, the pediatric safety data base discussed is based on Study 2301. It is noted that there was no extension study or longer term study in the pediatric

population submitted; therefore, the safety data base for the pediatric population is based solely on a maximum exposure time of 49 days.

For the adult population, the safety data base used in this review includes a pooling of studies **2302**, a 5 week placebo controlled study, and the extension study **2302E** (29 week open label) for Phase II/III integrated safety data base.

7.1.1 Deaths

There are no deaths reported in this current submission.

7.1.2 Other Serious Adverse Events

In the pediatric population, there are no serious adverse events identified.

In the adult population, there are 5 serious adverse events identified in 4 patients (Pt 0513/00008 had a serious event in both studies 2302 and 2302E1); it is interesting to note that most of these events are gastrointestinal events. Only one of the adult patients discontinued the drug due to the serious event (Patient 0506/00004 for a cecal vovulus); all other patients temporarily interrupted treatment. Please see Table 7.1.2 below for details.

Table 7.1.2 Summary of nonfatal serious adverse events occurring in adult patients taking Focalin XR.

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
0504/00004	31/M	10	6	Ulcerative Colitis (h/o colitis) Hypovolemic shock
0513/00008	22/M	10	6	High Fever Loss of Consciousness Treated with antibiotic with resolution.
0513/00008	22/M	30	197	Perirectal abscess
0506/00004	43/F	30	56	Cecal volvulus
0516/00002	53/F	40	44	Diverticulitis

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts and associated adverse events

In the pediatric population safety data base, no patients discontinued due to an adverse event while being treated with the study drug. There were two patients who discontinued while randomized to a placebo group: 1) Patient 503/00011 (Study 2301) discontinued due to restlessness seven days after randomization, and 2) Patient 002/005 discontinued due to nausea attributed to viral illness seven days after randomization.

In the adult population safety data base, of the 204 patients exposed to Focalin XR, 43 (or 21.1%) patients withdrew prior to completing the study because of an adverse event. The most common reasons for withdrawal were "feeling jittery" (3.4%), insomnia (2.9%), and anxiety (2.5%) as can be seen in the sponsor's table below.

Table 7.1.3.1
Summary of Dropouts for the adult population safety data base with more that one incident*
(adapted from sponsor's safety summary)

	Focalin LA ≤ 20 mg n (%)	Focalin LA > 20-30 mg n (%)	Focalin LA > 30 mg n (%)	All Focalin LA n (%)
Patients studied				
Total no. studied	58 (100)	89 (100)	57 (100)	204 (100)
No. of patients discontinued due to AE	30 (51.7)	13 (14.6)	0 (0.0)	43 (21.1)
Preferred term				
Feeling jittery	6 (10.3)	1 (1.1)	0 (0.0)	7 (3.4)
Insomnia	6 (10.3)	0 (0.0)	0 (0.0)	6 (2.9)
Anxiety	4 (6.9)	1 (1.1)	0 (0.0)	5 (2.5)
Anorexia	1 (1.7)	2 (2.2)	0 (0.0)	3 (1.5)
Depression	3 (5.2)	0 (0.0)	0 (0.0)	3 (1.5)
Psychomotor hyperactivity	2 (3.4)	1 (1.1)	0 (0.0)	3 (1.5)
Fatigue	1 (1.7)	1 (1.1)	0 (0.0)	2 (1.0)
Gastrointestinal upset	1 (1.7)	1 (1.1)	0 (0.0)	2 (1.0)
Headache	2 (3.4)	0 (0.0)	0 (0.0)	2 (1.0)
Nausea	1 (1.7)	1 (1.1)	0 (0.0)	2 (1.0)
Palpitations	1 (1.7)	1 (1.1)	0 (0.0)	2 (1.0)
Panic attack	2 (3.4)	0 (0.0)	0 (0.0)	2 (1.0)
Restlessness	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.0)

(*in addition to the above list, one incident occurred for the following adverse events in Study 2302: abdominal pain, aggression, bronchitis, bruxism, CNS nervous system stimulation, diarrhea, dyspepsia, palpitations, pruritus and sedation.)

It would appear that the withdrawal rate is higher in the adult population, but it must also be kept in mind that the adult population had a larger patient exposure for a longer period of time. It could also be observed that the majority of events associated with withdrawal in adults occurred at doses ≤ 20 mg Focalin XR. The sponsor offers the explanation that these events occurred during the titration phase; however, the majority of these events occurred during the extension study 2302E. It is unclear how many of these patients were randomized to placebo in the study 2302, preceding the extension study.

7.1.4 Other Search Strategies

There were no other search strategies utilized in this review.

7.1.5 Common Adverse Events

In the pediatric study 2301, 53 patients were given the study drug, 40 (75.5%) patients experienced at least one treatment-emergent adverse event. The most common adverse events reported for the Focalin XR pediatric safety data base occurring in ≥ 5% and twice the incidence in the placebo group are the following: decrease appetite (30.2%) [note: 3 patients had accompanied clinically significant weight loss], headache (24.5%), nausea (11.3%), dyspepsia (7.5%), and anxiety (5.7); abdominal pain was observed in 10 of 53(18.9%) compared to 12.8% of the placebo group. The incidents of adverse events ≥ 5% are listed in the sponsor's table below.

Table 7.1.5.1 Incidents of adverse events in ≥ 5% pediatric patients in Study 2301 (adapted from sponsor's table)

	Focalin LA N=53	**Placebo N=47**
Total no. of patients with AEs	40 (75.5)	27 (57.4)
Adverse events		
Decreased appetite	16 (30.2)	4 (8.5)
Headache	13 (24.5)	5 (10.6)
Abdominal pain upper	7 (13.2)	6 (12.8)
Nausea	6 (11.3)	3 (6.4)
Nasopharyngitis	5 (9.4)	3 (6.4)
Upper respiratory tract infection	5 (9.4)	3 (6.4)
Dyspepsia	4 (7.5)	2 (4.3)
Insomnia	4 (7.5)	3 (6.4)
Abdominal pain	3 (5.7)	0 (0.0)
Anxiety	3 (5.7)	0 (0.0)
Cough	3 (5.7)	3 (6.4)
Initial insomnia	3 (5.7)	2 (4.3)
Influenza	2 (3.8)	4 (8.5)

For Study 2302 (adult population), the most common adverse events are headache (31.5%), decreased appetite (18%), insomnia (16%), dry mouth (16%), "feeling jittery" (12%), anxiety (9%), dyspepsia (8%), irritability (7%), dizziness (6%), and nausea (6%). Please refer to Table 7.1.5.2 for further details.

Table 7.1.5.2 Treatment-Emergent Adverse Events Occurring During Double-Blind Study 2302 in adults (adapted from sponsor's table)

	Focalin LA 20 mg N=57 n (%)	Focalin LA 30 mg N=54 n (%)	Focalin LA 40 mg N=54 n (%)	Focalin LA 30&40 mg N=108 n (%)	All Focalin LA N=165 n (%)	Placebo N=53 n (%)
n (%) of patients with AEs (total)	48 (84.2)	51 (94.4)	46 (85.2)	97 (89.8)	145 (87.9)	36 (67.9)
Adverse events						
Headache	15 (26.3)	16 (29.6)	21 (38.9)	37 (34.3)	52 (31.5)	10 (18.9)
Decreased appetite	11 (19.3)	9 (16.7)	10 (18.5)	19 (17.6)	30 (18.2)	6 (11.3)
Insomnia	10 (17.5)	7 (13.0)	10 (18.5)	17 (15.7)	27 (16.4)	6 (11.3)
Dry mouth	4 (7.0)	11 (20.4)	11 (20.4)	22 (20.4)	26 (15.8)	2 (3.8)
Feeling jittery	5 (8.8)	10 (18.5)	5 (9.3)	15 (13.9)	20 (12.1)	1 (1.9)
Anxiety	3 (5.3)	6 (11.1)	6 (11.1)	12 (11.1)	15 (9.1)	1 (1.9)
Dyspepsia	3 (5.3)	5 (9.3)	5 (9.3)	10 (9.3)	13 (7.9)	1 (1.9)
Irritability	3 (5.3)	5 (9.3)	4 (7.4)	9 (8.3)	12 (7.3)	3 (5.7)
Dizziness	5 (8.8)	2 (3.7)	3 (5.6)	5 (4.6)	10 (6.1)	1 (1.9)
Nausea	6 (10.5)	1 (1.9)	3 (5.6)	4 (3.7)	10 (6.1)	2 (3.8)
Anorexia	3 (5.3)	2 (3.7)	3 (5.6)	5 (4.6)	8 (4.8)	2 (3.8)
Fatigue	2 (3.5)	1 (1.9)	5 (9.3)	6 (5.6)	8 (4.8)	6 (11.3)
Pharyngolaryngeal pain	2 (3.5)	2 (3.7)	4 (7.4)	6 (5.6)	8 (4.8)	1 (1.9)
Hyperhidrosis	0 (0.0)	5 (9.3)	2 (3.7)	7 (6.5)	7 (4.2)	0 (0.0)
Nasopharyngitis	3 (5.3)	0 (0.0)	4 (7.4)	4 (3.7)	7 (4.2)	0 (0.0)
Initial insomnia	3 (5.3)	3 (5.6)	0 (0.0)	3 (2.8)	6 (3.6)	1 (1.9)
Agitation	3 (5.3)	1 (1.9)	1 (1.9)	2 (1.9)	5 (3.0)	0 (0.0)
Tremor	3 (5.3)	1 (1.9)	1 (1.9)	2 (1.9)	5 (3.0)	0 (0.0)
Heart rate increased	3 (5.3)	1 (1.9)	0 (0.0)	1 (0.9)	4 (2.4)	0 (0.0)
Palpitations	0 (0.0)	3 (5.6)	1 (1.9)	4 (3.7)	4 (2.4)	0 (0.0)
Somnolence	0 (0.0)	3 (5.6)	1 (1.9)	4 (3.7)	4 (2.4)	0 (0.0)
Constipation	1 (1.8)	1 (1.9)	1 (1.9)	2 (1.9)	3 (1.8)	3 (5.7)
Rash	0 (0.0)	3 (5.6)	0 (0.0)	3 (2.8)	3 (1.8)	0 (0.0)
Upper respiratory tract infection	1 (1.8)	1 (1.9)	1 (1.9)	2 (1.9)	3 (1.8)	3 (5.7)
Depression	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.9)	1 (0.6)	3 (5.7)

7.1.6 Less Common Adverse Events

Please refer to Tables 7.1.5.1 and 7.1.5.2 above, for a listing of less common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Post baseline laboratory values were collected from Studies 2301, US08, 2302 and 2302E; Studies 2301, US08 and 2302 all had a placebo arm allowing for a comparison base. The following laboratory values were assessed: **Biochemistry:** glucose, creatinine, BUN, total protein, AST, ALT, GGTP alkaline phosphatase, sodium, potassium, total bilirubin, uric acid, chloride, phosphate, albumin, and calcium. **Hematology:** hematocrit, hemoglobin, platelet count, MCV, RBC, WBC, absolute basophils, absolute eosinophils, absolute neutrophils, absolute monocytes and absolute lymphocytes **Urinalysis:** pH, specific gravity, WBC, RBC, protein and glucose. Laboratory values were obtained at baseline and repeated at the end of the study or termination.

For the purposes of the review of laboratory values, the mean, median, and standard deviation values of change from baseline were assessed.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The review of laboratory values will concentrate on clinical laboratory values collected from the placebo controlled Studies 2301, US08 and 2302; this allows for comparison to be made to the placebo group. Although it is difficult to eliminate the confounding variable of time period, outliers from the longer term study 2302E are mentioned for completeness.

7.1.7.3 Standard analyses and explorations of laboratory data

For the 7 week pediatric Study 2301, the only noted differences occurs for the lab values of alkaline phosphatase where the Focalin group has a greater mean decrease than the placebo group (-21.0 ± 38.3 vs. -7.4 ± 32.2). Otherwise, there were unremarkable changes observed for the mean, median and standard deviation when comparing the placebo and treatment groups. No patient was withdrawn because of an abnormal laboratory value.

For the 2 week pediatric cross-over Study US08, the placebo and treatment groups had comparable changes in mean, median, and standard deviation. No patient withdrew because of an abnormal laboratory value.

In the 5 week adult Study 2302, the mean, median and standard deviation when comparing placebo and the treatment groups was unremarkable. In the treatment group, there were 7 (or 5.6%) patients reported to have abnormal potassium levels (3 patients below normal and 4 patients above normal) compared to no changes in the placebo group; the sponsor did not mention any associated clinical symptoms with the potassium changes. One patient (0513/00008 on Focalin XR 40 mg) who experienced a high fever and loss of consciousness also had elevations of SGPT (124 U/L) and lymphocytes (62%). Otherwise, there were no significant differences observed between the treatment groups regarding percent of abnormal findings. No patient withdrew because of an abnormal laboratory value.

7.1.8 Vital Signs

Vital signs including sitting 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. Orthostatic changes were not measured.

In order to establish a comparator control, it is helpful to look in more depth at the pediatric Study 2301, and the adult Study 2302, which are both placebo controlled pivotal study. The sponsor did not provide weekly changes, so the following discussion is based on changes from baseline to termination/discontinuation. As can be seen from the Table 7.1.8.1 below, there was a greater increase in mean pulse rate, diastolic and systolic pressure in the Focalin XR treatment group compared to the placebo group; these findings are consistent with the increases observed in methylphenidate products.

For weight changes observed in pediatric study 2301, it appears from Table 7.1.8.1 that there was a decrease in mean weight for the Focalin XR treatment group compared to placebo; however, the extent of these changes is not readily apparent, because the sponsor did not perform z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean). The sponsor reported that a decrease of $\geq$ 7% body weight was reported in 6 (of 47) pediatric patients treated with Focalin XR (range 1.9 to 5.4 kg) and no placebo patients.

Table 7.1.8.1 Vital signs at sitting for **pediatric Study 2301**; Mean change from baseline

	Pulse (bpm)	Diastolic bp (mmHg)	Systolic bp (mmHg)	Weight (kg)
Focalin XR (n=53)	2.7 ± 9.5	1.8 ± 8.0	3.5 ± 11.4	-0.5 ± 1.4
Placebo (n=47)	1.3 ± 8.9	0.4 ± 7.4	-0.2 ± 7.5	0.4 ±1.3

In the placebo controlled **adult** Study 2302, there is a dose dependant increase for mean pulse and diastolic blood pressure in the Focalin XR group which was greater than mean placebo changes for all dose groups (see Table 7.1.8.2 below). The mean systolic pressure change for the 30 mg and 40 mg Focalin XR groups was greater than placebo. The mean change of weight loss was greater in all Focalin treatment groups compared to placebo where there was no weight loss observed. The sponsor reported that "clinically notable" weight loss was reported in 6 adult patients treated with Focalin XR (range 5.7 to 9.6 kg) and one placebo patient (21.4 kg).

Table 7.1.8.2 Vital signs at sitting for **adult Study 2302**; Mean change from baseline

	Pulse (bpm)	Diastolic bp (mmHg)	Systolic bp (mmHg)	Weight (kg)
Focalin XR 20 mg (n=57)	3.1 ± 11.1	-.02 ±8.2	-2.0 ± 10.7	-1.4 ± 2.0
Focalin XR 30 mg (n=54)	4.3 ± 11.7	1.2 ± 8.9	2.4± 11.8	-1.2 ±1.9
Focalin XR 40 mg (n=54)	6.0 ± 10.1	2.1 ± 8.0	-1.6 ± 11.7	-1.7 ± 2.3
Placebo (n=53)	-1.4 ± 9.3	0.3 ± 7.8	-1.7 ± 11.3	0

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

Post-baseline ECGs were performed in the adult population only. The pediatric study US08 had baseline ECGs performed only; there were no ECGs performed in the placebo controlled pediatric study 2301.

For the 5 week adult, placebo controlled study 2302, ECGs were administered at baseline and at termination or discontinuation; however, it is unclear when the ECGs were administered in relation to study drug administration. The sponsor reported that "no patients had clinically relevant abnormalities post-baseline." Table 7.1.9.1 summarizes the observed ECG abnormal changes from a normal baseline in Study 2302. The sponsor did not provide information regarding change from baseline of the QT or QTc interval.

Table 7.1.9.1 ECG abnormalities observed as changed from a normal baseline for adult Study 2302

Patient Number	**Age/Gender**	**ECG reading**
0512/00007	42/M	First degree AV block
0507/00006	43/M	First degree AV block
0507/00011	32/M	Flat T wave; U wave
0509/00003	39/F	Flat T wave
0509/00005	29/F	Ectopic Supraventricular rhythm
0517/00003	31/F	First degree AV block
0518/00006	32/F	First degree AV block

7.1.10 Immunogenicity

No immunogenicity studies were submitted in this application.

7.1.11 Human Carcinogenicity

No Carcinogenicity studies were submitted with this application. Methylphenidate has been shown to cause hepatoblastomas in mice.

7.1.12 Special Safety Studies

There are no special safety studies submitted with this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no studies on withdrawal phenomena and/or abuse potential submitted with this application. Focalin XR is a methylphenidate derivative, and all methylphenidate derivatives have been marketed as Schedule II drugs.

7.1.14 Human Reproduction and Pregnancy Data

There are no studies assessing the effects of Focalin XR on human reproduction and pregnancy. The immediate release form of Focalin has a Pregnancy Category C.

In the sponsor's safety update (11/23/05), there was one report of a 23 year old female [Patient #0518/00002] who became pregnant while taking Focalin XR 20 mg/day for approximately one and a half months at the beginning of her first trimester; according to the sponsor's report, the birth of her child was medically unremarkable and the child did not have evidence of any identifiable disorder.

7.1.15 Assessment of Effect on Growth

The sponsor did not assess the effects of growth using z-scores for the pediatric population in this submission. In the 7 week study in children, the sponsor reported that a decrease of $\geq 7\%$ body weight was reported in 6 (of 47) pediatric patients treated with Focalin XR (range 1.9 to 5.4 kg) and no placebo patients. The mean weight change observed in Study 2301 was a weight loss for the Focalin XR group (-0.5 ± 1.4 kg) compared to a weight gain for the placebo group (0.4 ± 1.3). No assessments of height changes were made in this submission (the pediatric studies were all short term).

For the adult population, the mean change of weight loss was greater in all Focalin treatment groups compared to placebo where there was no weight loss observed. The sponsor reported that "clinically notable" weight loss was reported in 6 adult patients treated with Focalin XR (range 5.7 to 9.6 kg) and one placebo patient (21.4 kg). Please refer to section 7.1.8 above for details.

7.1.16 Overdose Experience

The sponsor reports that there were four cases of overdoses in the adult population. Patients 0503/00003, 507/00022 and 515/00012 all received 80 mg for one day through a dosing error. Patient 503/00015 received 60 mg for one day through a dosing error. In their search of the database for adverse events occurring within one week of overdose, the sponsor reports that there were no adverse events resulting from these overdoses.

7.1.17 Postmarketing Experience

Focalin XR has not yet been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

In their safety analysis, the sponsor identified the two distinct populations of pediatrics and of adults. For the pediatric population, the sponsor focused primarily on the pivotal study 2301 (7 week pediatric placebo controlled study), and did not combine the safety analyses for Study 2301 and Study US08 (2 week pediatric cross over study).

To support safety claims for the adult population, the sponsor focused on the pivotal study 2302 (5 week placebo controlled adult study) and the combined data from studies 2302 and 2302E1 (24 week extension study of 2302).

Please see Table 7.2.1.1 for a summary of patients participating in each study.

Table 7.2.1.1 Summary of Patient Enrollment

	AGE (YEAROLD)	DESIGN/DURATION	FOCALIN XR (N/DOSE RANGE)	PLACEBO (N)
Study 2301	6-17	7 week placebo controlled	n=53 5-30 mg	n=50
Study US 08	6-12	2 week cross-over	n=53 20 mg	n=54
Study 2302	18-59	5 week placebo controlled	n=165 10-40 mg	n=53
Combined Studies 2302 and 2302E	18-59	Up to 29 weeks Pbo controlled and open label	N=204	N/A

7.2.1.2 Demographics

For both pediatric studies 2301 and US 08, the majority of patients were Caucasian males with a mean age of approximately 9.5 years old. The majority of patients in the combined adult safety data base (Studies 2302 and 2302E) were Caucasian males with a mean age of 38.6 years old.

Please see Appendix Tables 10.3.1, 10.3.2, Table 10.3.3 for details regarding the demographics of the safety data base.

7.2.1.3 Extent of exposure (dose/duration)

7.2.1.3a Pediatric Population

There were two studies submitted to support the safety of Focalin XR in the pediatric population, Study 2301, a 7 week pediatric placebo controlled study, and Study US08, a 2 week cross over study. Study US08 did not provide much data to support safety, given that there was only 6 days of exposure of Focalin 20 mg/day for the 53 patients enrolled (there was one more patient who had placebo only, and withdrew due to an event of nausea). **There were no longer term safety studies in the pediatric population submitted supporting this NDA.**

For Study 2301, the 7 week pediatric placebo controlled study, the mean exposure to study drug was 47.1 days (range of 12-56 days) for the Focalin XR group and 43.1 days (range of 4-58 days) for the placebo group. There were 36 patients (of 53 or 67.9%) with an exposure of at least 49 days in the Focalin XR group. The dose of Focalin was titrated from 5-30 mg/day in 5 mg weekly intervals, as tolerated, for the first 5 weeks of the study, and then a stable dose was maintained for the last two weeks. As can been seen from the table below (Table 7.2.1.3a.1), approximately half of the patients were able to be titrated to the highest dose of 30 mg/day by the end of the 7 week study. Table 7.2.1.3a.2 provides a summary of doses in terms of mg/kg/day.

Table 7.2.1.3a.1 Final Maintenance dose for Study 2301, 7 week pediatric placebo controlled study. (adapted from sponsor's table 2-5 in safety summary)

	Focalin LA N=52	Placebo N=45
5-15 mg/day	9 (17.3)	6 (13.3)
20 mg/day	15 (28.8)	2 (4.4)
30 mg/day	28 (53.8)	37 (82.2)

Table 7.2.1.3a.2 Final Maintenance dose (on mg/kg/day basis) for Study 2301 (adapted from sponsor' table 28.1-8 in the study report for Study 2301)

	Focalin LA N=53
n	53
Mean	0.67
SD	0.310
Median	0.65
Min	0.07
Max	1.43

A subgroup analysis for age revealed that there were 83 children aged 6-12, and 17 adolescents aged >12 to <18 years of age. The mean duration of exposure in the Focalin XR group for children (6-12) was 49.2 days (n=45) and for **adolescents (n=7) was 34.9 days.** There was a higher rate of adolescents who discontinued from the study (8 of n=20 or 40%) compared with the children (10 of n=83 or 12 %). Final doses reached for children 6-12 was 20 mg/day for 13 patients (28.9%), 30 mg/day for 26 patients (57/8%).

Table 7.2.1.3a.3 Dosing by age subgroup for Study 2301

Level of final dose	Children (6-12)		Adolescents (>12 to <18)	
	Focalin XR n=45 (%)	Placebo n=35 (%)	Focalin XR n=7 (%)	Placebo n=10 (%)
5 mg/day	0	0	1 (14.3)	1 (10)
10 mg/day	2 (4.4)	3 (8.6)	1 (14.3)	1 (10)
15 mg/day	4 (8.9)	1 (2.9)	1 (14.3)	0
20 mg/day	13 (28.9)	2 (5.7)	2 (28.6)	0
30 mg/day	26 (57.8)	29 (82.9)	2 (28.6)	8 (80)

Table 7.2.1.3a.4 Dosing by weight for Study 2301
(adapted from sponsor's table 8.1-6 of safety report)

Treatment	Level of Final dose	>20-30 kg n (%)	>30-40 kg n (%)	>40 kg n (%)	All n (%)
Focalin LA	Total	12 (100)	19 (100)	21 (100)	52 (100)
	5 mg/day	0 (0.0)	0 (0.0)	1 (4.8)	1 (1.9)
	10 mg/day	0 (0.0)	2 (10.5)	1 (4.8)	3 (5.8)
	15 mg/day	3 (25.0)	1 (5.3)	1 (4.8)	5 (9.6)
	20 mg/day	1 (8.3)	8 (42.1)	6 (28.6)	15 (28.8)
	30 mg/day	8 (66.7)	8 (42.1)	12 (57.1)	28 (53.8)

It appears that the adolescent treatment group had a higher dropout rate and was less tolerant of the higher doses than the younger group of children. However, it must be kept in mind that the number of adolescents exposed was significantly less than the number of younger children, and it

is even questionable if the adolescent exposure to Focalin XR is sufficient. The following table summarizes the exposure broken down by age subgroups.

Table 7.2.1.3a.5 Mean exposure time and dose by age subgroup in the pediatric population.

	Children (6-12 yo)		Adolescents (>12 - <18 yo)	
	Focalin (n=45)	Placebo (n=37)	Focalin (n=7)	Placebo (N=10)
Mean Exposure [Range]	49.2 days [41-56]	42.8 days [8-53]	34.9 days [12-55]	44.3 days [4-58]
Mean Dose [Range]	24.9 mg/day (10-30)		18.6 mg/day (5-30)	

Unfortunately, the sponsor did not separate the doses out in terms of mg/kg/day by age subgroup. The following table summarizes the dosing by mg/kg/day.

Table 7.2.1.3a.6 Dosing for pediatric study 2301 by mg/kg/day, combined children and adolescent population (adapted from sponsor's table)

Descriptive statistics of maximum daily dose by weight (mg/kg/day)
(Safety population)

	Focalin LA N=53
n	53
Mean	0.69
SD	0.311
Median	0.65
Min	0.11
Max	1.43

7.2.1.3b Adult Population

The exposure data for adults was based on Study 2302 and 2302E. The mean duration of exposure for the adult safety data base was 4.8 months (range: 9.0 months to 0.1 months). Table 7.2.1.3b provides the exposure by duration and mean daily dose for the adult safety data base.

Table 7.2.1.3b Cumulative overall exposure by duration and mean daily dose (Adult population) (adapted from sponsor's table 2-10 in the Safety Summary)

	Focalin LA ≤ 20 mg N=58 n (%)	Focalin LA > 20-30 mg N=89 n (%)	Focalin LA > 30 mg N=57 n (%)	All Focalin LA N=204 n (%)
≥ 1 month	30 (51.7)	85 (95.5)	57 (100.0)	172 (83.5)
≥ 2 months	18 (31.0)	74 (83.1)	57 (100.0)	149 (72.3)
≥ 3 months	15 (25.9)	66 (74.2)	56 (98.2)	137 (66.5)
≥ 4 months	13 (22.4)	59 (66.3)	56 (98.2)	128 (62.1)
≥ 5 months	11 (19.0)	52 (58.4)	53 (93.0)	116 (56.3)
≥ 6 months	8 (13.8)	44 (49.4)	49 (86.0)	101 (49.0)
≥ 7 months	7 (12.1)	30 (33.7)	37 (64.9)	74 (35.9)

*A patient is counted in the maximum applicable category of duration and in each lower category.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate the safety of this data base.

7.2.2.2 Postmarketing experience

Focalin XR has not been yet been marketed.

7.2.2.3 Literature

There was no literature or literature summary addressing the safety or efficacy of Focalin XR located in this submission.

7.2.3 Adequacy of Overall Clinical Experience

There are several deficiencies identified in the exposure data for this NDA. There is concern that very few adolescents in this NDA data base were exposed to Focalin XR, a total of n=7, which is an insufficient number to comfortably comment on safety or efficacy of Focalin XR in this patient population. Also, there is no longer term safety data in the pediatric population (the longest study is 7 weeks in the pediatric population). This becomes quite concerning given that ADHD is a disorder that often results in years of treatment with medication.

ECGs were not performed in the pediatric population.

In the adult study, 2302, and it is unclear if ECGs were administered at a timing to correlate with tmax. The sponsor also did not provide any data regarding any QT intervals in the ECG data that was submitted.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no special animal and/or in vitro testing accompanying this submission.

7.2.5 Adequacy of Routine Clinical Testing

There were only seven adolescent patients exposed to Focalin XR which is an insufficient number to make any conclusions regarding efficacy or safety in this population. Post-baseline ECGs were not conducted in the pediatric population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to the biopharmaceutical review (unavailable at the time of this review).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A major concern for this drug is the long term effects on patients. There were no longer term studies conducted in the pediatric population for Focalin XR. This becomes even more concerning in light of the recent article describing cytogentic effects in children treated with methylphenidate suggesting a relationship of chromosomal aberrations and methylphenidate use (El-Zein, 2005).

7.2.8 Assessment of Quality and Completeness of Data

Of concern has been the small number of adolescents providing an inadequate safety and efficacy profile for this patient population. The sponsor did not perform post-baseline ECGs in the pediatric population.

The presentation of ECG data in the adult population did not provide QT or QTc data. Also it was unclear if the timing of the ECGs was conducted in a consistent manner at the drugs tmax.

The sponsor also did not present the weight change data in the pediatric population using z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean).

7.2.9 Additional Submissions, Including Safety Update

In the sponsor's safety update (11/23/05), there was one report of a 23 year old female [Patient #0518/00002] who became pregnant while taking Focalin XR 20 mg/day for approximately one and a half months at the beginning of her first trimester; according to the sponsor's report, the birth of her child was medically unremarkable and the child did not have evidence of any identifiable disorder.

Otherwise, there were no other additional safety reports in this Safety Update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In both the pediatric and adult population, there was evidence that Focalin XR increased the mean change from baseline of sitting pulse, sitting diastolic and systolic blood pressure. Orthostatic changes were not assessed in the studies submitted.

It is difficult to assess the extent that Focalin XR had on growth in the pediatric population, because the sponsor did not assess this data in terms of z-scores scores (a method utilizing a

change based on the number of standard deviations a patient is from their gender/age standardized mean). The sponsor reported that a decrease of ≥ 7% body weight was reported in 6 (of 47) pediatric patients treated with Focalin XR (range 1.9 to 5.4 kg) and no placebo patients. For the adult population, the sponsor reported that "clinically notable" weight loss was reported in 6 adult patients treated with Focalin XR (range 5.7 to 9.6 kg) and one placebo patient (21.4 kg).

Considering the format of the data presented by the sponsor in this submission, it is not possible to ascertain the QT and QTc intervals in the adult population tested. There were no post-baseline ECGs conducted in the pediatric population.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The pediatric, placebo-controlled study 2301 utilized a flexible dosing of Focalin XR 5-30 mg/day with a mean final dose of 24 mg/day. The majority of patients were maintained on doses of 20 mg/day or 30 mg/day. The sponsor has proposed a starting dose for pediatric patients of 5 mg/day with a recommended maximum dose of Focalin XR [redacted] mg/day. This proposal is consistent with the findings from the clinical trial.

The adult placebo-controlled study 2302 was a fixed dose study with dose groups including Focalin XR 20 mg/day, 30 mg/day, and 40 mg/day. The results of the study showed a statistically significant difference when comparing all Focalin XR groups to placebo. It is noted that the primary efficacy variable focused on the Focalin 30 mg/day and 40 mg/day groups. The sponsor has proposed a starting dose for adult patient of 10 mg/day up to a maximum of [redacted] mg/day. This proposal is consistent with the findings from the clinical trial.

8.2 Drug-Drug Interactions

There was no data submitted with the NDA regarding drug-drug interactions.

8.3 Special Populations

There were no special populations addressed in this NDA.

8.4 Pediatrics

This drug was tested in the pediatric population, as ADHD is a disorder that has traditionally been a disease encountered in children. There is a question as to whether or not the sponsor exposed an adequate number of adolescents to provide a safety and efficacy profile for adolescent patients.

8.5 Advisory Committee Meeting

There was no advisory committee meeting to discuss Focalin XR.

8.6 Literature Review

The sponsor did not submit any literature that specifically discussed the safety or efficacy of Focalin XR.

8.7 Postmarketing Risk Management Plan

It will be important to watch for long term effects of Focalin XR exposure, especially in the pediatric population, as there were no longer term studies conducted in this population.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has shown that Focalin XR is effective and reasonably safe for the treatment of pediatric and adult ADHD. There are concerns that the subgroup population of adolescents was not adequately exposed in this NDA data base to make definitive conclusions regarding safety or efficacy.

Missing from the data submitted with this NDA are z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean) for the pediatric patients; this does not allow for an accurate assessment of difficulties with growth with the use of Focalin XR. Also missing from the submitted data are the details of QT and QTc intervals on the ECGs in the adult patients studied as well as clarification as to the timing of ECGs in terms of tmax.

It is concerning that the sponsor did not conduct any studies longer than 7 weeks in the pediatric population; especially in light of the fact that ADHD is a disorder that is commonly treated with medication for many years. It is also disappointing that the sponsor only exposed seven adolescents to Focalin XR thus far in the drug's development. Also of concern is that the sponsor has not conducted any post-baseline ECGs in the pediatric population.

9.2 Recommendation on Regulatory Action

It is recommended that this NDA receive an approvable action. The sponsor has been able to establish efficacy in one study in the pediatric population and one study in the adult population for the treatment of ADHD. The safety profile, as presented thus far, resembles other currently marketed stimulant mediations that are also used to treat ADHD.

It is recommended that the sponsor supply the data omitted in this NDA submission (discussed in Conclusions Section above) to allow a more accurate labeling of this medication.

It is also recommended that the sponsor commit to studying a larger adolescent population, conduct long term safety studies in the pediatric population, and perform post-baseline ECGs in the pediatric population.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Given that ADHD is a disorder that may be treated with medication for many years, it is important that the sponsor continue to monitor closely any adverse events that occur in the treated populations. Ideally, the sponsor could conduct long term studies (even observational) in which patients are followed for several years. Post marketing concerns that have been identified with the long term use of methylphenidate include cardiovascular (i.e. hypertension, myocardial infarction, arrhythmia, cardiomyopathy, and sudden death), cerebrovascular (stroke), cancer (hepatoblastoma), and neuropsychiatric (psychosis, hallucinations, seizures) events in addition to chromosomal aberrations.

9.3.2 Required Phase 4 Commitments

It is recommended that the sponsor conduct a more detailed study of the adolescent population as there was a very small number exposed to Focalin XR in this study. Also, it is recommended that the sponsor conduct long term studies (at least 1 year) in the pediatric population to assess adverse events in addition to conducting post-baseline ECGs in the pediatric population.

9.4 Labeling Review

Please refer to Section 10.2 for a line by line review of the sponsor's proposed labeling of Focalin XR. One main point is that all references to Study US08 be omitted as this was not designated a pivotal study, and results were not confirmed by FDA statisticians; also there were design flaws that may have skewed the results (Please refer to Appendix 10.1.3 Conclusions in this review).

A review by the Division of Medications Errors and Technical Support (DMETS) is not available at the time of this review.

The proposed patient package insert appears appropriate. One recommended addition is "nausea" as a common adverse event in the pediatric population (See Item 6 of Section 10.2, below).

9.5 Comments to Applicant

1. Please provide z-scores (a method utilizing a change based on the number of standard deviations a patient is from their gender/age standardized mean) for the pediatric patients studied in the placebo controlled study 2301. If there is any longer term study in the pediatric population, please also submit data regarding growth in terms of z-score.

2. Please provide details of mean QT and QTc intervals for adult patient in Study 2302. Please also provide details of all outliers; change from baseline signals of interest include the following:

- QT/QTc interval increases from baseline ≥ 30 msec.
- QT/QTc interval increases from baseline ≥ 60 msec.
- Please clarify if ECGs were conducted in terms of tmax
- If plasma level data is available for Study 2302 in which ECGs were measured at Cmax, a QTc-plasma level relationship should be evaluated.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 2301

Investigators/Location

This study was conducted at 12 centers. There were 12 principal investigators involved in this study. Please refer to the sponsor's study report of 2301 Appendix 2 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of Focalin XR (at doses of 5-30 mg one time daily) compared to placebo in pediatric patients 6-17 y.o. diagnosed with ADHD.

Population

Patients chosen for this study were 6-17 years of age, physically healthy, and diagnosed with ADHD according to DSM-IV criteria by psychiatric evaluation. At baseline, patients were required to have a minimum total DSM-IV subscale score of Connor ADHD DSM IV Scale CADS-T as follows (based on normative data from the Conner's Teacher Rating Scale):

	Male	Female
Between 6-8 years	27	16
Between 9-11 years	24	13
Between 12-14 years	19	12
Between 15-17 years	14	6

Excluded from the study were patients with a history of seizures, psychosis, obsessive-compulsive disorder, autism, tic disorder (including Tourette's syndrome), and a current mood disorder (including bipolar or MDD). Also excluded were patients with a positive urine drug screen, a positive pregnancy test or a history of poor response/intolerance to stimulants.

Design

This was a 12 site, 7 week, randomized, double blind, placebo controlled study. Patients were required to have at least a 7 day wash out period; baseline assessments were made after the washout period and prior to randomization. A flexible dosing schedule (doses at Focalin XR 5, 10, 20 or 30 mg/day) allowed up to a 5 week titration period (in increments of 5 mg/day/week for Weeks 1-4 and increments of 5 or 10 mg/day for Week 5); following the titration period, patients were required to have at least a two week maintenance of the optimal dose. Doses were administered each morning.

The concomitant use of psychotropic medications which could interfere with efficacy interpretations was forbidden. Patients were also forbidden to initiate any psychological or behavioral therapies during the study, but were allowed to continued these treatments if ongoing for at least 3 months prior to randomization, and continued throughout the randomization period. Screening included a history and physical, routine labs, pregnancy test (for sexually active females), urinalysis, and urine drug screen. Vital signs were monitored weekly; laboratory analyses were obtained at completion of the study.

Analysis Plan

The primary efficacy variable is the change from baseline to final rating of the DSM-IV total subscale score of the Connor ADHD DSM IV Scale-Teacher (CADS-T). The primary efficacy analysis was to be performed on the Intent-To-Treat population, with the completers analysis serving as a sensitivity analysis of the primary efficacy variable. If the assumptions for the ANCOVA model were not valid, a Mann-Whitney-Wilcoxon test was to be used to compare the treatment groups.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 141 patients screened, 103 patients were randomized into double-blind treatment. Reasons given for ineligibility for the study included the following: didn't meet diagnostic/severity criteria (n=15), subject withdrew consent (n=8), unacceptable past medical history/concomitant diagnosis (n=5), unacceptable laboratory values (n=1) , and other/not specified by sponsor (n=9). There were 97 patients in the intent-to-treat population (6 patient did not complete rating scores after baseline).

A total of 85 (of 103) patients completed the study (Focalin XR: n=48; placebo: n=37). Table 10.1.1a (below) summarizes the reasons for early withdrawal. As can be seen from Table 10.1.1a , there was no statistically significant difference between the Focalin XR and the placebo groups with regard to reasons for early withdrawal; it is noted that there were no patients in the Focalin group who discontinued due to an adverse event.

Table 10.1.1a Reasons for Early Withdrawal
(Based on Sponsor's table 7.1 from Study report 2301)

	Focalin XR (%)	Placebo	All
Adverse event(s)	0	1 (2.0)	1 (1.0)
Unsatisfactory therapeutic effect	2 (3.8)	4 (8.0)	6 (5.8)
Lost to follow-up	2 (3.8)	6 (12.0)	8 (7.8)
Administrative problems	1 (1.9)	0	1 (1.0)
Patient withdrew consent	0	2 (4.0)	2 (1.9)
Total Discontinued	5 (9.4)	13 (26.0)	18 (17.5)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males with a mean age of 10.0 years old (range of 6.0 to 17.0). The population consisted of 66 males (64.1%) and 22 females (41.5%) of which there were 62 (60.2%) Caucasians, 24 (23.3%) African-Americans, 17 (16.5 %) categorized by the sponsor as "Other." Although there did not appear to be any statistically significant differences in demographics between treatment groups at baseline, there was a clear majority of males in the placebo group (70% male vs. 30 % female) compared to the treatment group (58.5 % males vs. 41.5 % female).

There were two subgroups identified: 1) 90 **children** aged 6-12 y.o. (88% completed), of which 45 patients were randomized to Focalin XR treatment and 2) 17 **adolescents**, aged >12-<18 y.o. (76% completed) of which only 7 patients were randomized to Focalin XR treatment.

Concomitant Medications

Concomitant medications used most frequently included paracetamol, ibuprofen and multivitamins. There were no notable differences between the treatment group and the placebo group.

Efficacy Results

The sponsor was able to demonstrate a statistically significant result ($p<0.001$) using the CADS-T DSM-IV total subscale score; the mean changes from baseline to final visit were 16.3 for Focalin XR group compared to 5.7 for the placebo group.

Table 10.1.1b
Change from baseline in the CADS-T DSM-IV Total Subscale Score by Treatment/LOCF (ITT Population for Study 2301
(Table excerpt from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	33.3 (9.18)	34.9 (10.03)
Final Visit (Visit 9)	Mean (SD)	17.4 (12.42)	29.0 (15.62)
Change from Baseline*	Mean (SD)	15.8 (15.39)	5.9 (13.18)
	Adjusted Mean Change	16.3	5.7
	P-Value	<0.001	

* The reported values are the amount of changes

From the table below (Table 10.1.1c), it can be seen that a statistically significant result is observed for children aged 6-12 ($p<.001$) , but not for the adolescent patients aged 13 to 17 ($p=0.361$). Although the data for adolescents does not demonstrate a statistical significance, the numerical trend of change from baseline does demonstrate a greater improvement for Focalin XR compared to placebo (mean change of 9.6 vs. 3.3, respectively). It is also noted that these results are based on a very small population (n=7 adolescents exposed to Focalin XR), and that this study is not powered to detect a difference in this subgroup population.

From her statistical review, Dr. Chen concluded that both male and female patients showed a statistically significant treatment effect in favor of Focalin XR.

Table 10.1.1c Analysis of Change from Baseline in the CADS-T Total Subscale Score from Age Subgroups for Study 2301
(Table from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

Age: 6-12 years		Focalin LA N = 45	Placebo N = 35
Baseline (Visit 2)	Mean (SD)	34.0 (9.04)	35.0 (9.15)
Final Visit (Visit 9)	Mean (SD)	17.1 (12.74)	28.5 (14.84)
Change from Baseline*	Mean (SD)	16.9 (15.97)	6.5 (13.03)
	Adjusted Mean Change	17.5	6
	P-Value	<0.001	
Age: >12 - <18 years		Focalin LA N = 7	Placebo N = 10
Baseline (Visit 2)	Mean (SD)	29.0 (9.57)	34.4 (13.23)
Final Visit (Visit 9)	Mean (SD)	19.7 (10.73)	30.7 (18.92)
Change from Baseline*	Mean (SD)	9.3 (9.12)	3.7 (14.15)
	Adjusted Mean Change	9.6	3.3
	P-Value	0.361	

Conclusions

Study 2301 demonstrated that Focalin XR is effective for the treatment of ADHD in the pediatric population. It is unclear from this study if efficacy has been demonstrated for the adolescent age group (13-17 y.o.).

10.1.2 Study 2302

Investigators/Location

This study was conducted at 18 centers. There were 18 principal investigators involved in this study. Please refer to the sponsor's study report of 2301 Appendix 2 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of Focalin XR (at doses of 20-40 mg one time daily) compared to placebo in adult patients diagnosed with ADHD.

Population

Patients chosen for this study were between the ages of 18-60 years of age, physically healthy, and diagnosed with ADHD according to DSM-IV criteria by psychiatric evaluation. At baseline, patients were required to have a minimum score of 24 on the DSM-IV ADHD Rating Scale total score, and a Global Assessment of Functioning (GAF) score of = 60.

Excluded from the study were patients with a history of seizures, alcohol/substance abuse (within past 6 months), and poor response/intolerance to stimulants. Patients receiving any psychological or behavioral therapies for ADHD were also excluded.

Design

This was a multi-site, 5 week, randomized, double blind, fixed dose placebo controlled study. At baseline, patients were randomized to one of four groups: Focalin XR [20 mg, 30 mg, or 40 mg] or placebo. Dosing was titrated in increments of 10 mg/week, so that by Week 4, all patients were taking their assigned dosing. Doses were administered each morning.

The concomitant use of psychotropic medications which could interfere with efficacy interpretations was forbidden. Patients were also forbidden to initiate any psychological or behavioral therapies during the study, but were allowed to continue these treatments if ongoing for at least 3 months prior to randomization if being treated for a diagnosis other than ADHD.

Screening included a history and physical, routine labs, pregnancy test (for sexually active females), urinalysis, urine drug screen, and EKG. Pharmacogentic blood draws were optional, and a separate consent form was administered to patients participating in this aspect of the study. Vital signs were monitored weekly; laboratory analyses were obtained at completion of the study. A physical, urine pregnancy test, routine labs and ECG were repeated at the end of the study.

Analysis Plan

The primary efficacy variable is the change from baseline to final rating of the total score of the DSM-IV ADHD Rating Scale. DSM IV Scale-Teacher (CADS-T). The primary efficacy analysis plan was to use the least square means derived by an analysis of covariance (ANCOVA) model assessing the variables of treatment, center and Baseline total score of the DSM-IV ADHD RS and also utilize a ninety-five percent confidence interval to compare treatment groups.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 295 patients screened, 221 patients were randomized into double-blind treatment. Reasons given for ineligibility for the study included the following: unacceptable laboratory values (n=17 or 23%), didn't meet diagnostic/severity criteria (n=13 or 17.6%), subject withdrew consent (n=12 or 16.2%), intercurrent medical event (n=2 or 2.7%), unacceptable test procedure results (n=6 or 8.1%), unacceptable use of excluded medication/therapies (n=7 or 9.5%), unacceptable past medical history/concomitant diagnosis (n=5), , and other/not specified by sponsor (n=13 or 17.6%). There were 218 patients in the intent-to-treat population (2 patients were lost to follow up, and 1 patient withdrew consent after baseline).

A total of 184 patients completed the study (Focalin XR: n=141 or 83.9%; placebo: n=43 or 81.1%). Table 10.1.2a (below) summarizes the reasons for early withdrawal. As can be seen from Table 10.1.2a, there does not appear to be a significant difference between the Focalin XR and the placebo groups with regard to reasons for early withdrawal; it is noted that adverse events occurred more frequently in the Focalin XR groups compared to the placebo group.

Table 10.1.2a Reasons for Early Withdrawal and Patient disposition
(Table excerpt from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

	Focalin LA 20 mg N (%)	Focalin LA 30 mg N (%)	Focalin LA 40 mg N (%)	All Focalin LA N (%)	Placebo N (%)	All N (%)
Screened						295
Randomized	58 (100)	55 (100)	55 (100)	168 (100)	53 (100)	221 (100)
Completed	49 (84.5)	45 (81.8)	47 (85.5)	141 (83.9)	43 (81.1)	184 (83.3)
Discontinued	9 (15.5)	10 (18.2)	8 (14.5)	27 (16.1)	10 (18.9)	37 (16.7)
Adverse Event(s)	6 (10.3)	7 (12.7)	5 (9.1)	18 (10.7)	4 (7.5)	22 (10.0)
Lost to Follow-Up	2 (3.4)	0 (0.0)	3 (5.5)	5 (3.0)	1 (1.9)	6 (2.7)
Subject Withdrew Consent	0 (0.0)	2 (3.6)	0 (0.0)	2 (1.2)	3 (5.7)	5 (2.3)
Protocol Violation	1 (1.7)	1 (1.8)	0 (0.0)	2 (1.2)	1 (1.9)	3 (1.4)
Unsatisfactory Therapeutic Effect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males with a mean age of 38.7 years old (range of 18 to 62 The population consisted of 127 males (57.5%) and 94 females (42.5%) of which there were 189 (85.5%) Caucasians, 10 (4.5%) African-Americans, 7 (3.2 %) "Oriental," and 15 (6.8%) categorized by the sponsor as "Other."). FDA statistician Dr. Chen found that the Focalin XR 20 mg group had a statistically significantly higher proportion of Caucasians (100%) compared to Focalin XR 30 mg, 40 mg and placebo groups (87.3%, 68.2% and 75.5%, respectively); otherwise, does not appear to be any statistically significant differences in demographics between treatment groups at baseline.

Concomitant Medications

Concomitant medications used most frequently included ibuprofen, multivitamins, paracetamol, and acetylsalicyclic acid. The use of NSAIDs appeared to be slightly higher in the Focalin XR groups compared to placebo, but the differences does not appear to be grossly significant.

Efficacy Results

The sponsor was able to demonstrate a statistically significant difference when comparing the change from baseline scores in the DSM-IV ADHD RS total score when comparing all treatment groups with placebo (Focalin XR 20 mg: p=0.006; Focalin XR 30 mg: p=0.012; Focalin XR 40 mg: p<0.001). Dr. Chen was able to confirm these results, and pointed out that the sponsor's primary efficacy variable was based on only the comparison of the Focalin XR 30 and 40 mg groups to placebo.

Table 10.1.2b Change from baseline in the DSM-IV ADHD RS Total Score by Treatment/LOCF (ITT Population for Study 2302)
(Table from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

		Focalin LA 20 mg (N=57)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=54)	Placebo (N=53)
Visit 2 (Baseline)	Mean	36.8	36.9	36.9	37.5
	SD	7.20	8.07	8.25	7.82
Final DB Visit	Mean	23.1	23.5	20.0	29.6
	SD	11.65	11.80	11.50	13.58
Change from Baseline	Mean	13.7	13.4	16.9	7.9
	SD	10.69	10.81	13.34	11.20
Adjusted Mean Change		13.3	12.9	16.5	7.6
P-Value		0.006	0.012	<0.001	

As can be seen from Table 10.1.2c (below), an analysis looking at age subgrouping of patients ≤ 40 years old and patients >40 to 60 years old demonstrated that both the younger and older patients showed statistically significant treatment effect in favor of Focalin XR. Dr. Chen was able to confirm that both males and females demonstrated a statistically significant treatment effect in favor of Focalin XR.

Table 10.1.2c Analysis of Change from Baseline in the DSM-IV ADHD RS Total Score for Age Subgroups for Study 2302.
(Table from FDA Statistical Review by Yeh-Fong Chen, Ph.D.)

Age: ≤ 40 years		Focalin LA N = 87	Placebo N = 28
Baseline (Visit 2)	Mean (SD)	37.3 (7.63)	38.3 (7.33)
Final Visit (Visit 7)	Mean (SD)	22.7 (11.23)	29.9 (13.40)
Change from Baseline*	Mean (SD)	14.6 (11.82)	8.4 (11.21)
	Adjusted Mean Change	14.3	7.5
	P-Value	0.006	
Age: > 40 years		Focalin LA N = 78	Placebo N = 25
Baseline (Visit 2)	Mean (SD)	36.3 (7.99)	36.6 (8.40)
Final Visit (Visit 7)	Mean (SD)	21.6 (12.21)	29.3 (14.06)
Change from Baseline*	Mean (SD)	14.7 (11.64)	7.3 (11.40)
	Adjusted Mean Change	14.1	6.8
	P-Value	0.006	

10.1.3 Study US08

Please Note: This is not a pivotal study, and the results of this study have not been confirmed by FDA Division of Biometrics.

Investigators/Location

This study was conducted at 3 centers. There were 3 principal investigators involved in this study. Please refer to the sponsor's study report of US08 Appendix 2 for a full listing of all principal investigators.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to determine the safety and efficacy of Focalin XR 20 mg compared to placebo in pediatric patients 6-12 y.o. diagnosed with ADHD during a 12 hour laboratory classroom setting.

Population

Patients chosen for this study were 6-12 years of age, physically healthy, and diagnosed with ADHD according to DSM-IV criteria (no clinical evaluation was conducted). According to the protocol, the diagnosis was established using the DISC-Child; there is no mention that a psychiatric evaluation was conducted at screening or during the study to confirm the ADHD diagnosis. **All patients were required be stabilized on a total daily dose of 20-40 mg of methylphenidate for at least one month prior to the screening visit.** Co-morbid illnesses (as established by the screening DISC-Child) were forbidden.

Excluded from the study were patients with a history of seizures, schizophrenia, bipolar disorder, autism, substance abuse/dependence, tic disorder (including Tourette's syndrome). Also excluded were patients who are home schooled, have a positive urine drug screen, a positive pregnancy test, or a history of poor response/intolerance to stimulants. Psychotropic use of any medication other than methylphenidate would also exclude a subject from the study.

Design

This was a 3 site, randomized, double blind, cross-over placebo controlled study to assess the efficacy and safety of Focalin XR 20 mg compared to placebo during a 12 hour laboratory classroom setting. Within 14 days after screening, patients were randomized to one of two groups. Patients are instructed to take the last dose of their regular methylphenidate treatment on Day -2 (Thursday); Day 0 (a Saturday) was a practice day in the laboratory classroom, after which patients were given the beginning of their six day daily dosing of either placebo or Focalin

XR 20 mg. Patients were instructed to take the medication until Day 5 (Thursday) and then return to the laboratory classroom on Day 7 (Saturday). Patients were then switched over to the other treatment of either placebo or Focalin XR 20 mg, and take the medication until Day 12 (Thursday). The final laboratory classroom was conducted on Day 14. All patients were instructed to skip a dose of their medication on the Friday before each classroom setting which may have resulted in a rebound effect for patients who had been taking methylphenidate, thus, worsening their pre-laboratory classroom baseline scores.

The concomitant use of psychotropic medications which could interfere with efficacy interpretations was forbidden. Patients were also forbidden to initiate any psychological or behavioral therapies during the study, but were allowed to continued these treatments if ongoing for at least 3 months prior to randomization, and continued throughout the randomization period.

Screening included a history and physical, EKG, routine labs, pregnancy test (for sexually active females), urinalysis, and urine drug screen. Vital signs were monitored on Days 0, 7, and 14. weekly; laboratory analyses and pregnancy tests were obtained at completion of the study.

Analysis Plan

The change from pre-dose (Time 0) to the 1-hour post-dose in SKAMP Rating Scale "Combined" was the primary efficacy using an analysis of covariance (ANCOVA) model that includes the effects of center, sequence, treatment, period, and baseline (Hour 0 value), and the random effects of subjects within sequences and within subject errors. Paired differences were formed by subtracting the Day 7 pre-dose value from the Day 14 pre-dose values. These paired differences were analyzed with an ANOVA model including sequence effect to test unequal carryover effect. If the unequal carryover effect was statistically significant and clinically meaningful, the protocol allowed that a supportive analysis would be performed based on Period I data only.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 54 patients screened, 54 patients were randomized into double-blind treatment.
A total of 53 patients completed the study (Focalin XR-placebo treatment sequence: n=27; placebo-Focalin XR sequence: n=26. There was one patient in the placebo-Focalin XR treatment sequence who discontinued due to an adverse event while receiving placebo (details: a 10 year old Caucasian male with complaint of nausea of moderate severity).

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males with a mean age of 9.4 years old (range of 6.0 to 12.0). The population consisted of 38 males (70.4%) and 16 females (29.6%) of

which there were 34 (63.0%) Caucasians, 7 (13.0%) African-Americans, 13 (24.1 %) categorized by the sponsor as "Other." There does not appear to be any statistically significant differences in demographics between treatment groups at baseline.

Concomitant Medications

Given that this is a cross-over study design, it is difficult to comment on concomitant medications as it was not clear from the sponsor's submission which medications were taken during the placebo or Focalin XR treatment week. Concomitant medications used most frequently during the study included paracetamol/acetominophen, multivitamins, and loratadine. There were no notable differences between the treatment group and the placebo group.

Efficacy Results

According to the sponsor, there was a statistically significant result using a repeated measures mixed model ($p<0.001$). The adjusted mean change from Baseline to final visit in the CADS-T DSM-IV total subscale score was 16.3 for Focalin XR and 5.7 for placebo. The sponsor also performed the primary efficacy analysis with the completers population and found that Focalin XR was statistically significantly superior compared to placebo ($p=0.004$).

Miscellaneous Issues

Conclusions

A limitation to this study design is that it appears that, according to the protocol, the diagnosis was established using the DISC-Child; there is no mention that a psychiatric evaluation was conducted at screening to confirm the ADHD diagnosis. This does not provide an adequate reassurance that the study population was accurately diagnosed with ADHD.

Another concern with this study design is that a "rebound effect" may have skewed the data. Patients who were assigned to treatment group were instructed to discontinue the dosing on Thursday, and have no medication of Friday; the pre-test baseline was taken on the following day, Saturday, prior to dosing. The Focalin treatment group may have experienced some rebound effects, which could add a confounding variable and perhaps make patients appear to have more intensity of ADHD symptoms at the "baseline" value." This flaw in the design could possibly result in an artificial inflation of the change from "baseline to 1 hour post-dosing."

The statistical results discussed above in the Results Section were not independently confirmed by FDA statisticians, but lend support to the efficacy of Focalin XR in the treatment of ADHD in children.

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

10.3 Supporting Tables

Table 10.3.1 Demographic details of pediatric Study 2301 (adapted from sponsor's Table 3-1 in the Summary of Clinical Safety)

	Focalin LA 5-30 mg/day N=53	Placebo N=50	All N=103
Age (yr)			
N	53	50	103
Mean	9.6	10.4	10.0
SD	2.75	2.70	2.74
Median	10.0	10.0	10.0
Range	6-17	6-16	6-17
Sex -n (%)			
Male	31(58.5)	35(70.0)	66(64.1)
Female	22(41.5)	15(30.0)	37(35.9)
Race – n (%)			
Caucasian	33(62.3)	29(58.0)	62(60.2)
Black	13(24.5)	11(22.0)	24(23.3)
Other	7(13.2)	10(20.0)	17(16.5)

Table 10.3.2 Demographic details of pediatric Study US08 (adapted from sponsor's Table 3-2 in the Summary of Safety)

	Sequence 1 Focalin LA → Placebo n (%)	Sequence 2 Placebo → Focalin LA n (%)	All patients n (%)
Age (yr)			
N	27	27	54
Mean	9.4	9.4	9.4
SD	1.6	1.6	1.6
Median	9.0	10.0	9.5
Range	7 – 12	6 – 12	6 – 12
Sex -n (%)			
Male	18 (66.7)	20 (74.1)	38 (70.4)
Female	9 (33.3)	7 (25.9)	16 (29.6)
Race – n (%)			
Caucasian	15 (55.6)	19 (70.4)	34 (63.0)
Black	3 (11.1)	4 (14.8)	7 (13.0)
Oriental	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (33.3)	4 (14.8)	13 (24.1)

Table 10.3.3 Demographic details of adult safety data base (Studies 2302 and 2302E1)(adapted from sponsor's Table 3-4 in the Summary of Safety)

	All Focalin LA N=204
Age (yr)	
Mean	38.6
SD	10.54
Median	40
Range	18-59
Sex -n (%)	
Male	122 (59.8)
Female	82 (40.2)
Race – n (%)	
Caucasian	176 (86.3)
Black	10 (4.9)
Oriental	6 (2.9)
Other	12 (5.9)

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

/s/

Roberta Glass
4/26/05 11:32:54 AM
MEDICAL OFFICER

Paul Andreason
5/2/05 02:50:22 PM
MEDICAL OFFICER
I agree with Dr Glass that this application is potentially approvable. Please see memo to the file.

MEMORANDUM

DATE: May 26, 2005

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

TO: NDA 21-802

SUBJECT: Action Memo for NDA 21-802, for the use of Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children, Adolescents, and Adults

NDA 21-802, for the use of Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children, Adolescents, and Adults, to be given once a day, was submitted by Novartis, Inc., on 7/28/04. Focalin, the immediate release product, is marketed for the treatment of ADHD in patients aged 6-17; the maximum recommended dose is 20 mg/day (given in a BID regimen). This application contains reports of three controlled trials (Studies 2301 and 08 in pediatric patients, and Study 2302, in adults), as well as long term (6 months) safety data in adults. The application has been reviewed by Dr. Roberta Glass, medical officer, Dr. Yeh-Fong Chen, statistician, Dr. Ron Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics, Dr. Ed Fisher, pharmacologist, Dr. Chhagan Tele, chemist, Todd D. Bridges and Dr. Kristina Arnwine, Division of Medication Errors and Technical Support, and Dr. Paul Andreason, Psychiatric Drugs Team Leader. The clinical team has concluded that the application should be considered Approvable at this time. I will briefly review the relevant data and provide the rationale for the division's action.

Effectiveness

Pediatric Patients

As noted above, the sponsor has submitted the results of two trials in pediatric patients (ages 6-17) and one in adults. Study 08, a single dose classroom study was designed to assess the effect of the drug primarily at one hour post dosing on the SKAMP (in addition, the sponsor wanted to rely on the results to establish that the drug was effective for 12 hours). As described by Dr. Kavanagh, there were problems with the study as designed and conducted.

Specifically, 54 patients ages 6-12 were treated with a single 20 mg dose of Focalin XL or placebo in a counter-balanced cross over design, despite the fact that many patients had previously been treated with lower doses of immediate release racemic methylphenidate (the division had urged the sponsor to utilize, in

a given patient, the equivalent dose of d-methylphenidate that they had been receiving as the racemate). Further, the sponsor did not assess the primary outcome at a time coincident with the inter-peak trough, raising questions about whether or not the drug would be effective at that time. Nonetheless, the drug-placebo contrast at 1 hour (the primary time to assess effectiveness) was highly significant (as were all other time points tested), both in all patients, as well as in patients considered to have been dosed appropriately (p=0.00035 in this latter group at one hour). In order to more adequately examine the time course of the effect of Focalin XL over the 12 hour period after dosing, the sponsor performed an additional study, Study 09, that ostensibly is better suited to address our concerns. Because the report of this study was submitted only several weeks ago, the team has not reviewed it at this time.

Study 2301 was a randomized, double-blind study performed in patients with ADHD aged 6-17 years old. It was a 7 week study, with a 5 week titration period (patients were started on 5 mg/day, then could be titrated by 5 mg/day/week for 4 weeks; they could then receive an additional 5-10 mg/day in week 5; thereafter, they remained on their final dose for the next two weeks, which could be no more than 30 mg/day). The primary outcome measure was the change from baseline to endpoint in the CADS-T. A total of 103 patients were randomized (Focalin XL 53; Placebo 50). The drug-placebo contrast was clearly statistically significant ($p<0.001$). Results on multiple secondary outcomes, including global outcomes, were similar. A total of 17 patients (Focalin XL 7, Placebo 10), were aged 12-17. The final dose was 20 mg in 15 patients (29%) and 30 mg in 28 patients (54%).

Drug-placebo contrasts were not reported by week for the primary outcome measure, but, according to Dr. Chen (see her review, page 13), there were a greater proportion of patients on drug compared to placebo in the "very much improved" and "much improved" categories on a Clinical Global Impression scale at early time points (the only outcome about which any reviewer has commented about weekly differences).

Adult Patients

Study 2302 was a five week randomized, double blind study in which patients were randomized to received either Focalin XL 20, 30, or 40 mg/day or placebo. The primary outcome measure was change from baseline to endpoint in the ADHD-RS. The results on the ITT analysis of this outcome are displayed below:

Drug	Change from Baseline ADHD-RS	P-value
Foc 20 mg (N=57)	13.3	0.006
Foc 30 mg (N=54)	12.9	0.012
Foc 40 mg (N=54)	16.5	<0.001
Placebo (N=53)	7.6	

Results of analyses of multiple secondary outcomes demonstrate similar patterns; that is, slight numerical superiority of the 20 mg dose compared to the 30 mg dose, and slight numerical superiority of the 40 mg dose compared to the 20 mg dose (i.e., not a strict monotonic dose response).

Safety

Dr. Glass has reviewed the safety data. There are no unexpected adverse events seen. In particular, however, pediatric patients treated with Focalin XL had small mean increases in pulse and blood pressure. In addition, they experience a 0.5 kg mean loss of weight, compared to a similar gain in placebo patients. Further, 6/47 (12%) of pediatric patients treated with Focalin XL lost at least 7% of their body weight, compared to no placebo patients. In adults, as expected, there is a dose related increase in pulse and blood pressure (there is no fixed-dose data in pediatric patients). There is no long-term safety data in pediatric patients, and the longest duration of exposure in adults is about 6 months. She notes that the sponsor has not analyzed EKG intervals in the adult data (no post-treatment EKGs were assessed in pediatric patients); however, the sponsor has since submitted these analyses (see below).

COMMENTS

The sponsor has submitted the results of two controlled trials that establish the effectiveness, in the short-term, of Focalin XL in pediatric and adults. There were no obvious safety concerns that would preclude approval. However, the team has made numerous recommendations:

1) The sponsor has not provided sufficient evidence of effectiveness (and safety) in the adolescent population, and, therefore, recommends that Focalin XL should not be approved for use in this population until a trial demonstrates effectiveness in adolescents.
2) Dr. Glass recommends that the sponsor provide z-scores for growth in the pediatric patients, and analyses of the QTc interval from the adult EKGs.
3) Dr. Glass recommends that the sponsor commit to providing studies in adolescents, and long-term safety data in pediatric patients, as well as EKG data in pediatric patients.
4) Dr. Kavanagh recommends that the sponsor adopt specific dissolution specifications, and perform, prior to approval, an in vitro study examining whether alcohol can produce dose-dumping.
5) Dr. Tele recommends an 18 month expiry.

First, I agree with Dr. Andreason that the sponsor need not submit z-score data for growth in pediatric patients. As he notes, z-scores are examined for long-term, non-placebo controlled data; this has proven to be a very useful approach for this sort of data, but, given that the sponsor has submitted no long-term

uncontrolled data in this population, we are left to accept (at this time) the data from the controlled trials, which, of course, can only provide very short-term effects. Also, I agree with Dr. Andreason that other sponsors are evaluating the long-term safety of methylphenidate products, which should provide useful data on this point.

All members of the clinical review team note that the sponsor has not provided sufficient data to permit a conclusion about the effectiveness of the treatment in adolescents. Certainly, I agree that there is inadequate information in Study 2301 to be able to reach any conclusion about the drug's effects in adolescents. However, with regard to the question of safety and effectiveness in adolescents, I believe several points can be made.

As Dr. Andreason notes, the division has typically required that data in adolescents be submitted in order to support a conclusion about effectiveness in adolescents, even in circumstances in which a drug has been found to be effective in children and adults. However, in one important case in the past, Luvox for OCD, in which clinical trial evidence demonstrated effectiveness in children and adults but not adolescents (circumstances that are different from this case, in which there simply is essentially no data in adolescents), the division determined that plasma levels of the drug were lower in adolescents than in children or adults. Importantly, that drug was approved in adolescents based on pharmacokinetic considerations, not clinical trial data (that is, a dosing regimen was derived in adolescents that was expected to give similar plasma levels to those in children and adults).

Can similar considerations be brought to bear in this case?

Dr. Kavanagh has concluded that the pharmacokinetics of Focalin XL in patients six years and above are "relatively consistent...when normalized for dose and weight...". Does this help us determine a dosing regimen in adolescents that can assure effectiveness?

I believe that it does. Specifically, we have previously concluded that Focalin (immediate release) is effective in patients in the age group 6-17 years old. Further, we have determined that Focalin XL is effective in children ages 6-12 and in adults. Finally, as noted above, the kinetics of Focalin XL are similar in children, adolescents, and adults. I believe that, taken together, these facts permit us to conclude that Focalin XL will be effective in adolescents, for whom we do not have empirical evidence of effectiveness.

The question of what doses should be recommended in labeling remains a critical one (for all age groups).

In children, we have seen that the drug is effective in a dose range of 5-30 mg/day, but that most patients received 30 mg/day, and almost all children

received at least 20 or 30 mg/day. However, given the design of the trial, it is impossible to know whether or not the doses achieved were necessary (that is, whether higher doses give increased benefit). Indeed, it is well-known that patients may be treated with higher doses than necessary in flexible-dose design trials. We do know that the maximum recommended dose of Focalin immediate release is 20 mg/day, for both children and adolescents (even the study on which the approval of that drug was based was a flexible dose study, with the maximum dose to be achieved being 20 mg/day; an adequate dose-response study with that product might have determined that a lower dose was equally effective). Given the knowledge that 20 mg/day of immediate release Focalin is effective (again, it is possible that lower doses are equi-effective), and that we have no useful information about the best dose of Focalin XL, but that the kinetic profile of the two products are quite similar, it seems to me that, despite the fact that over half the patients in Study 2301 received 30 mg/day of Focalin XL, we should consider 20 mg/day the maximum recommended dose.

Similarly, although the 40 mg dose in adults shows slight numerical superiority to the 20 mg dose on most (highly correlated) outcomes, the response in the 30 mg dose group is typically smaller than that seen at 20 mg/day. These findings suggest that there is no real clear dose response in adults above 20 mg. For this reason (and especially because of the increasing effects on blood pressure at higher doses) I also believe that 20 mg/day should be the maximum recommended dose in adults. It then seems clear that the maximum recommended dose in adolescents should be 20 mg/day as well.

These considerations also argue for limiting the maximum approved dosage strength to the 20 mg tablet ([redacted] . This is consistent with our conclusion that higher doses should not be encouraged (of course, total daily doses greater than 20 mg can still be achieved with combinations of the lower strengths), and also with our recent action on Adderall in adults.

However, because we do not have adequate dose-response data in children and adolescents, I believe that we should require that the sponsor commit to performing an adequate fixed-dose response study in Phase 4, with particular attention to the identification of a lowest effective dose. In that study, adequate EKG data should also be obtained.

As noted earlier, Dr. Glass recommends that the sponsor analyze the QT data in adults before the drug is approved for adults, and we have spoken to the sponsor about this. They have now submitted analyses of the QT data from Study 2302 in adults. The relevant data are displayed below:

Dose	Change From Baseline (msec) QTcF
Placebo (N=48)	-5.85
Focalin XL 20 mg (N=55)	-8.47
Focalin XL 30 mg (N=52)	-4.33
Focalin XL 40 mg (N=50)	-9.18

Clearly, these changes do not suggest any QT prolongation.

Although these data are reassuring, these EKGs were not assessed in any standardized relationship to the timing of dosing. In addition, we do not know if the doses studied exposed patients to the maximum plasma levels that may be achieved during the use of this drug in practice. Further, although methylphenidate has been marketed for many years, and we are not aware of reports of torsades de pointes, there certainly have been reports of sudden deaths with stimulant use, and we have no good data on the extent of exposure in adults, or on the effects of stimulants on the QT interval (there are small hints from the Adderall data in adults that there may be a possible increase in the QTc interval). For these reasons, and because this will be the first approval of methylphenidate in adults, I believe that the sponsor should also commit to performing, in Phase 4, a thorough QT study.

Finally, I believe it is reasonable to ask the sponsor to perform the in vitro alcohol interaction study in Phase 4. As Dr. Kavanagh suggests, given that the drug is taken in the morning, such an interaction (if there is one) is likely to be relatively rare.

The sponsor has agreed to perform the in vitro alcohol study, the fixed dose study in pediatric patients, and the thorough QT study in adults in Phase 4. Further, we have agreed with the sponsor on labeling language. For these reasons, and for those discussed earlier, I have concluded that the application can be approved for patients 6 years old and older, and I will issue the attached Approval letter with appended agreed-upon labeling.

Russell Katz, M.D.

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

/s/

Russell Katz
5/26/05 02:01:48 PM
MEDICAL OFFICER