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

DATE: March 3, 2006

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SUBJECT: Psychiatric Adverse Events Associated with Drug Treatment of ADHD: Review of Postmarketing Safety Data

PID: D050243

DRUGS: Listed in following Table:

Approved Products			
NDA #	**Name**	**Company**	**Date of Approval**
11-522	Adderall (mixed salts of a single entity amphetamine product) Tablets	Shire Pharmaceuticals, Inc.	1/19/1960; Re-established approval on 2/13/1996
21-303	Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules	Shire Pharmaceuticals, Inc.	10/11/2001
21-278	Focalin (dexmethylphenidate HCL) Tablets	Novartis Pharmaceuticals Corporation	11/13/2001
21-802	Focalin XR (dexmethylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	5/26/05
21-121	Concerta (methylphenidate HCL) Extended-Release Tablets	McNeil Consumer and Specialty Pharmaceuticals	8/11/2000
21-259	Metadate CD (methylphenidate HCL) Extended-Release Capsules	UCB Pharma, Inc.	4/3/2001
21-475	Methylin (methylphenidate HCL) Chewable Tablets	Tyco Healthcare/ Mallinckrodt	4/15/2003
21-419	Methylin (methylphenidate HCL) Oral Solution	Tyco Healthcare/ Mallinckrodt	12/19/2002
10-187	Ritalin (methylphenidate HCL) Tablets	Novartis Pharmaceuticals Corporation	12/5/1955
21-284	Ritalin LA (methylphenidate HCL) Extended-Release Capsules	Novartis Pharmaceuticals Corporation	6/5/2002
18-029	Ritalin SR (methylphenidate HCL) Sustained-Release Tablets	Novartis Pharmaceuticals Corporation	3/30/1982
21-411	Strattera (atomoxetine HCL) Capsules	Eli Lilly & Company	11/26/2002
17-078	Dexedrine (dextroamphetamine sulfate)	GlaxoSmithKline	8/2/1976
Pending NDAs/sNDAs			
20-717/S-019	Provigil (modafinil) Tablets	Cephalon, Inc.	pending
21-514	Methylphenidate Transdermal system	Noven Pharmaceuticals, Inc (Shire is a co-development partner with Noven	pending

1 EXECUTIVE SUMMARY / INTRODUCTION

A BPCA (Best Pharmaceuticals for Children Act) review of methylphenidate products, prompted by Concerta pediatric exclusivity requirements, identified psychiatric adverse events as a possible concern. The review found some psychiatric adverse events mentioned in labeling, but a need for improved clarity was identified. The Pediatric Advisory Committee[1] agreed at the June 2005 meeting at which the methylphenidate reviews were discussed, that the issue of psychiatric adverse events with all drugs indicated to treat ADHD should be examined with the goal of better characterizing these events so that drug labeling could be updated and made consistent between products. Thus, DDRE embarked on reviews of postmarketing and clinical trial reports of psychiatric adverse events associated with drugs used to treat ADHD. This document presents the results of the

[1] Pediatric Advisory Committee Meeting, June 29 and 30, 2005; http://www.fda.gov/oc/advisory/accalendar/2005/fda12604dd06293005.html

review of postmarketing reports. A companion document[2], from Dr. Andrew Mosholder, presents the results of the review of clinical trial reports.

Information pertaining to selected psychiatric adverse event reports received since January 1, 2000 was requested from the manufacturers of products approved or with pending applications for the treatment of ADHD. Sponsors were asked to provide information regarding four broad categories of psychiatric adverse events: 1) signs and/or symptoms of psychosis or mania; 2) suicidal ideation and behavior; 3) aggression and violent behavior; and, 4) miscellaneous serious adverse psychiatric events. In addition, searches of the FDA AERS safety database were conducted covering the same time period, and the identified cases were assessed by a DDRE Review Team. Duplicates, and reports which were considered to be of poor quality or highly unlikely to be related to the drug of interest were excluded from this analysis.

Cases received from Sponsors, as well as those identified from the FDA AERS safety database, were systematically reviewed and analyzed to assess the probability of adverse drug reactions and to describe characteristics or risk factors observed in these reports. This review focuses on postmarketing safety data from the first three search categories. The miscellaneous category was considered to be beyond the scope of this current analysis due to the large volume of data for review.

The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD. Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs or symptoms of psychosis or mania (such as hallucinations) in patients without identifiable risk factors, and occurring at usual dosages. In addition, current labeling does not clearly state the importance of stopping drug therapy in any patient who develops hallucinations, or other signs or symptoms of psychosis or mania, during drug treatment of ADHD. We recommend that these issues be addressed.

A substantial proportion of psychosis-related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common. The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents. The predominance in young children of hallucinations, both visual and tactile, involving insects, snakes and worms is striking, and deserves further evaluation.

Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of adverse events. Cases of psychosis-related events which included a positive rechallenge were identified in this review for each of the drugs included in this analysis.

In many patients, the events resolved after stopping the drug. In the FDA AERS review, resolution of the events after stopping the drug was reported in 58% of amphetamine / dextroamphetamine cases, 60% of modafinil cases, 33% of atomoxetine cases, and 48% of

[2] Mosholder. Psychiatric Adverse Events in Clinical Trials of Drugs for Attention Deficit Hyperactivity Disorder (ADHD). March 3, 2006. PID# D050243.

methylphenidate cases. (*Note:* Outcome of the psychiatric adverse events was not reported in 21% of amphetamine / dextroamphetamine cases, 9% of modafinil cases, 41% of atomoxetine cases, and 30% of methylphenidate cases.)

For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events. For instance, drug abuse was reported in fewer than 3% of overall cases from the FDA AERS analysis of psychosis-related events. Also of note, in the overwhelming majority of cases (roughly 90% overall), the patient had no prior history of a similar condition.

Numerous postmarketing reports of aggression or violent behavior during drug therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles. The majority of the reports of aggression for drugs currently approved for the treatment of ADHD were in children and adolescents, with a striking male predominance. No specific risk factors for aggression or violent behavior were identified in this analysis. For instance, drug abuse was reported in fewer than 5% of overall cases identified from the FDA AERS search. Also of note, a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events. Several cases describing positive rechallenge were reported for each of the drugs included in this analysis. Consideration should be given to stopping the medication in patients who develop aggressive or violent behavior during drug therapy of ADHD.

Suicidality has been identified as a safety issue for STRATTERA (atomoxetine), and this information is clearly conveyed in current labeling. A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. For instance, clinical case review of data obtained for this analysis may yield additional insights regarding possible co-occurrence of undesired psychiatric effects in some vulnerable patients that could contribute to suicidal ideation or behaviors.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY/INTRODUCTION 2

2 BACKGROUND 6

2.1 LABELING 7
2.2 SPONSOR SAFETY DATA REQUEST 7
2.3 AERS DATA RETRIEVAL AND SPREADSHEET PREPARATION 7
2.3.1 AERS Search Strategy 7
2.3.2 Spreadsheet preparation 8

3 REVIEW AND ANALYSIS OF POSTMARKETING SPONTANEOUS OR LITERATURE REPORTS FOR PSYCHIATRIC ADVERSE EVENTS OF INTEREST 8

3.1 METHODS 8
3.2 SIGNS AND/OR SYMPTOMS OF PSYCHOSIS OR MANIA 9
3.2.1 Sponsor Submissions 9
3.2.1.1 ADDERALL and PSYCHOSIS or MANIA 9
3.2.1.2 ADDERALL XR and PSYCHOSIS or MANIA 10
3.2.1.3 CONCERTA and PSYCHOSIS or MANIA 12
3.2.1.4 PROVIGIL (MODAFINIL) and PSYCHOSIS or MANIA 13
3.2.1.5 RITALIN and PSYCHOSIS or MANIA 13
3.2.1.6 STRATTERA (ATOMOXETINE) and PSYCHOSIS or MANIA 14
3.2.2 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE 15
3.2.2.1 AMPHETAMINE / DEXTROAMPHETAMINE and PSYCHOSIS or MANIA 15
3.2.2.2 ATOMOXETINE and PSYCHOSIS or MANIA 15
3.2.2.3 METHYLPHENIDATE and PSYCHOSIS or MANIA 16
3.2.2.4 MODAFINIL and PSYCHOSIS or MANIA 17
3.2.3 DISCUSSION 17
3.2.4 REGULATORY CONSIDERATIONS 20
3.3 SIGNS AND/OR SYMPTOMS OF AGGRESSION OR VIOLENT BEHAVIOR 21
3.3.1 Sponsor Submissions 21
3.3.1.1 ADDERALL and AGGRESSION 21
3.3.1.2 ADDERALL XR and AGGRESSION 21
3.3.1.3 CONCERTA and AGGRESSION 21
3.3.1.4 PROVIGIL (MODAFINIL) and AGGRESSION 22
3.3.1.5 RITALIN and AGGRESSION 22
3.3.1.6 STRATTERA (ATOMOXETINE) and AGGRESSION 22
3.3.2 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE 23
3.3.3 DISCUSSION 23
3.3.4 REGULATORY CONSIDERATIONS 25
3.4 SIGNS AND/OR SYMPTOMS OF SUICIDALITY 25
3.4.1 Sponsor Submissions 25
3.4.1.1 ADDERALL and SUICIDALITY 25
3.4.1.2 ADDERALL XR and SUICIDALITY 26
3.4.1.3 CONCERTA and SUICIDALITY 26
3.4.1.4 PROVIGIL (MODAFINIL) and SUICIDALITY 26
3.4.1.5 RITALIN and SUICIDALITY 27
3.4.1.6 STRATTERA (ATOMOXETINE) and SUICIDALITY 27
3.4.2 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE 28
3.4.3 DISCUSSION 28
3.4.4 REGULATORY CONSIDERATIONS 30
3.5 SUMMARY AND CONCLUSION 30
3.6 DDRE ADHD PSYCHIATRIC REVIEW TEAM 32

4 ATTACHMENTS 32

4.1 ATTACHMENT 1: PSYCHIATRIC ADVERSE EVENTS IN LABELING 33
4.1.1 ADDERALL and ADDERALL XR 34
4.1.2 ADDERALL XR 34
4.1.3 STRATTERA 35
4.1.4 FOCALIN XR 38
4.1.5 DEXEDRINE 40

4.1.6 CONCERTA, METADATE CD, METHYLIN, M-ER, RITALIN, R-SR, R-LA 41
4.2 ATTACHMENT 2 INFORMATION REQUESTED FROM SPONSORS 43
4.3 ATTACHMENT 3: AERS SEARCH TERMS 48
4.4 ATTACHMENT 4: TABULAR SUMMARIES OF PM SAFETY DATA FROM SPONSOR SUBMISSIONS 50
4.4.1 <ADDERALL> 51
4.4.2 <CONCERTA> 57
4.4.3 < METADATE > 60
4.4.4 < PROVIGIL (modafinil) > 63
4.4.5 <RITALIN> 66
4.4.6 <STRATTERA (atomoxetine)> 68
4.5 ATTACHMENT 5: TABULAR SUMMARIES OF PM SAFETY DATA FROM FDA AERS DATABASE 71
4.5.1 <AMPHETAMINE / DEXTROAMPHETAMINE> 72
4.5.2 <ATOMOXETINE> 78
4.5.3 <METHYLPHENIDATE> 84
4.5.4 <MODAFINIL> 90

1 BACKGROUND

The Division of Drug Risk Evaluation (DDRE) in the Office of Drug Safety (ODS) monitors reports received by the FDA Adverse Event Reporting System (AERS) of adverse events associated with marketed drugs. In addition, ODS is consulted by Office of New Drugs review divisions and others to review specific drug safety issues using AERS reports and drug usage data. The Office of Counter-Terrorism and Pediatric Drug Development (OCTAP) consults ODS to perform Best Pharmaceuticals for Children Act (BPCA) reviews of drugs that have been granted pediatric exclusivity under the act.

A BPCA review of methylphenidate products, prompted by Concerta pediatric exclusivity, identified psychiatric adverse events as a possible concern. The review found some psychiatric adverse events mentioned in labeling, but a need for improved clarity was identified. The Pediatric Advisory Committee agreed at the June 2005 meeting, at which the methylphenidate reviews were discussed, that the issue of psychiatric adverse events with all drugs indicated to treat ADHD should be examined with the goal of better characterizing these events so that drug labeling could be updated and made consistent between products. Thus, DDRE embarked on reviews of postmarketing and clinical trial reports of psychiatric adverse events associated with drugs used to treat ADHD. This document presents the results of the review of postmarketing reports. A companion document, from Dr. Andrew Mosholder, presents the results of the review of clinical trial reports.

Milestones of the DDRE exploration of psychiatric adverse events are:

- June 14, 2005. Reviews of AERS reports associated with Concerta and other methylphenidate products during the first year since granting of pediatric exclusivity for Concerta were completed by K. Phelan.[3] These reviews illuminated psychiatric adverse events as an area needing further examination.

[3] Phelan. One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review. June 14, 2005. PID# D040058. Adverse events with methylphenidate products other than Concerta in pediatric patients during the first year after granting of pediatric exclusivity for Concerta. June 14, 2005. PID# D050249.

- September 2005. Reviews of psychiatric adverse events in each manufacturer's clinical trial and postmarketing data and in AERS was undertaken by DDRE for the drugs approved by FDA to treat ADHD. The goal of the review was to characterize the psychiatric adverse events and to identify risk factors for these events if possible. This document presents results of the review of postmarketing data.
- January 2006. Reviews of AERS reports associated with Adderall XR and immediate-release mixed amphetamine salts during the first year since pediatric exclusivity was granted to Adderall XR were completed by K. Phelan[4]. Again, psychiatric adverse events emerged as an area of possible concern.

1.3 LABELING

Attachment 1 contains the labeling that pertains to psychiatric adverse events for the drugs that are FDA-approved to treat ADHD. For drugs with more than one trade product, information from labeling that is very similar for different products is grouped at the beginning of the section for that drug. Labeling that differs between products follows the common information for that drug.

1.3 SPONSOR SAFETY DATA REQUEST

Attachment 2 contains the request for postmarketing and clinical trial reports of psychiatric adverse events that was sent in a letter to sponsors of drugs used to treat ADHD. The data provided in response to the letters, in addition to AERS data, forms the basis of the analyses described in this document.

1.3 AERS DATA RETRIEVAL AND SPREADSHEET PREPARATION

1.3.8 AERS Search Strategy

AERS was searched for adverse events coded with MedDRA terms corresponding to four general areas of psychiatric events: psychosis and mania, suicidal ideation and behavior, aggression and violent behavior, and miscellaneous psychiatric events. These are the same categories of adverse events requested of drug sponsors. Attachment 3 contains lists of the MedDRA terms in each of these four general areas of psychiatric events. Also, consistent with the request to drug sponsors, all adverse events in the first three areas were retrieved but, for the miscellaneous psychiatric adverse events, only those with a serious outcome were retrieved. Serious outcomes, as listed on the MedWatch adverse event report forms 3500 and 3500A comprise death, life-threatening, initial or prolonged hospitalization, disability, congenital anomaly, requiring intervention to prevent permanent impairment or damage, and other. Reports

[4] Phelan. Adderall XR one year post-pediatric exclusivity postmarketing adverse event review. January 5, 2006. PID# D040761. Adverse events reported with immediate-release mixed amphetamine salt products during the Adderall XR 1-year post-pediatric exclusivity period. February 6, 2006. PID# D060042.

received by the FDA from January 1, 2000 through June 30, 2005 were retrieved. These dates were chosen so the scope of work would be manageable and so we would capture the most current prescribing trends. In addition, previous AERS searches showed that the majority of reports for ADHD drugs were received after January 2000.

1.3.8 Spreadsheet preparation

Retrieved AERS adverse event reports for each drug were put in Excel spreadsheets. Thus, four spreadsheets were created, one each for methylphenidate, including dexmethylphenidate; amphetamines in all isomers, combinations, salts and dosage forms; atomoxetine; and modafinil. Duplicate reports within each of the four psychiatric adverse event categories were removed. However, an individual case may have been retrieved by more than one of the four psychiatric adverse event category AERS searches. Thus, the same case may be included in the counts for more than one of the categories: psychosis and mania, suicidal ideation and behavior, aggression and violent behavior, and miscellaneous psychiatric events.

Hands-on review of each case was completed by the DDRE ADHD Psychiatric Review Team with the capture of additional information, such as whether a family history of psychotic illness was reported or whether the patient had a seizure disorder. In addition, each reviewer determined whether each case was generally well-documented and unconfounded or, conversely, if the case was substantially confounded or seriously lacking in information required for analysis. Based on this information, cases were designated as "thumbs up", "thumbs down", or neither of the above, respectively. Cases designated as "thumbs down" were excluded from the analysis. Because of their large numbers, atomoxetine and methylphenidate cases were divided among six reviewers; although, most of the methylphenidate cases were reviewed by one reviewer. To foster consistency, a column-by-column guide to the spreadsheet was provided to each reviewer; however, because the gathering of pertinent information and the assessment of each case required judgment, differences between reviewers are inevitable.

1 REVIEW AND ANALYSIS OF POSTMARKETING SPONTANEOUS OR LITERATURE REPORTS FOR PSYCHIATRIC ADVERSE EVENTS OF INTEREST

1.3 Methods

Information pertaining to selected psychiatric adverse event reports received since January 1, 2000 was requested from the manufacturers of products approved or with pending applications for the treatment of ADHD. As described previously in Section 2.2, Sponsors were asked to provide information regarding four broad categories of psychiatric adverse events: 1) signs and/or symptoms of psychosis or mania; 2) suicidal ideation and behavior; 3) aggression and violent behavior; and, 4) miscellaneous serious adverse psychiatric events. This review focuses on the first three categories, which correspond to the first three search requests described in Attachment 2.

In addition, searches of the FDA AERS safety database were conducted covering the same time period, and the identified cases were assessed by a DDRE Review Team, as described in Section 2.3. Reports which were considered to be of poor quality or highly unlikely to be related to the drug of interest were excluded from further review. Duplicate reports were identified and the information was combined into a single case.

Cases received from Sponsors, as well as those identified from the FDA AERS safety database, were systematically reviewed and analyzed using criteria adapted from Naranjo[5] to assess the probability of adverse drug reactions and to describe characteristics or risk factors observed in these reports. Tabular summaries of the information from the Sponsor submissions are presented in Attachment 4. Summaries of the information from the FDA AERS review are presented in Attachment 5.

Criteria for assessment of reports of psychiatric events of interest include the following:

- Are there published case reports in medical literature which are consistent with a causal association between drug administration and the adverse event of interest?
- Was the temporal association between drug administration and the occurrence of the adverse event consistent with a possible causal association?
- Did the adverse event improve or resolve when the drug was discontinued (positive dechallenge)?
- Did the adverse event recur when the drug was readministered (positive rechallenge)?
- Are there alternative factors that could have caused or contributed to the adverse event such as: Concomitant medications? Drug abuse? A pre-existing condition with history of similar signs and/or symptoms prior to drug administration?
- Was the adverse event confirmed by objective evidence, such as medical confirmation from a health care professional?

1.1 SIGNS and/or SYMPTOMS of PSYCHOSIS or MANIA[6]

1.1.0 Sponsor Submissions

1.1.0.0 ADDERALL and PSYCHOSIS or MANIA

During the period, a total of 84 reports pertaining to psychosis or mania were received by the Sponsor, all of which were domestic in origin. Of these, 35% were reported in children age 10 years or younger, and 21% were in patients age 11 to 20 years. A case report from published medical literature was identified during the review, although it was not identified as such in the

[5] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2):239-245.
[6] Search terms for this condition include hallucination (any type, including visual, auditory, tactile, mixed, etc.), delusion, psychotic disorder, acute psychosis, catatonia, mania, hypomania (see Attachment 2 for complete list).

Sponsor's submission.[7] Most frequently stated MedDRA Preferred Terms (PTs) in these reports included HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, and MANIA. The majority (70%) of the reports were in males. Confounding factors were not identified in the majority of the reports: only 2% of cases were stated to be an exacerbation of a pre-existing condition and 25% of cases reported a psychiatric history other than ADHD. No reports described a history of seizure disorder. Concomitant medications were not reported in 51% of cases, and were stated as none in 19% of the total 84 reports. Drug abuse was described in 18% of cases, and overdose was stated in 15%. One case was considered life-threatening and 23% of cases required hospital admission. The events resolved after discontinuation of drug in 33% of cases. A positive rechallenge was reported in two cases.

1.1.0.0 ADDERALL XR and PSYCHOSIS or MANIA

During the period, a total of 92 reports were received by the Sponsor, of which 99% were domestic in origin and one was from Canada. Most frequently stated MedDRA PTs included HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, and MANIA. Half (50%) of the reports were from health professionals. Most reports involved children or adolescents, with 48% of reports in children age 10 years or younger. Most (68%) reports were in males. Concomitant medications were not reported in 36% of cases, and were stated as none in 22%. A psychiatric history other than ADHD was reported in 23% of reports, but only 3% of cases were considered to be an exacerbation of a pre-existing condition. History of seizure disorder was reported in 5% of cases. Drug abuse was reported in 8% of cases, and overdose in 11%. One case was considered to be life-threatening, and 18% of cases required hospital admission. The events resolved after drug was stopped in 37% of cases. A positive rechallenge was reported in three cases.

Selected Case Narratives:

Selected case narratives from the Sponsor's submission are presented below.

Report #STX1-2002-00004 – A 7 year old male experienced visual hallucinations consisting of "saw people sitting in a rocking chair and saw people coming into the house and stealing Christmas presents" and paranoid behaviors, while taking Adderall XR, 20 mg/day, for ADHD. Other events experienced by the patient included: Irrational behaviors and bizarre behaviors. There were no concomitant medications, concurrent medical conditions or past medical history. Outcome of visual hallucinations and paranoid behaviors: resolved with discontinuation of the medication.

Report #STX1-2002-00210 – A 5 year old male experienced a psychotic reaction (hallucinations and illusions described as seeing snakes and polka dot alligators), while taking Adderall XR, 10 mg/day, for ADHD. Other events experienced by the patient included: nightmares (woke up crying and screaming that he had bugs crawling on him). Concomitant medications included: clonidine. Concurrent medical conditions and past medical history included: exposed to multiple drugs as a fetus and adopted at age 2. Outcome: hallucinations stopped when Adderall XR was stopped.

Report #STX1-2002-00218 – An 8 year old female experienced hallucinations (described as seeing people), while taking Adderall XR, 10 mg/day, for ADHD. Other events experienced by the patient included: sleeplessness, weepy, irritable, and appetite suppression. Concomitant medications included:

[7] Surles LK, et al. Adderall-induced psychosis in an adolescent. *J Am Board Fam Prac* 156:498-500, 2002.

none. Concurrent medical conditions and past medical history included: allergies to penicillin, amoxicillin, Keflex, and Cipro. Outcome of hallucinations: Adderall was stopped and the hallucinations resolved (it was thought that this was a drug reaction).

Report #STX1-2002-00225 – A 9 year old female experienced visual hallucinations (started seeing jellyfish on the floor and bugs crawling on her), while taking Adderall XR, 20 mg/day, for ADHD. Co-suspect drug: Adderall (5 mg/day for ODD). Concomitant medications included: Zyrtec. Concurrent medical conditions and past medical history included: ODD. Outcome: resolved (Both suspects medications were stopped).

Report #STX1-2002-00290 – An 8 year old male experienced auditory hallucinations, while taking Adderall XR, 20 mg/day, for ADHD. Other events experienced by the patient included: nightmares. Concomitant medications included: none. Concurrent medical conditions and past medical history included: none. Outcome: Adderall XR was discontinued and the hallucinations have ceased.

Report #STX1-2002-00310 – A 6 year old male experienced a psychotic episode and visual hallucinations (saw and felt snakes on his body) that resulted in hospitalization, while taking Adderall XR, 15mg/day (indication not reported). Concomitant medications included: none. Concurrent medical conditions and past medical history included: not reported. Outcome: resolved.

Report #STX1-2002-00319 – A 9 year old male experienced auditory hallucinations (hearing voices), while taking Adderall XR, either 10 mg/day or 20 mg/day (indication not reported). Concomitant medications included: not reported. Concurrent medical conditions and past medical history included: not reported. Outcome: Adderall XR was discontinued and the patient has not had any further problems.

Report #STX1-2002-00344 – A 10 year old female experienced auditory and visual hallucinations ("someone getting her with a gun"), while taking Adderall XR, 20 mg/day, for ADHD. Other events experienced by the patient included: generalized tremor, dizzy, weak, and did not want to walk. Concomitant medications included: none. Concurrent medical conditions and past medical history included: none. Outcome: She was discharged from the hospital and was "doing fine".

Report # STX1-2003-00100 – A 4 year old male began scratching at "bugs", experienced hallucinations, and saw bugs on his body while taking Adderall XR 10 mg/day for ADHD. Concomitant medications were not reported. Concurrent medical conditions and past medical history was not reported. Adderall XR was discontinued and the patient recovered.

Report # STX1-2003-00115 – A 7 year old female began hallucinating, felt like bugs were crawling on her, and saw bugs in her bed while taking Adderall XR 30 mg/day for ADHD. There were no concomitant medications. Concurrent medical conditions and past medical history was corrective lens user. Adderall XR was decreased to 20 mg/day and the patient recovered.

Report # STX1-2003-00140 – A 7 year old male became scared, didn't sleep, experienced hallucinations and became jumpy while taking Adderall XR, 20 mg/day for ADHD. There were no concomitant medications. Concurrent medical conditions were eczema and asthma. Adderall XR was decreased to 10 mg/day and the patient recovered.

Report # SUS1-2003-00464 – An 11 year old female experienced hearing voices while taking Adderall XR, 25 mg/day for ADHD. There were no concomitant medications, concurrent medical conditions or past medical history. Adderall XR was continued and the voices continued.

Report #SUS1-2004-00791 – A 7 year old male experienced visual hallucinations (seeing water bugs all over the place) while taking Adderall XR 10mg daily for ADHD. Other events experienced by the patient

included: agitation, crying, vomiting, and headache. No concurrent medical conditions, past medical history, and concomitant medications. Outcome of visual hallucinations: resolved.

1.1.0.0 CONCERTA and PSYCHOSIS or MANIA

During the period, a total of 160 reports pertaining to psychosis or mania were received by the Sponsor, of which 71% were domestic in origin. Of the total, 54% were reported in children age 10 years or younger, and 21% were in patients age 11 to 20 years. The majority of reports (78%) were from health professionals, and one report was from published medical literature. Most frequently stated MedDRA Preferred Terms (PTs) included HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, and MANIA. The majority (74%) of the reports were in males. Confounding factors were not identified in the majority of the reports: 6% of cases were stated to be an exacerbation of a pre-existing condition and 16% of cases reported a psychiatric history other than ADHD. Two reports described a history of seizure disorder. No concomitant medications were reported in 69% of cases. Drug abuse was described in 4% of cases, and overdose was stated in 3%. Three cases had a fatal outcome, and 12% of cases required hospital admission. The events resolved after discontinuation of drug in 44% of cases. A positive rechallenge was reported in one case.

Selected Case Narratives:

Selected case narratives from the Sponsor's submission are presented below.

20031001519 Report received from a health professional, United Kingdom: UK/2003/1324. A 6-year-old boy received CONCERTA 36 mg XL from 23-Sep-2003 to 01-Oct-2003. On 01-Oct-2003 the patient developed hallucinations of spiders under the mattress, becoming very upset and frightened and unable to sleep. CONCERTA was stopped and the patient recovered. The causality was considered to be probably related. This event was considered as disabling and therefore serious.

20031005987 Report received from a physician via a sales representative: A 7-year-old boy (weight unspecified), initiated therapy with OROS methylphenidate hydrochloride 18 mg, on an unspecified date, for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) of childhood. No concomitant medications reported. The physician reported that on an unspecified date, the boy's father split the OROS methylphenidate tablet in half. After taking the medication, the boy had a psychotic experience of hallucinations and pulling at his skin. The boy was hospitalized as a result. As of 28-Oct-2003, the continuation of OROS methylphenidate and event outcome was unknown. This report is serious (hospitalization).

20040502009 Report received from a physician via a sales representative. A 6 year old girl (weight unspecified), initiated therapy with OROS methylphenidate hydrochloride 18 mg daily for the treatment of attention-deficit hyperactivity disorder (ADHD) of childhood. The physician reported that, after approximately two weeks of therapy, the patient experienced hallucinations and a "feeling of bugs crawling all over her". The patient was treated for the event in the emergency department with diphenhydramine hydrochloride 25 mg. He confirmed that on 17-Apr- 2004, therapy was discontinued and the event resolved. The physician noted that the patient is a slow metabolizer and is heavy set. This report is not serious. The relationship of the event to OROS methylphenidate hydrochloride was reported as related.

1.1.0.0 PROVIGIL (MODAFINIL) and PSYCHOSIS or MANIA

Although Modafinil is not approved for the treatment of ADHD, there is currently some off label use of this drug in ADHD patients, and an application for this indication is currently under review. For this reason, the Sponsor was asked to provide information about marketed safety experience with this drug as it is currently used. A total of 94 reports pertaining to psychosis or mania have been received by the Sponsor, of which 82% are domestic in origin. The majority of reports (85%) were from health professionals, and one report was from published literature. Only 10% of the reports were in patients younger than 20 years of age. Most (63%) of reports were in patients older than 30 years. The adverse events were considered to be an exacerbation of a pre-existing condition in 26% of cases. Concomitant medications were not reported in 31% of cases. Drug abuse was reported in 4% of cases, and overdose was stated in 2%. The events were considered to be life-threatening in one case, and required hospital admission in 26% of cases. The events resolved after discontinuation of drug in 50% of cases, and a positive rechallenge was described in four cases.

Selected Case Narratives:

Selected case narratives from the Sponsor's submission are presented below.

Clintrace #: US008182: A 6 year old male began treatment on 1-MAY-01 with 100 mg day of modafinil for attention deficit disorder. After one dose, the patient experienced visual hallucinations. Concomitant medications: None. Modafinil therapy was discontinued and the symptoms abated.

Clintrace #: US011131: A 31 year old female with a history of schizophrenia began treatment with 200 mg daily modafinil. One month later, she developed psychotic symptoms. The symptoms resolved when modafinil therapy was discontinued, and Zyprexa dose was increased. Subsequently, the patient was re-challenged with modafinil, and the psychotic symptoms returned.

1.1.0.0 RITALIN and PSYCHOSIS or MANIA

Searches conducted by the Sponsor included both short- and longer-acting formulations of RITALIN brand of methylphenidate, as well as information about dexmethylphenidate (FOCALIN). Very few cases were identified for dexmethylphenidate, corresponding to the relatively limited utilization of this drug. During the period, a total of 130 reports pertaining to psychosis or mania were received by the Sponsor, of which 33% were domestic in origin, 18% were from Japan, and 49% were from other countries. MedDRA PTs included HALLUCINATION, PSYCHOTIC DISORDER, and MANIA. Most reports (67%) were in males. Age distribution included 26% of reports in children age ten years or less, 26% of reports in the age group 11 to 20 years of age, and age was not reported in 22% of the total. The majority of reports (75%) were from health professionals. The events were considered to be an exacerbation of a pre-existing condition in 10% of cases, and 31% of patients had a psychiatric history other than ADHD. No concomitant medications were reported in 69% of cases. A history of seizure disorder was reported in three cases, drug abuse was reported in 11% of reports, and overdose was stated in 10% of the total. A fatal outcome was described in two cases, the events were considered life-threatening in two cases, and hospital admission was required in 22% of

cases. The events resolved after discontinuation of drug in 25% of cases, and a positive rechallenge was reported in one case.

1.1.0.0 STRATTERA (ATOMOXETINE) and PSYCHOSIS or MANIA

During the period, a total of 360 reports pertaining to psychosis or mania were received by the Sponsor, of which 94% were domestic in origin. Most frequently reported MedDRA PTs included MANIA, HALLUCINATION, PSYCHOTIC DISORDER, and PARANOIA. The majority of reports were in children, with 37% describing patients ten years or younger and 36% of patients between the ages of 11 and 20 years. Most reports were in males (66%). The majority of reports (69%) were from health professionals, and three cases in the Sponsor's submission were from published medical literature. The events were considered to be an exacerbation of a pre-existing condition in 9% of cases. A psychiatric history other than ADHD was reported in 44% of cases; however, many of the stated conditions appeared to be relatively minor. A history of seizure disorder was reported in 1% of cases, and drug abuse was stated in 5% of the reports. In 4% of the cases, overdose was reported. No concomitant medications were reported in 31% of the reports, and were stated to be none in an additional 21% of the total. The events were considered to be life-threatening in one case, and required hospital admission in 16% of reports. The events resolved after discontinuation of drug in 26% of cases. A positive rechallenge was reported in one case.

Selected Case Narratives:

Selected case narratives from the Sponsor's submission are presented below.

USA030330912: A physician reported that a 9-year-old female developed hallucinations during treatment with atomoxetine for ADHD. The patient told her mother that it felt like someone was trying to slash her wrists. Concomitant medications included cephalexin. Atomoxetine was discontinued after three days of therapy. The event resolved.

USA030332113: A physician reported that a 12-year-old male with a history of obsessive-compulsive disorder and diagnosed with ADHD at age 7, developed mixed manic episode with hallucinations, paranoia, and delusions after approximately three months of therapy with atomoxetine 40 mg daily for the treatment of increased hyperactivity and inattentiveness. There were no concomitant medications. Atomoxetine was discontinued and risperidone was initiated. The events had not resolved at the time of the report. Prior therapy included methylphenidate and amphetamine / dextroamphetamine with no change in mood reported.

USA030433792: A physician reported that a 7-year-old female received atomoxetine 18 mg daily for the treatment of ADHD. Within hours of taking the first dose, the patient started talking non stop, and stated that she was happy. The next morning the child was still elated. Two hours after taking her second dose of atomoxetine, the patient started running very fast, stopped suddenly, and fell to the ground. The patient stated that she had run into a wall (there was no wall there). The patient slept a lot that day, and was hallucinating. Atomoxetine was discontinued. The outcome of the events was not reported.

USA030536309: A psychiatrist reported that an 8-year-old male developed hallucinations immediately after taking atomoxetine. The patient had no significant medical history, and there were no concomitant medications. Atomoxetine was discontinued and methylphenidate was started. The events resolved.

USA030537127: A physician reported that a 9-year-old female developed auditory and visual hallucinations after three or four weeks of therapy with atomoxetine 40 mg daily (indication not stated). The child told her school counselor that she was hearing voices and seeing things. The reporter planned to discontinue atomoxetine therapy. Outcome of the events was not reported.

1.1.0 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE

Searches of the FDA AERS Safety Database were conducted and reviewed as described previously. Duplicate reports, reports which were considered to be of poor quality, as well as cases which were considered by the Safety Evaluators to be very unlikely causally-associated with the drug(s) of interest, were excluded from this analysis.

1.1.0.0 AMPHETAMINE / DEXTROAMPHETAMINE and PSYCHOSIS or MANIA

A total of 77 non-excluded cases describing signs or symptoms of psychosis or mania were identified in the FDA AERS safety database for the period. The majority (87%) were domestic in origin. Nine cases were from published medical literature, and an additional 35% of reports were from health professionals. Most frequently reported MedDRA PTs included HALLUCINATION, PSYCHOTIC DISORDER, and MANIA. Concomitant medications were not reported in 49% of cases, and were stated as none in an additional 22% of reports. No prior history of similar signs and symptoms was reported in the majority (87%) of cases, and the events were considered to be an exacerbation of a pre-existing condition in 13% of cases. Psychiatric history other than ADHD was reported in 35% of cases. A history of seizure disorder was stated in one case, drug abuse was stated in two cases, and overdose was involved in three cases. The majority of cases were reported in children and adolescents with 30% occurring in patients age ten years or less. An additional 30% of reports were in the age group 11 to 20 years. The events were reported to occur shortly after the initiation of drug in 17% of cases (within minutes to days); however, some cases did not occur until after months (27%) or years (10%) of prescription drug use. The events resulted in a fatal outcome in four cases, were considered life-threatening in one case, and required hospital admission in 52% of the total reports. The events resolved after discontinuation of drug in most (58%) cases. Positive rechallenge was reported in two cases.

1.1.0.0 ATOMOXETINE and PSYCHOSIS or MANIA

A total of 292 non-excluded cases pertaining to psychosis or mania were identified in the FDA AERS safety database for the period. Almost all (97%) were domestic in origin, and most (66%) were reported by health professionals. Three reports were identified from published medical literature. The author[8] of one of these three reports (ISR #4398235-X) states that he has observed 10 cases of atomoxetine-induced mania induction in his pediatric psychiatry practice. The most frequently stated MedDRA PTs from the AERS search included MANIA, HALLUCINATION,

[8] Henderson TA, Hartman K. Aggression, mania, and hypomania induction associated with atomoxetine. *Pediatrics* 2004; 114:895-896.

PSYCHOTIC DISORDER, and PARANOIA. Most reports were in children and adolescents, with 36% of reports in children ten years of age or less, and 40% of reports in patients age 11 to 20 years. Concomitant medications were not reported in 33% of cases, and were stated to be none in an additional 19% of total reports. The psychiatric adverse events occurred within days of drug initiation in 21% of reports; however, the events did not occur until after months of atomoxetine therapy in 12% of reports, and two cases occurred after years of treatment with atomoxetine. The events were considered to be an exacerbation of a pre-existing condition in 9% of cases. A psychiatric history other than ADHD was reported in 34% of cases. There was a history of seizure disorder in 2% of cases. Drug abuse was stated in 2% of reports, and overdose was described in 3% of the total. One case was considered life-threatening, and 16% of cases required hospital admission. The events resolved after discontinuation of drug in 33% of cases, and a positive rechallenge was reported in four cases.

1.1.0.0 METHYLPHENIDATE and PSYCHOSIS or MANIA

A total of 148 non-excluded reports pertaining to psychosis or mania were identified in the FDA AERS safety database for the period. Most reports (63%) were domestic in origin, and 14% of the total originated from the United Kingdom. Most (68%) reports were from health professionals, and eleven cases were identified in published medical literature. Most frequently stated MedDRA PTs included HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, and MANIA. Most reports described children or adolescents, with 48% occurring in children age ten years or less, and 26% in patients age 11 to 20 years. Males predominated (70%). The events reportedly occurred within days of initiating drug treatment in 29% of cases; however, in some cases the events did not occur until after months (11%) or years (7%) of methylphenidate therapy. Concomitant medications were not reported in 42% of cases, and were stated to be none in 5% of the total. The psychiatric adverse events were considered to be an exacerbation of a pre-existing condition in 7% of cases; however, a psychiatric history other than ADHD was reported in 24% of patients. History of seizure disorder was stated in two cases, drug abuse in five cases, and overdose was reported in nine (6%) cases. A fatal outcome was reported in two cases, and the events were considered life-threatening in three cases. Admission to hospital was required in 28% of cases. The events resolved after stopping drug in 48% of cases, and a positive rechallenge was reported in four cases.

Selected case reports from published literature[9]:

Case 1: A 7-year-old boy with ADHD and oppositional defiant disorder was treated with methylphenidate, 0.3 mg/kg (7.5 mg) once daily. After one year of treatment, he reported seeing and feeling snakes crawling on and around him starting approximately one hour after drug ingestion. The teaching staff assumed an emotional problem and used psychological interventions to free him of these behaviors. When these proved ineffective and to rule out drug-induced hallucinations, placebo was substituted for methylphenidate with immediate cessation of hallucinations. Pemoline was begun, and no psychiatric problems reappeared during a follow-up period of more than two years.

Case 2: A 12-year-old boy with cerebral palsy, low normal intelligence, and ADHD, combined subtype, was treated with methylphenidate 0.3 mg/kg (10 mg) once daily with marked improvement in attention and hyperactivity. One morning, he was observed crawling on the floor complaining that roaches were

[9] Gross-Tsur V, Joseph A, Shalev RS. Hallucinations during methylphenidate therapy. *Neurology* 2004; 63:753-4.

surrounding him. This phenomenon appeared two hours after ingesting methylphenidate, continuing for almost two hours, and disappeared without any specific intervention. Methylphenidate was withdrawn, and there was no recurrence. However, deterioration in school performance was so dramatic that rechallenge with methylphenidate was attempted at his previous dose. Immediate recurrence of hallucinations necessitated stopping methylphenidate. Three-year follow-up evaluation has been uneventful.

Case 3: A 7.5-year-old boy with normal intelligence was diagnosed with ADHD and mild learning disabilities. He had been treated successfully with 0.25 mg/kg methylphenidate once daily (7.5 mg). Several months later, he became distressed, claiming that mosquitoes and other crawling creatures were in his bedroom and on him. He refused to sleep in his bed and would not enter his room. After several days, methylphenidate was stopped, the visual and haptic sensations ceased, and within a week he returned to sleep in his room. During a follow-up period of two years, there was no recurrence of the hallucinations.

1.1.0.0 MODAFINIL and PSYCHOSIS or MANIA

A total of 43 non-excluded reports pertaining to psychosis or mania were identified in the FDA AERS safety database for the period. The indication for modafinil in most of these cases was narcolepsy, although a few reports indicated off-label use in ADHD. Most (91%) reports were domestic in origin, and two reports were from France. Most (88%) reports were from health professionals. One case report from published literature was included in the Sponsor submission, but was not identified in the AERS search. The most frequently stated MedDRA PTs included HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, and MANIA. Concomitant medications were not reported in 23% of cases, and were stated to be none in an additional 5% of the total. Most of the reports (63%) were in adults older than 30 years of age. Three cases were reported in children ten years or less, and four cases were in the age group 11 to 20 years. Slightly more than half of the reports (53%) were in female patients. The onset of the psychiatric adverse events was within weeks of initiating modafinil treatment in 45% of cases; however, the events did not occur until after months (16%) or years (12%) in some patients. The events were considered to be an exacerbation of a pre-existing condition in 30% of cases, and a psychiatric history was reported in 60% of cases. History of seizure disorder was reported in two cases, drug abuse in five cases, and overdose was stated in six cases. The events were considered life-threatening in two cases, and required hospital admission in 47% of patients. The events resolved after drug was stopped in most (60%) cases, and a positive rechallenge was reported in four cases.

1.1.0 DISCUSSION

This review of marketed experience with amphetamine/dextroamphetamine, atomoxetine, methylphenidate, and modafinil, presents compelling evidence for a likely causal association between each of these four drugs and treatment emergent onset of signs and/or symptoms of psychosis or mania, notably hallucinations, in some patients.

Cases identified in this review are characterized by the following attributes:

- Published case reports in medical literature;
- Strong temporal association in some cases;
- Positive dechallenge in many cases;

- Reports of positive rechallenge;
- Reports with few confounders such as pre-existing history of similar condition, concomitant medications, drug abuse;
- Medical confirmation.

These data show that some patients, including some with no identifiable risk factors, can develop drug-related signs or symptoms of psychosis or mania, such as hallucinations, at usual doses of these drugs. With the exception of modafinil, a consistent male predominance was observed in reports of psychosis-related events, with roughly two-thirds of cases occurring in males. With the same exception, likely reflecting the difference in the current modafinil-treated patient population (i.e., narcolepsy), a substantial proportion of psychosis-related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common[10]. The occurrence of such symptoms in young children may be particularly traumatic and undesirable, both to the child and the parents. The predominance noted in these cases of hallucinations, both visual and tactile involving insects, snakes and worms, is striking, and deserves further evaluation, such as review by clinical experts in Child Psychiatry.

Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of drug-induced adverse effects. Cases which include a positive rechallenge were reported by the Sponsors for each of the drugs included in this analysis (see Table 3.2.3.1), and were also identified in the FDA AERS analysis (see Table 3.2.3.2).

In many patients, the events resolved after stopping the drug. In the FDA AERS review, resolution of the events after stopping the drug was reported in 58% of amphetamine / dextroamphetamine cases, 60% of modafinil cases, 33% of atomoxetine cases, and 48% of methylphenidate cases. (*Note:* Outcome of the psychiatric adverse events was not reported in 21% of amphetamine / dextroamphetamine cases, 9% of modafinil cases, 41% of atomoxetine cases, and 30% of methylphenidate cases.)

For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events. For instance, drug abuse was reported in fewer than 3% of overall cases from the FDA AERS analysis. In the overwhelming majority of cases (roughly 90%), there was no prior history of a similar condition.

A tabular summary of these data are presented below in Table 3.2.3.1 (Sponsor Submissions) and Table 3.2.3.2 (FDA AERS Safety Database).

[10] Mosholder. Psychiatric Adverse Events in Clinical Trials of Drugs for Attention Deficit Hyperactivity Disorder (ADHD). March 3, 2006. PID# D050243.

TABLE 3.2.3.1
POSTMARKETING SAFETY DATA FROM SPONSOR SUBMISSIONS
SIGNS and/or SYMPTOMS of PSYCHOSIS or MANIA

DRUG	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event	Medical confirmation from HCP
ADDERALL	*	84 (100)	28 (33)	2 (2)	16 (19)	82 (98)	25 (30)
ADDERALLXR	*	92 (100)	34 (37)	3 (3)	20 (22)	89 (97)	46 (50)
CONCERTA	1 (0.6)	160 (100)	70 (44)	1 (0.6)	110 (69)	150 (94)	125 (78)
METADATE	*	39 (100)	23 (59)	1 (3)	21 (54)	36 (92)	20 (51)
PROVIGIL	1 (1)	94 (100)	47 (50)	4 (4)	29 (31)	70 (74)	80 (85)
RITALIN	*	130 (100)	32 (25)	1 (1)	90 (69)	116 (89)	97 (75)
STRATTERA	3 (0.8)	360 (100)	95 (26)	1 (0.3)	77 (21)	323 (90)	250 (69)

* Although not identified as such in the Sponsor's submission, published case reports for amphetamine and methylphenidate products were identified in the AERS safety database during this review.

TABLE 3.2.3.2
ANALYSIS OF FDA AERS DATA FOR REPORTS of PSYCHOSIS or MANIA
MedWatch Reports received by FDA from January 1, 2000 through June 30, 2005

DRUG [11]	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event reported	Medical confirmation from HCP
Amphetamine / dextroamphetamine	9 (12)	77 (100)	45 (58)	2 (3)	55 (71)	67 (87)	36 (47)
Atomoxetine	3 (1)	292 (100)	96 (33)	4 (1)	151 (52)	265 (91)	197 (67)
Methylphenidate	11 (7)	148 (100)	71 (48)	4 (3)	69 (47)	137 (93)	111 (75)
Modafinil	*	43 (100)	26 (60)	4 (9)	12 (28)	30 (70)	38 (88)

* A case report from medical literature was included in the Sponsor's submission but was not identified in the AERS search.

[11] Includes all branded and generic products, and all formulations available during the time period

1.1.0 REGULATORY CONSIDERATIONS FOR DRUGS CURRENTLY APPROVED TO TREAT ADHD: PSYCHOSIS OR MANIA

Current approved labeling for ADDERALL and ADDERALL XR includes a WARNING regarding use of amphetamine in psychotic children. The ADVERSE REACTIONS section describes psychotic episodes at recommended doses (rare). The DRUG ABUSE AND DEPENDENCE section states that the most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. The OVERDOSAGE section states that individual response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Current approved labeling for STRATTERA includes a WARNING regarding suicidal ideation. A description of symptoms which have been reported with STRATTERA lists mania, and states that, although a causal link between the emergence of such symptoms and the emergences of suicidal impulses has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality.

Current approved labeling for most brands of methylphenidate (e.g., CONCERTA and RITALIN) include a WARNING for psychosis which states that clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder. A section on Drug Dependence states that frank psychotic episodes can occur, especially with parenteral abuse. The ADVERSE REACTIONS section states that toxic psychosis has been reported. The OVERDOSAGE section describes signs and symptoms of acute overdosage, which may include hallucinations.

Recommendation

Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs or symptoms of psychosis or mania (such as hallucinations) in patients without identifiable risk factors, and occurring at usual dosages. In addition, current labeling does not clearly state the importance of stopping drug therapy in any patient who develops signs and/or symptoms of psychosis or mania during treatment of ADHD. We recommend that these issues be addressed.

1.2 SIGNS and/or SYMPTOMS OF AGGRESSION or VIOLENT BEHAVIOR[12]

1.2.0 Sponsor Submissions

1.2.0.0 ADDERALL and AGGRESSION

During the period, 83 reports pertaining to aggression or violent behavior were received by the Sponsor, all of which were domestic in origin. Most reports were in children, with 57% of the total describing children age ten years or younger. Males predominated (78%). Most frequent MedDRA PTs included AGGRESSION, ANGER, HOSTILITY, and HOMICIDAL IDEATION. Concomitant medications were not reported in 51% of cases, and were stated as none in an additional 14% of the total. The events were considered to be an exacerbation of a pre-existing condition in 8% of reports, and 19% of patients were reported to have a psychiatric history other than ADHD. Seizure disorder was reported in three cases, drug abuse in four cases, and overdose was stated in four cases. The events required hospital admission in four cases (5%); however, most reports (88%) were classified as non-serious. The events resolved after drug was stopped in 22% of cases, and a positive rechallenge was reported in three cases.

1.2.0.0 ADDERALL XR and AGGRESSION

During the period, a total of 95 reports were received by the Sponsor, of which most (97%) were domestic in origin. Most frequent MedDRA PTs included AGGRESSION, ANGER, HOSTILITY, and HOMICIDAL IDEATION. Reports in the pediatric age group were most common with 65% of cases occurring in children age ten years or less. Males predominated (79%). The events were considered to be an exacerbation of a pre-existing condition in three cases, and a psychiatric history other than ADHD was reported in 16% of cases. Seizure disorder was reported in three cases, drug abuse was reported in zero cases, and overdose was stated in one case. The events required hospital admission in one case; however, most reports (95%) were classified as non-serious. Concomitant medications were not reported in 47% of cases, and were stated as none in an additional 22% of reports. The events resolved after stopping drug in 25% of cases, and a positive rechallenge was stated in two cases.

1.2.0.0 CONCERTA and AGGRESSION

During the period, a total of 219 reports were received by the Sponsor, of which 71% were domestic in origin, and 11% originated from the UK. Most reports (69%) were from health professionals. Most frequent MedDRA PTs included AGGRESSION, ANGER, HOSTILITY, and HOMICIDAL IDEATION. Reports in the pediatric age group were most common with 44% of cases occurring in children age ten years or less, and 20% occurring in patients age 11 to 20

[12] Search terms for this condition include aggression, anger, hostility, physical assault, murder, imprisonment, homicidal ideation (see Attachment 2 for complete list).

years. Males predominated (76%). The events were considered to be an exacerbation of a pre-existing condition in 15% of cases, and a psychiatric history other than ADHD was reported in 12% of cases. Concomitant medications were not reported in 70% of cases. Seizure disorder was reported in zero cases, drug abuse was reported in four cases, and overdose was stated in nine (4%) cases. One case included a fatal outcome and hospital admission was required in 3% of cases. Most cases (78%) were classified as non-serious. Seizure disorder was stated in no cases, drug abuse was reported in four cases, and overdose was stated in nine cases (4%). The events resolved after stopping the drug in 37% of cases, and a positive rechallenge was reported in eight cases.

1.2.0.0 PROVIGIL (MODAFINIL) and AGGRESSION

A total of 22 reports pertaining to aggression during modafinil use were received by the Sponsor during the period. The indication for modafinil use in most of these reports was narcolepsy. Half (50%) of the reports were domestic in origin, 27% of reports originated from the UK. Most reports (64%) were from health professionals. Most cases (64%) described adult patients older than 21 years, with an equal number of males and females. Most frequent MedDRA PTs included AGGRESSION, ANGER, and AGITATION. One report was considered life-threatening, two reports required hospital admission, and 86% of reports were classified as non-serious. The events resolved after stopping drug in 55% of cases, and a positive rechallenge was reported in one case.

1.2.0.0 RITALIN and AGGRESSION

The Sponsor did not provide a separate analysis of reports of aggression. It appears that these cases may have been included under the miscellaneous category. Due to time constraints, these reports have not been included in this analysis.

1.2.0.0 STRATTERA (ATOMOXETINE) and AGGRESSION

During the period, a total of 992 reports pertaining to aggression or violent behavior were received by the Sponsor, of which 93% were domestic in origin. Most reports (59%) were from consumers, and 39% of reports were from health professionals. One report was from published medical literature. Most cases described children less than ten years of age (47%), or adolescents between the ages of 11 and 20 years (30%). Males predominate (76%). Concomitant medications were not reported in 30% of reports and were stated as none in an additional 23% of the total. The events were considered to be an exacerbation of a pre-existing condition in 9% of reports, and a psychiatric history other than ADHD was reported in 37% of cases. Most frequent MedDRA PTs included AGGRESSION, ANGER and HOMICIDAL IDEATION. The events were considered life-threatening in one report, and required hospital admission in 3% of cases; however, the majority of reports (93%) were classified a non-serious. Seizure disorder was reported in 2% of cases, drug abuse was stated in 1% of cases, and overdose was reported in 4% of cases. The events resolved after drug was stopped in 13% of reports, and a positive rechallenge was reported in thirteen cases.

1.2.0 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE

Analysis of cases identified from searches of the FDA AERS safety database was completed, and was found to be consistent with the data included in the Sponsors' submissions, with one exception. Searches of the FDA AERS safety database identified seven case reports from published literature describing aggression in ADHD patients receiving methylphenidate. However, on review, some of these reports had been published prior to the time period under study, but were entered into the AERS database during this period.

Tabular summaries describing characteristics of the AERS MedWatch reports pertaining to aggression are presented in Attachment 5, and also below in Table 3.3.3.2.

1.2.0 DISCUSSION

Cases of aggression or violent behavior included in this review were generally classified as non-serious, although approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles. The majority of the reports of aggression for drugs currently approved for the treatment of ADHD were in children and adolescents, with a striking male predominance.

No specific risk factors for aggression or violent behavior were identified in this analysis. For instance, drug abuse was reported in fewer than 5% of overall cases identified from the FDA AERS search. Also of note, a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events. Several cases describing positive rechallenge were reported for each of the drugs included in this analysis.

Summary information supporting a positive causality assessment is presented below in Tables 3.3.3.1 and 3.3.3.2.

TABLE 3.3.3.1
POSTMARKETING SAFETY DATA FROM SPONSOR SUBMISSIONS
SIGNS and/or SYMPTOMS of AGGRESSION

Drug-Event Combinations	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event	Medical confirmation from HCP
ADDERALL Aggression	0	83 (100)	18 (22)	3 (4)	52 (63)	76 (92)	13 (16)
ADDERALL XR Aggression	0	95 (100)	24 (25)	2 (2)	21 (22)	92 (97)	16 (17)
CONCERTA Aggression	0	219 (100)	80 (37)	8 (4)	154 (70)	185 (84)	152 (69)
METADATE Aggression	0	42 (100)	20 (48)	4 (10)	28 (67)	37 (88)	14 (33)
PROVIGIL[13] Aggression	0	22 (100)	12 (55)	1 (5)	12 (55)	17 (77)	14 (64)
RITALIN Aggression	nr	nr	nr	nr	nr	nr	nr
STRATTERA Aggression	1 (0.1)	992 (100)	132 (13)	13 (1)	232 (23)	887 (89)	382 (39)

TABLE 3.3.3.2
ANALYSIS OF FDA AERS DATA FOR REPORTS OF AGGRESSION
MedWatch Reports received by FDA from January 1, 2000 through June 30, 2005

Drug[14]-Event Combinations	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event reported	Medical confirmation from HCP
Amphetamine / dextroamphetamine Aggression	0	28 (100)	11 (39)	1 (4)	17 (61)	25 (89)	11 (39)
Atomoxetine Aggression	3 (0.5)	566 (100)	96 (17)	16 (3)	115 (20)	456 (81)	197 (35)
Methylphenidate Aggression	7 (6)	110 (100)	57 (52)	6 (5)	69 (63)	100 (91)	70 (64)
Modafinil[15] Aggression	0	8 (100)	3 (38)	0	3 (38)	5 (63)	7 (88)

[13] Most frequent indication reported for PROVIGIL (modafinil) use was narcolepsy, although some off-label use in ADHD was also reported.

[14] Includes all branded and generic products, and all formulations available during the time period

[15] Most frequent indication reported for Modafinil use was narcolepsy, although some off-label use in ADHD was also reported.

1.2.0 REGULATORY CONSIDERATIONS FOR DRUGS CURRENTLY APPROVED TO TREAT ADHD: AGGRESSION AND VIOLENT BEHAVIOR

Current approved labeling for amphetamine / dextroamphetamine and methylphenidate products does not include information about drug-induced aggression or violent behavior.

Current approved labeling for STRATTERA includes the following PRECAUTION:

> PRECAUTIONS
> Aggressive Behavior or Hostility — Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that Strattera causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with Strattera compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Recommendation

We recommend updating prescribing information for amphetamine / dextroamphetamine and methylphenidate products to include information about aggression or violent behavior.

Consideration should be given to stopping the dose of medication in patients who develop aggression or violent behavior during drug therapy of ADHD. Further thoughts should be given to exploring whether these aggression or violent behaviors may be dose-related adverse events.

1.3 SIGNS and/or SYMPTOMS OF SUICIDALITY[16]

1.3.0 Sponsor Submissions

1.3.0.0 ADDERALL and SUICIDALITY

During the period, a total of 18 reports pertaining to suicidality were received by the Sponsor, all of which were domestic in origin. Most frequent MedDRA PTs included OVERDOSE, SELF INJURIOUS BEHAVIOR, SUICIDE ATTEMPT, and COMPLETED SUICIDE. Five reports (28%) were in children ten years old or younger, and four reports were in the age group 11 to 20 years. Males predominated (83%). The events were considered to be an exacerbation of a pre-

[16] Search terms for this condition include suicidal ideation, intentional self-injury, overdose, self injurious behavior, self-mutilation, suicide attempt, completed suicide (see Attachment 2 for complete list).

existing condition in one case, and a psychiatric history other than ADHD was reported in four cases (22%). Concomitant medications were not reported in 24% of reports, and were stated as none in an additional 24% of the total. Seizure disorder was reported in no cases, drug abuse in five cases, and overdose was stated in 44% of cases. The events resulted in a fatal outcome in two cases, were considered life-threatening in one case, and required hospital admission in four cases. The events were classified as non-serious in 39% of reports. The events resolved after drug was stopped in two cases, and a positive rechallenge was reported in one case.

1.3.0.0 ADDERALL XR and SUICIDALITY

During the period, a total of 33 reports were received by the Sponsor, all of which were domestic in origin. Most frequent MedDRA PTs included OVERDOSE, SUICIDAL IDEATION, COMPLETED SUICIDE, SUICIDE ATTEMPT, and SELF INJURIOUS BEHAVIOR. Seventeen reports (52%) were in children age ten years or younger. Most reports were in males (67%). The events were considered to be an exacerbation of a pre-existing condition in none of the reports. Concomitant medications were not reported in 39% of cases, and were stated as none in an additional 18% of the total. Psychiatric history other than ADHD was reported in 21% of cases. A history of seizure disorder was reported in two cases, drug abuse in seven cases (21%), and overdose was stated in 45% of reports. A fatal outcome was reported in two cases, and the events were considered to be life-threatening in two cases. Seven patients (21%) required hospital admission, and the events were considered non-serious in 42% of cases. The events resolved after drug was stopped in 33% of cases, and a positive rechallenge was reported in one case.

1.3.0.0 CONCERTA and SUICIDALITY

During the period, a total of 121 reports were received by the Sponsor, of which 67% were domestic in origin, and 9% were from Germany. Most reports were received from health professionals (70%). Most frequent MedDRA PTs included OVERDOSE, SUICIDAL IDEATION, SUICIDE ATTEMPT, COMPLETED SUICIDE, and SELF INJURIOUS BEHAVIOR. Most reports were in children and adolescents with 34% in children age ten or younger and 38% in patients age 11 to 20. Males (64%) outnumber females. The events were considered to be an exacerbation of a pre-existing condition in 8% of cases. Psychiatric history other than ADHD was reported in 17% of cases. Concomitant medications were not reported in 74% of cases. A history of seizure disorder was stated in one case, drug abuse was reported in 12% of cases, and overdose was stated in 61% of cases. A fatal outcome was reported in six cases, and the events were considered life-threatening in one case. Hospital admission was required in 8% of cases, and the report was classified as non-serious in 50% of the total. The events resolved after drug was stopped in 26% of cases, and a positive rechallenge was reported in four cases.

1.3.0.0 PROVIGIL (MODAFINIL) and SUICIDALITY

A total of 18 reports pertaining to suicidality were received by the Sponsor during the period. The indication for modafinil use in most of the cases was narcolepsy. Most reports (83%) were domestic in origin and were reported by a health professional (78%). Most reports (56%) were

in females. All but one case occurred in adults. Concomitant medications were not reported in 72% of cases. Most frequently reported MedDRA PTs included SUICIDE ATTEMPT, DEPRESSION SUICIDAL, COMPLETED SUICIDE, and SUICIDAL IDEATION. The events were considered to be an exacerbation of a pre-existing condition in three cases, and a psychiatric history other than ADHD was reported in 44% of cases. Seizure disorder was reported in no cases, drug abuse in one case, and overdose was stated in 22% of cases. A fatal outcome was reported in three cases, and the events were considered to be life-threatening in two cases. Hospital admission was required in 28% of cases, and 50% of the reports were classified as non-serious. The events resolved after drug was stopped in 39% of cases.

1.3.0.0 RITALIN and SUICIDALITY

A total of 67 reports were received by the Sponsor during the period, of which 27% were domestic, 27% were from Japan, 15% were from Germany, and 31% were from other countries. Most reports (75%) were from health professionals. Most frequently stated MedDRA PTs included SUICIDAL IDEATION, COMPLETED SUICIDE, and SUICIDE ATTEMPT. Eleven reports (16%) were in children ten years of age or younger and 27% of reports were in patients age 11 to 20. Concomitant medications were not reported in 63% of the total. Males predominate (64%). The events were considered to be an exacerbation of a pre-existing condition in 4% of reports, and a psychiatric history other than ADHD was reported in 30% of the total. A history of seizure disorder was reported in zero cases, drug abuse was stated in 31% of reports, and overdose was described in 66% of cases. A fatal outcome was reported in seven cases ((10%), and the events were considered life-threatening in four cases. Hospital admission was required in 36% of cases. The events resolved after drug was stopped in 16% of cases.

1.3.0.0 STRATTERA (ATOMOXETINE) and SUICIDALITY

During the period, a total of 399 reports pertaining to suicidality were received by the Sponsor, of which 93% were domestic in origin. Most reports (55%) were from health professionals, and 42 cases (11%) were from published medical literature. Most frequently stated MedDRA PTs included SUICIDAL IDEATION, ACCIDENTAL OVERDOSE, OVERDOSE, INTENTIONAL SELF INJURY, SUICIDE ATTEMPT, COMPLETED SUICIDE, and SELF INJURIOUS IDEATION. Most reports were in children and adolescents with 21% of reports in children ten years or younger and 39% of reports in patients age 11 to 20 years. Males predominate (65%). Concomitant medications were not reported in 31% of cases, and were stated as none in an additional 28% of the total. The events were considered to be an exacerbation of a pre-existing condition in 7% of cases. A psychiatric history other than ADHD was reported in 32% of cases. A history of seizure disorder was stated in 2% of cases, drug abuse in 3%. The Sponsor considered that overdose occurred in 55% of reports; however, the definition of overdose used in the analysis appears to include all cases where the administered dose exceeded the usual prescribed dose for that individual patient (as well as cases where obviously excessive doses were taken). In addition, it appears the Sponsor included some cases in their submission where a relatively slight overdose was accidental and suicidal intentions seem unlikely. A fatal outcome was reported in seven cases (2%), and the events were considered life-threatening in five cases (1%). Hospital admission was required in 13% of cases, and the events were classified as non-

serious in 73% of reports. The events resolved after drug was stopped in 17% of cases, and a positive rechallenge was reported in three cases.

1.3.0 ANALYSIS OF MEDWATCH REPORTS FROM FDA AERS SAFETY DATABASE

Analysis of cases identified from searches of the FDA AERS safety database was completed, and was found to be generally consistent with the data included in the Sponsors' submissions, with two exceptions. For STRATTERA (atomoxetine), the Sponsor identified more reports from published literature than were identified in the FDA AERS safety database search. Conversely, for methylphenidate, more reports from published literature were identified in the FDA AERS safety database than were identified in the Sponsor's submissions.

Tabular summaries describing characteristics of the AERS MedWatch reports pertaining to suicidality are presented in Attachment 5, and also below in Table 3.4.3.2.

1.3.0 DISCUSSION

Current approved labeling for STRATTERA (atomoxetine) includes a BOXED WARNING regarding an increased risk of suicidal ideation in children. This review of marketed safety experience with atomoxetine confirms the likelihood of a causal association between atomoxetine therapy and suicidality in some patients.

A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. For instance, further case review by a clinical expert of data obtained for this analysis may yield additional insights regarding possible co-occurrence of undesired psychiatric effects in some vulnerable patients that could contribute to suicidal ideation or behaviors.

Criteria for assessment are summarized below in Tables 3.4.3.1 and 3.4.3.2.

TABLE 3.4.3.1
POSTMARKETING SAFETY DATA FROM SPONSOR SUBMISSIONS
SIGNS and/or SYMPTOMS of SUICIDALITY

Drug	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event	Medical confirmation from HCP
ADDERALL	0	18 (100)	2 (11)	1 (6)	16 (89)	17 (94)	5 (28)
ADDERALLXR	0	33 (100)	11 (33)	1 (3)	6 (18)	33 (100)	12 (36)
CONCERTA	0	121 (100)	32 (26)	4 (3)	89 (74)	111 (92)	85 (70)
METADATE	0	9 (100)	7 (78)	0	2 (22)	9 (100)	7 (78)
PROVIGIL	0	18 (100)	7 (39)	0	13 (72)	15 (83)	14 (78)
RITALIN	0	67 (100)	11 (16)	0	42 (63)	63 (94)	50 (75)
STRATTERA	42 (11)	399 (100)	69 (17)	3 (0.8)	113 (28)	313 (78)	220 (55)

TABLE 3.4.3.2
ANALYSIS OF FDA AERS DATA FOR REPORTS OF SUICIDALITY
MedWatch Reports received by FDA from January 1, 2000 through June 30, 2005

Drug[17]	Number (percent) of cases with selected criteria present						
	Published medical literature	Temporal association	Positive dechallenge	Positive rechallenge	No concomitant medications reported	No prior history of event reported	Medical confirmation from HCP
Amphetamine / dextroamphetamine	0	29 (100)	10 (34)	1 (3)	21 (72)	23 (79)	13 (45)
Atomoxetine	2 (1)	214 (100)	65 (30)	9 (4)	119 (56)	172 (80)	134 (63)
Methylphenidate	15 (15)	100 (100)	38 (38)	2 (2)	54 (54)	91 (91)	83 (83)
Modafinil	0	18 (100)	11 (61)	0	7 (39)	11 (61)	16 (89)

[17] Includes all branded and generic products, and all formulations available during the time period

1.3.0 REGULATORY CONSIDERATIONS FOR DRUGS CURRENTLY APPROVED TO TREAT ADHD: SUICIDALITY

Current approved labeling for amphetamine / dextroamphetamine and methylphenidate products does not contain information regarding suicidality. Further evaluation of this issue is recommended.

Current approved labeling for STRATTERA (atomoxetine) clearly describes issues related to suicidality in a BOXED WARNING.

1.3 SUMMARY AND CONCLUSION

An extensive review of marketed safety experience of drugs widely used in the treatment of ADHD, as well as a currently marketed product for which application is under review for this indication, was undertaken as a result of issues raised by the Pediatric Advisory Committee in June 2005. A high level analysis of the Sponsor's submissions, as well as case review from the FDA AERS safety database, was accomplished. Conclusions and recommendations based on that analysis are presented in this consult; however, more in-depth review and discussion of these data are clearly desirable, and may provide additional insights into risk factors, as well as levels of risk for occurrence of psychiatric adverse effects during drug therapy of ADHD.

The most important finding of this current review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors at usual doses of any of the drugs currently used to treat ADHD. The predominance in young children of hallucinations, both visual and tactile, involving insects, snakes and worms is striking, and deserves further evaluation, such as review by clinical experts in Child Psychiatry. Positive rechallenge (i.e., recurrence of symptoms when drug is re-introduced) is considered a hallmark for causality assessment of drug-induced adverse effects. Cases which include a positive rechallenge were reported by the Sponsors for each of the drugs included in this analysis, and were also identified in the FDA AERS analysis.

In many patients, the events resolved after stopping the drug. In the FDA AERS review, resolution of the events after stopping the drug was reported in 58% of amphetamine / dextroamphetamine cases, 60% of modafinil cases, 33% of atomoxetine cases, and 48% of methylphenidate cases. (*Note:* Outcome of the psychiatric adverse events was not reported in 21% of amphetamine / dextroamphetamine cases, 9% of modafinil cases, 41% of atomoxetine cases, and 30% of methylphenidate cases.)

For drugs currently approved for ADHD treatment, no risk factors were identified which could account for the majority of reports of psychosis-related events. For instance, drug abuse was reported in fewer than 3% of overall cases from the FDA AERS analysis. In the overwhelming majority of cases (roughly 90%), the patient had no prior history of similar signs or symptoms.

Numerous postmarketing reports of aggression or violent behavior during drug therapy of ADHD have been received, most of which were classified as non-serious, although

approximately 20% of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles. The majority of the reports of aggression for drugs currently approved for the treatment of ADHD were in children and adolescents, with a striking male predominance. No specific risk factors for aggression or violent behavior were identified in this analysis. For instance, drug abuse was reported in fewer than 5% of overall cases identified from the FDA AERS search. Also of note, a striking majority (80 to 90% overall) of patients identified in this review had no prior history of similar events. Several cases describing positive rechallenge were reported for each of the drugs included in this analysis. Consideration should be given to stopping drug in patients who develop aggressive or violent behavior during drug therapy of ADHD.

Suicidality has been identified as a safety issue for STRATTERA (atomoxetine), and this information is clearly conveyed in current labeling. A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. For instance, further case review by a clinical expert of data obtained for this analysis may yield additional insights regarding possible co-occurrence of undesired psychiatric effects in some vulnerable patients that could contribute to suicidal ideation or behaviors.

6.0 DDRE ADHD Psychiatric Review Team

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1 ATTACHMENTS

1. Psychiatric adverse events in labeling.
1. Information requested from sponsors.
1. AERS search terms.
1. Tabular Summaries of Postmarketing Safety Data from Sponsor Submissions
1. Tabular Summaries of Postmarketing Safety Data from FDA AERS Safety Database

1.0 ATTACHMENT 1: PSYCHIATRIC ADVERSE EVENTS IN LABELING

1.0.0 ADDERALL and ADDERALL XR

(Dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate USP, amphetamine sulfate USP)
Labeling revised 6/05 and 8/05, respectively

Wording of each drug's label may not be identical to that below, but is very similar.

WARNINGS:
Psychosis: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

ADVERSE REACTIONS:
Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness,...euphoria,...dysphoria, depression,...

DRUG ABUSE AND DEPENDENCE:
Dextroamphetamine sulfate, amphetamine sulfate, amphetamine aspartate monohydrate, and dextroamphetamine saccharate are Schedule II controlled substances. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. .... Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include ... irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE:
Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.
Symptoms: Manifestations of acute overdosage with amphetamines include restlessness ... confusion, assaultiveness, hallucinations, panic states....
Fatigue and depression usually follow the central stimulation.

1.3.0 ADDERALL XR

ADVERSE REACTIONS:
Adverse events associated with discontinuation of treatment:

Adverse event, % of pediatric patients discontinuing (n=595)	
Emotional lability 1.0%	Depression 0.7%

Adverse events reported by more than 1% of pediatric patients receiving Adderall XR® (n=374) with higher incidence than on placebo (n=210) in a 584 patient clinical study

Nervous System: Emotional Lability 9%, PBO 2%; Nervousness 6%, PBO 2%

3.0.0 **STRATTERA**

(Atomoxetine HCl)
Labeling revised 11/05

BOXED WARNING

Suicidal Ideation in Children and Adolescents — Strattera (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). ... Anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera is approved for ADHD in pediatric and adult patients. Strattera is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera compared to placebo. The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.

WARNINGS

Suicidal Ideation

Strattera increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving Strattera and 851 receiving placebo). The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with Strattera. No suicides occurred in these trials. All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of Strattera.

All pediatric patients being treated with Strattera should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes. Such monitoring would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

The following symptoms have been reported with Strattera: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the emergence of suicidal impulses has not been established, there is a concern that such symptoms

may represent precursors to emerging suicidality. Thus, patients being treated with Strattera should be observed for the emergence of such symptoms.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who are experiencing emergent suicidality or symptoms that might be precursors to emerging suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with Strattera should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder — In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with Strattera, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

PRECAUTIONS

Aggressive Behavior or Hostility — Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that Strattera causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with Strattera compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Information for Patients

Suicide Risk — Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, depression, and suicidal ideation, especially early during Strattera treatment and when the dose is adjusted. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be instructed to call their doctor as soon as possible should they notice an increase in aggression or hostility.

ADVERSE EVENTS

Child and Adolescent Clinical Trials

Reasons for discontinuation of treatment due to adverse events in child and adolescent clinical trials — In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7% of poor metabolizer (PM) patients discontinued because of an adverse event. Among Strattera-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); ...were the reasons for discontinuation reported by more than 1 patient.
Commonly observed adverse events in acute child and adolescent, placebo-controlled trials — The most commonly observed adverse events in patients treated with Strattera (incidence of 5% or greater and at least twice the incidence in placebo patients, for either BID or QD dosing) were: ...mood swings.

Common Treatment-Emergent Adverse Events Associated with the Use of Strattera in Acute (up to 9 weeks) Child and Adolescent Trials		
Adverse Event	Percentage of Patients Reporting Events from BID Trials	
	Strattera (N=340)	Placebo (N=207)
Psychiatric Disorders		
Crying	2%	1%
Irritability	8%	5%
Mood swings	2%	0%

OVERDOSAGE
There is limited clinical trial experience with Strattera overdose and no fatalities were observed. During postmarketing, there have been reports of acute and chronic overdoses of Strattera. No fatal overdoses of Strattera alone have been reported. The most commonly reported symptoms accompanying acute and chronic overdoses were somnolence, agitation, hyperactivity, abnormal behavior, and gastrointestinal symptoms. Signs and symptoms consistent with sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth) have also been observed.

4.0.0 **FOCALIN XR**

(Dexmethylphenidate HCl)
Revised 2005

CONTRAINDICATIONS
Agitation
Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

WARNINGS
Psychosis
Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.
Drug Dependence
Focalin XR should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur.
Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

ADVERSE EVENTS

Treatment-Emergent Adverse Events Occurring During Double-Blind Treatment
pediatric patients

	Focalin XR N=53	Placebo N=47
Psychiatric disorders	26%	15%
Anxiety	6%	0%

Treatment-Emergent Adverse Events Occurring During Double-Blind Treatment
adults

	Focalin XR 20 mg N = 57	Focalin XR 30 mg N = 54	Focalin XR 40 mg N = 54	Placebo N = 53
Psychiatric disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%

Adverse Events with Other Methylphenidate HCl Dosage Forms
Nervous System: dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:
Psychiatric: transient depressed mood

OVERDOSAGE
Signs and Symptoms
Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

5.0.0 **DEXEDRINE**

(Dextroamphetamine sulfate)
Labeling revised 10/05

CONTRAINDICATIONS
Agitated states.

PRECAUTIONS
Pediatric Use: Clinical experience suggests that in psychotic children, administration of amphetamines may exacerbate symptoms of behavior disturbance and thought disorder.

ADVERSE REATIONS
Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics, and Tourette's syndrome.

DRUG ABUSE AND DEPENDENCE
Dextroamphetamine sulfate is a Schedule II controlled substance.
Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG.
Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE
Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rhabdomyolysis, rapid respiration, hyperpyrexia, confusion, assaultiveness, hallucinations, panic states.
Fatigue and depression usually follow the central stimulation.

6.0.0 **CONCERTA, METADATE CD, METHYLIN, M-ER, RITALIN, R-SR, R-LA**

(Methylphenidate HCl)

Concerta labeling approved 10/21/04, Metadate CD labeling revised 9/03, Methylin labeling revised 10/05, Methylin ER labeling revised 4/02, Ritalin and Ritalin-SR labeling revised 3/03, Ritalin LA labeling revised 4/04

Wording of each drug's label may not be identical to that below, but is very similar.

CONTRAINDICATIONS

[Methylphenidate] is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

WARNINGS

Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Drug Dependence

[Methylphenidate] should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

ADVERSE REACTIONS

Adverse Events with Other Methylphenidate HCl Dosage Forms (This heading is not in the Ritalin and Ritalin-SR label.)

Nervousness and insomnia are the most common adverse reactions reported with [methylphenidate]. ...Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: ...transient depressed mood.

OVERDOSAGE

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: ...agitation...euphoria, confusion, hallucinations, delirium...

CONCERTA

ADVERSE REACTIONS
Adverse Findings in Clinical Trials with Concerta®
Adverse Events Associated with Discontinuation of Treatment
In the 4-week placebo-controlled, parallel-group trial in children one Concerta®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).
In the 2-week placebo-controlled phase of a trial in adolescents, no Concerta®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).
In the two open-label, long-term safety trials (one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with Concerta®) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

METHYLIN, METHYLIN ER, RITALIN, RITALIN-SR

PRECAUTIONS
Patients with an element of agitation may react adversely; discontinue therapy if necessary.

RITALIN LA

Adverse Events in a Double-Blind, Placebo-Controlled Clinical Trial with Ritalin LA
Adverse Events Associated with Discontinuation of Treatment
In the two-week double-blind treatment phase of a placebo-controlled parallel-group study in children with ADHD, only one Ritalin LA-treated subject (1/65, 1.5%) discontinued due to an adverse event (depression).
In the single-blind titration period of this study, subjects received Ritalin LA for up to 4 weeks. During this period a total of six subjects (6/161, 3.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anger (in 2 patients), hypomania, anxiety, depressed mood, fatigue, migraine and lethargy.

2.0 ATTACHMENT 2

INFORMATION REQUESTED FROM SPONSORS
Sent in September 2005

Please find below a request for psychiatric adverse event data for <drug name>. This same request is being sent to the manufacturers of all products approved for the treatment of ADHD.

We ask that you respond to this request by December 1, 2005. The details of the request are provided below.

1. Cumulative review of postmarketing spontaneous or literature reports for psychiatric events of interest received by sponsor after January 1, 2000:

For each of the following four categories of events of interest, please provide a tabular summary of requested information for all spontaneous or literature reports, foreign and domestic, serious[18] and non-serious (except as otherwise noted), received from January 1, 2000 through June 30, 2005.

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

Signs and/or symptoms of psychosis/mania

- Hallucination *(any type, including visual, auditory, tactile, mixed, etc)*
- Delusion (*any type including somatic, persecutory, grandeur, reference)*
- Schizophrenia *(any type)*
- Psychotic disorder
- Transient psychosis
- Acute psychosis
- Paranoia
- Childhood psychosis
- Schizophreniform disorder
- Schizoaffective disorder
- Catatonia
- Mania
- Hypomania

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

 Suicidal ideation and behavior

- Depression suicidal
- Gun shot wound
- Intentional self-injury
- Non-accidental overdose
- Overdose
- Self injurious behavior
- Self injurious ideation
- Self-mutilation
- Suicidal ideation
- Suicide attempt
- Completed suicide

 Aggression and violent behavior

- Aggression
- Anger
- Hostility
- Homicidal ideation
- Sexual offense
- Murder
- Imprisonment

 Miscellaneous psychiatric events (include events with serious outcome only)

- Abnormal behavior
- Agitation
- Amnesia
- Confusional state
- Depressed mood
- Depression
- Disorientation
- Emotional disorder
- Emotional distress
- Feeling abnormal
- Memory impairment
- Mood altered
- Mood swings
- Personality change
- Thinking abnormal
- Anxiety
- Fearfulness
- Phobia
- Panic attack
- Sleep disturbance
- Tics
- Obsessive or compulsive behavior
- Trichotillomania

Please provide a tabular summary of each case with the following information:

- File ID number;
- Country of origin;
- Reporter type (i.e., health professional, consumer, literature, legal);
- Patient age;
- Patient gender;
- Suspect drug(s);
- Concomitant drug(s);
- Dose, duration, and indication for therapy with <drug name>;
- Reporter verbatim adverse effects;
- MedDRA Preferred Term (or other coded events as applicable);
- Is this event an exacerbation of a pre-existing condition (yes or no);
- Patient medical history and/or comorbid conditions;
- Past psychiatric history or comorbid conditions other than ADHD;
- Has patient been diagnosed with a seizure disorder (yes or no);
- Is drug abuse suspected (yes or no);
- Is drug overdose suspected or reported (yes or no);
- Serious outcome, if any (i.e., death, hospital admission, life-threatening, medically important, etc);
- Dechallenge (i.e., did event resolve or improve after drug was stopped);
- Rechallenge (i.e., did event recur after drug was restarted);
- Does patient have a family history of bipolar disorder or psychosis (yes or no).

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

2. Analysis of clinical trial database

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

again during week 4.) For adverse events designated as "serious" or as reasons for premature treatment discontinuation, we ask that you also provide a brief narrative summary of each case and the case report form.

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

Finally, in order to make comparisons between treatments, we ask that you provide the relevant exposure information (numbers of patients and patient-years) for all treatments studied. Please stratify the data according to open label run-in, open label extension, or double blind treatment; gender; and age group (age less than or equal to 12 years, age 13-17 years, and age over 17 years). We expect that some patients may contribute both open label and double blind exposure.

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

3.0 *Attachment 3*

AERS Search Terms

HLGT	MedDRA High Level Group Term
HLT	MedDRA High Level Term
PT	MedDRA Preferred Term

Psychosis and Mania Search Terms

MANIA	PT
PARANOIA	PT
CATATONIA	PT
HYPOMANIA	PT
SCHIZOTYPAL PERSONALITY DISORDER	PT
SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS	HLGT
DELUSIONAL SYMPTOMS	HLT
PERCEPTION DISTURBANCES	HLT
BIPOLAR DISORDERS	HLT
SCHIZOID PERSONALITY DISORDER	PT
PARANOID PERSONALITY DISORDER	PT

Suicidal Ideation and Behavior Search Terms

SUICIDAL AND SELF-INJURIOUS BEHAVIOURS NEC	HLGT
MULTIPLE DRUG OVERDOSE	PT
DEPRESSION SUICIDAL	PT
GUN SHOT WOUND	PT
INTENTIONAL MISUSE	PT
OVERDOSE	PT

Aggression and Violent Behavior Search Terms

AGGRESSION	PT
BELLIGERENCE	PT
ANGER	PT
HOSTILITY	PT
PHYSICAL ASSAULT	PT
SEXUAL OFFENCE	PT
MURDER	PT
IMPRISONMENT	PT
HOMICIDAL IDEATION	PT

Miscellaneous Psychiatric Adverse Event Search Terms

ABNORMAL BEHAVIOUR	PT
AMNESTIC SYMPTOMS	HLT
CONFUSIONAL STATE	PT
MOOD ALTERATIONS WITH DEPRESSIVE SYMPTOMS	HLT
DEPRESSION	PT
MAJOR DEPRESSION	PT
DISORIENTATION	PT
EMOTIONAL DISORDER	PT
EMOTIONAL DISTRESS	PT
FEELING ABNORMAL	PT
MOOD ALTERED	PT
MOOD SWINGS	PT
PERSONALITY CHANGE	PT
THINKING ABNORMAL	PT
ANXIETY DISORDERS AND SYMPTOMS	HLGT
HAIR PLUCKING	PT
TRICHOTILLOMANIA	PT
SLEEP DISORDER	PT
TIC DISORDERS	HLT

1.3 ATTACHMENT 4

TABULAR SUMMARIES

OF POSTMARKETING SAFETY DATA

FROM SPONSOR SUBMISSIONS

1.3.1 <ADDERALL[19]>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[20]> Received from January 1, 2000 through June 30, 2005 (n = 83)

		Number of Reports
Country of Origin	USA	83
Reporter Type	Health Professional	13
	Consumer	9
	Other	61
Age	1-10	47
	11-20	25
	21-30	1
	31-50	6
	NR	4
Sex	Male	65
	Female	18
Total Daily Dose (mg/day)	≤10	18
	>10 and ≤20	16
	>20 and ≤40	8
	>40	5
	NR	36
Exacerbation of pre-existing condition?	Yes	7
	No	76
Psychiatric history other than ADHD?	Yes	16
	No	45
	NR	22
History of seizure disorder?	Yes	3
	No	80
Drug Abuse?	Yes	4
	No	79
Overdose?	Yes	4
	No	79
Serious criteria (if any)	Hospitalization	4
	Medically Important	6
	Non-serious	73
Positive Dechallenge	Yes	18
	No	5
	NA	32
	NR	28
Positive Rechallenge	Yes	3
	No	3
	NA	48
	NR	29
Concomitant Medications	None	12
	NR	42

[19] Brand of immediate release amphetamine / dextroamphetamine, mixed salts
[20] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOSTILITY, HOMICIDAL IDEATION

<**ADDERALL**[21]>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[22]>

Received from January 1, 2000 through June 30, 2005 (n = 84)

		Number of Reports
Country of Origin	USA	84
Reporter Type	Health Professional	25
	Consumer	11
	Other[23]	46
	Legal	2
Age	1-10	29
	11-20	18
	21-30	8
	31-50	15
	>50	1
	NR	13
Sex	Male	59
	Female	24
	NR	1
Total Daily Dose (mg/day)	≤10	12
	>10 and ≤20	12
	>20 and ≤40	7
	>40	14
	NR	39
Exacerbation of pre-existing condition?	Yes	2
	No	82
Psychiatric history other than ADHD?	Yes	21
	No	31
	NR	31
History of seizure disorder?	Yes	0
	No	84
Drug Abuse?	Yes	15
	No	69
Overdose?	Yes	13
	No	71
Serious criteria (if any)	Death	0
	Life-threatening	1
	Hospitalization	19
	Medically Important	5
	Non-serious	59
Positive Dechallenge	Yes	28
	No	8
	NA	18
	NR	30
Positive Rechallenge	Yes	2
	NA	49
	NR	33
Concomitant medications	None	16
	NR	43

[21] Brand of immediate release amphetamine / dextroamphetamine, mixed salts

[22] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

[23] Literature case report was identified during review: Surles LK, et al. Adderall-induced psychosis in an adolescent. *J Am B Fam Prac* 156:498-500, 2002.

<**ADDERALL**[24]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[25]> Received from January 1, 2000 through June 30, 2005 (n = 18)

		Number of Reports
Country of Origin	USA	18
Reporter Type	Health Professional	5
	Consumer	3
	Other	10
Age	1-10	5
	11-20	4
	21-30	5
	NR	4
Sex	Male	15
	Female	3
Total Daily Dose (mg/day)	>20 and ≤40	1
	>40	2
	NR	15
Exacerbation of pre-existing condition?	Yes	1
	No	17
Psychiatric history other than ADHD?	Yes	4
	No	7
	NR	7
History of seizure disorder?	No	18
Drug Abuse?	Yes	5
	No	13
Overdose?	Yes	8
	No	10
Serious criteria (if any)	Death	2
	Life-threatening	1
	Hospitalization	4
	Medically Important	5
	Non-serious	7
Positive Dechallenge	Yes	2
	No	1
	NA	7
	NR	8
Positive Rechallenge	Yes	1
	NA	9
	NR	8
Family History of psychiatric illness	Yes	1
	NR	17
Concomitant medications	None	8
	NR	8

[24] Brand of immediate release amphetamine / dextroamphetamine, mixed salts

[25] Most frequent MedDRA PTs include: OVERDOSE, SELF INJURIOUS BEHAVIOR, SUICIDE ATTEMPT, COMPLETED SUICIDE

<**ADDERALL XR**[26]>

Tabular Summary of Spontaneous or Literature Reports for <AGRESSION[27]> Received from January 1, 2000 through June 30, 2005 (n = 95)

		Number of Reports
Country of Origin	USA	92
	CANADA	3
Reporter Type	Health Professional	16
	Consumer	16
	Other	63
Age	1-10	62
	11-20	21
	21-30	0
	31-50	3
	NR	9
Sex	Male	75
	Female	16
	NR	4
Total Daily Dose (mg/day)	≤10	25
	>10 and ≤20	29
	>20 and ≤40	19
	>40	4
	NR	18
Exacerbation of pre-existing condition?	Yes	3
	No	92
Psychiatric history other than ADHD?	Yes	15
	No	36
	NR	44
History of seizure disorder?	Yes	3
	No	92
Drug Abuse?	No	95
Overdose?	Yes	1
	No	94
Serious criteria (if any)	Hospitalization	3
	Medically Important	9
	Non-serious	83
Positive Dechallenge	Yes	24
	No	6
	NA	24
	NR	41
Positive Rechallenge	Yes	2
	NA	48
	NR	45
Concomitant Medications	None	21
	NR	45

[26] Brand of extended release amphetamine / dextroamphetamine, mixed salts
[27] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOSTILITY, HOMICIDAL IDEATION

<**ADDERALL XR**[28]>
Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[29]>
Received from January 1, 2000 through June 30, 2005 (n = 92)

		Number of Reports
Country of Origin	USA	91
	CANADA	1
Reporter Type	Health Professional	46
	Consumer	21
	Other	25
Age	1-10	44
	11-20	19
	21-30	9
	31-50	10
	>50	2
Sex	Male	63
	Female	28
	NR	1
Total Daily Dose (mg/day)	≤10	18
	>10 and ≤20	19
	>20 and ≤40	17
	>40	7
	NR	31
Exacerbation of pre-existing condition?	Yes	3
	No	89
Psychiatric history other than ADHD?	Yes	21
	No	34
	NR	37
History of seizure disorder?	Yes	5
	No	87
Drug Abuse?	Yes	7
	No	85
Overdose?	Yes	10
	No	82
Serious criteria (if any)	Life-threatening	1
	Hospitalization	17
	Disability	2
	Medically Important	17
	Non-serious	55
Positive Dechallenge	Yes	34
	No	7
	NA	14
	NR	37
Positive Rechallenge	Yes	3
	No	3
	NA	44
	NR	42
Concomitant Medications	None	20
	NR	33

[28] Brand of extended release amphetamine / dextroamphetamine, mixed salts
[29] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

<**ADDERALL XR**[30]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[31]> Received from January 1, 2000 through June 30, 2005 (n = 33)

		Number of Reports
Country of Origin	USA	33
Reporter Type	Health Professional	12
	Consumer	10
	Other	11
Age	1-10	17
	11-20	10
	21-30	1
	31-50	2
	>50	1
	NR	2
Sex	Male	22
	Female	10
	NR	1
Total Daily Dose (mg/day)	≤10	7
	>10 and ≤20	7
	>20 and ≤40	6
	>40	2
	NR	11
Exacerbation of pre-existing condition?	Yes	0
	No	33
Psychiatric history other than ADHD?	Yes	7
	No	11
	NR	15
History of seizure disorder?	Yes	2
	No	31
Drug Abuse?	Yes	7
	No	26
Overdose?	Yes	15
	No	18
Serious criteria (if any)	Death	2
	Life-threatening	2
	Hospitalization	7
	Medically Important	8
	Non-serious	14
Positive Dechallenge	Yes	11
	No	3
	NA	8
	NR	11
Positive Rechallenge	Yes	1
	NA	19
	NR	13
Concomitant Medications	None	6
	NR	13

[30] Brand of extended release amphetamine / dextroamphetamine, mixed salts

[31] Most frequent MedDRA PTs include: OVERDOSE, SUICIDAL IDEATION, COMPLETED SUICIDE, SUICIDE ATTEMPT, SELF INJURIOUS BEHAVIOR

1.3.2 <CONCERTA[32]>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[33]> Received from January 1, 2000 through June 30, 2005 (n = 219)

		Number of Reports
Country of Origin	USA	155
	UK	25
	Other	39
Reporter Type	Health Professional	152
	Consumer	54
	Other	13
Age	1-10	97
	11-20	44
	21-30	0
	31-50	3
	>50	2
	NR	73
Sex	Male	167
	Female	35
	NR	17
Total Daily Dose (mg/day)	≤ 18	75
	>18 and ≤ 36	52
	>36 and ≤ 54	18
	>54	11
	NR	63
Exacerbation of pre-existing condition?	Yes	33
	No	185
	NR	1
Psychiatric history other than ADHD?	Yes	26
	No	193
History of seizure disorder?	No	219
Drug Abuse?	Yes	4
	No	215
Overdose?	Yes	9
	No	210
Serious criteria (if any)	Death	1
	Hospitalization	6
	Medically Important	41
	Non-serious	171
Positive Dechallenge	Yes	80
	No	4
	NA	79
	NR	56
Positive Rechallenge	Yes	8
	No	5
	NA	149
	NR	58
Concomitant medications	None reported	154

[32] Brand of extended release OROS methylphenidate
[33] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOMICIDAL IDEATION, HOSTILITY

<**CONCERTA**[34]>
Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[35]>
Received from January 1, 2000 through June 30, 2005 (n = 160)

		Number of Reports
Country of Origin	USA	114
	UK	26
	Other	26
Reporter Type	Health Professional	125
	Consumer	27
	Other	8
	Literature	1
Age	1-10	87
	11-20	51
	21-30	3
	31-50	4
	NR	15
Sex	Male	119
	Female	30
	NR	11
Total Daily Dose (mg/day)	≤ 18	37
	>18 and ≤ 36	60
	>36 and ≤ 54	16
	>54	9
	NR	38
Exacerbation of pre-existing condition?	Yes	10
	No	150
Psychiatric history other than ADHD?	Yes	26
	No	132
History of seizure disorder?	Yes	2
	No	158
Drug Abuse?	Yes	6
	No	154
Overdose?	Yes	4
	No	156
Serious criteria (if any)	Death	3
	Hospitalization	19
	Medically Important	47
	Non-serious	91
Positive Dechallenge	Yes	70
	No	11
	NA	36
	NR	43
Positive Rechallenge	Yes	1
	No	5
	NA	111
	NR	43
Concomitant medications	None reported	110

[34] Brand of extended release OROS methylphenidate
[35] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

<**CONCERTA**[36]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[37]> Received from January 1, 2000 through June 30, 2005 (n = 121)

		Number of Reports
Country of Origin	USA	81
	GERMANY	11
	Other	29
Reporter Type	Health Professional	85
	Consumer	31
	Other	5
Age	1-10	41
	11-20	46
	21-30	3
	31-50	6
	>50	1
	NR	24
Sex	Male	77
	Female	35
	NR	9
Total Daily Dose (mg/day)	≤ 18	17
	>18 and ≤ 36	27
	>36 and ≤ 54	13
	>54	21
	NR	38
Exacerbation of pre-existing condition?	Yes	10
	No	111
Psychiatric history other than ADHD?	Yes	21
	No	100
History of seizure disorder?	Yes	1
	No	120
Drug Abuse?	Yes	15
	No	106
Overdose?	Yes	74
	No	47
Serious criteria (if any)	Death	6
	Life-threatening	1
	Hospitalization	10
	Medically Important	44
	Non-serious	60
Positive Dechallenge	Yes	32
	No	4
	NA	37
	NR	48
Positive Rechallenge	Yes	4
	NA	65
	NR	52
Concomitant medications	None reported	89

[36] Brand of extended release OROS methylphenidate

[37] Most frequent MedDRA PTs include: OVERDOSE, SUICIDAL IDEATION, SUICIDE ATTEMPT, COMPLETED SUICIDE, SELF INJURIOUS BEHAVIOR

1.3.3 < METADATE[38] >

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[39]> Received from January 1, 2000 through June 30, 2005 (n = 42)

		Number of Reports
Country of Origin	USA	41
	Germany	1
Reporter Type	Health Professional	14
	Consumer	28
Age	1-10	31
	11-20	8
	>50	1
	NR	2
Sex	Male	34
	Female	8
Total Daily Dose (mg/day)	≤10	3
	>10 and ≤20	20
	>20 and ≤40	7
	>40	3
	NR	9
Exacerbation of pre-existing condition?	Yes	5
	No	1
	NR	36
Psychiatric history other than ADHD?	Yes	16
	NR	26
History of seizure disorder?	Yes	1
	NR	41
Drug Abuse?	NR	42
Overdose?	Yes	1
	NR	41
Serious criteria (if any)	Hospitalization	4
	Medically Important	6
	NR	32
Positive Dechallenge	Yes	20
	No	3
	NA	16
	NR	3
Positive Rechallenge	Yes	4
	NA	23
	NR	15
Family History of psychiatric illness	Yes	2
	NR	40
Concomitant medications	None	4
	NR	24

[38] Brand of methylphenidate
[39] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOSTILITY, PYROMANIA

<**METADATE**[40]>
Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[41]>
Received from January 1, 2000 through June 30, 2005 (n = 39)

		Number of Reports
Country of Origin	USA	39
Reporter Type	Health Professional	20
	Consumer	19
Age	1-10	20
	11-20	11
	>50	2
	NR	6
Sex	Male	34
	Female	5
Total Daily Dose (mg/day)	≤10	0
	>10 and ≤20	21
	>20 and ≤40	2
	>40	9
	NR	7
Exacerbation of pre-existing condition?	Yes	3
	No	1
	NR	35
Psychiatric history other than ADHD?	Yes	10
	NR	29
History of seizure disorder?	NR	39
Drug Abuse?	NR	39
Overdose?	NR	39
Serious criteria (if any)	Hospitalization	4
	Medically Important	7
	NR	28
Positive Dechallenge	Yes	23
	No	4
	NA	5
	NR	7
Positive Rechallenge	Yes	1
	No	1
	NA	27
	NR	10
Concomitant medications	None reported	21

[40] Brand of methylphenidate
[41] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, DEPERSONALIZATION

<**METADATE**[42]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[43]> Received from January 1, 2000 through June 30, 2005 (n = 9)

		Number of Reports
Country of Origin	USA	9
Reporter Type	Health Professional	7
	Consumer	2
Age	1-10	6
	11-20	2
	21-30	1
Sex	Male	8
	Female	1
Total Daily Dose (mg/day)	≤10	0
	>10 and ≤20	4
	>20 and ≤40	0
	>40	5
Exacerbation of pre-existing condition?	NR	9
Psychiatric history other than ADHD?	Yes	4
	NR	5
History of seizure disorder?	NR	9
Drug Abuse?	NR	9
Overdose?	Yes	3
	NR	6
Serious criteria (if any)	Hospitalization	3
	Medically Important	4
	NR	1
Positive Dechallenge	Yes	7
	No	1
	NR	1
Positive Rechallenge	NA	8
	NR	1
Concomitant medications	None reported	2

[42] Brand of methylphenidate
[43] Most frequent MedDRA PTs include: INTENTIONAL SELF INJURY, OVERDOSE, SUICIDAL IDEATION

1.3.4 < PROVIGIL (modafinil)[44] >

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[45]> Received from January 1, 2000 through June 30, 2005 (n = 22)

		Number of Reports
Country of Origin	USA	11
	United Kingdom	6
	Other	5
Reporter Type	Health Professional	14
	Consumer	8
Age	1-10	0
	11-20	2
	21-30	5
	31-50	5
	>50	4
	NR	6
Sex	Male	11
	Female	11
Total Daily Dose (mg/day)	≤ 100	4
	>100 and ≤ 200	7
	>200 and ≤ 400	3
	>400	2
	NR	6
Exacerbation of pre-existing condition?	Yes	5
	No	15
	NR	2
Psychiatric history other than ADHD?	Yes	7
	NR	15
History of seizure disorder?	Yes	0
	No	22
Drug Abuse?	Yes	1
	No	21
Overdose?	Yes	1
	No	21
Serious criteria (if any)	Life-threatening	1
	Hospitalization	2
	Medically Important	1
	Non-serious	19
Positive Dechallenge	Yes	12
	No	1
	NA	4
	NR	5
Positive Rechallenge	Yes	1
	No	1
	NA	15
	NR	5
Concomitant medications	None reported	12

[44] The indication for modafinil use in most cases was narcolepsy
[45] Most frequent MedDRA PTs include: AGGRESSION, ANGER, AGITATION

<**PROVIGIL (modafinil)**[46]>
Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[47]>
Received from January 1, 2000 through June 30, 2005 (n = 94)

		Number of Reports
Country of Origin	USA	77
	UK	9
	Other	8
Reporter Type	Health Professional	80
	Consumer	13
	Literature	1
Age	1-10	7
	11-20	2
	21-30	6
	31-50	36
	>50	23
	NR	20
Sex	Male	33
	Female	51
	NR	10
Total Daily Dose (mg/day)	≤ 100	21
	>100 and ≤ 200	28
	>200 and ≤ 400	12
	>400	4
	NR	29
Exacerbation of pre-existing condition?	Yes	24
	No	58
	NR	12
Psychiatric history other than ADHD?	Yes	56
	No	3
	NR	35
History of seizure disorder?	Yes	2
	No	84
	NR	8
Drug Abuse?	Yes	4
	No	82
	NR	8
Overdose?	Yes	2
	No	84
	NR	8
Serious criteria (if any)	Life-threatening	1
	Hospitalization	24
	Disability	1
	Medically Important	7
	Non-serious	62
Positive Dechallenge	Yes	47
	No	13
	NA	12
	NR	22
Positive Rechallenge	Yes	4
	No	5
	NA	61
	NR	24
Concomitant medications	NR	29

[46] The indication for modafinil use in most cases was narcolepsy
[47] Most frequent MedDRA PTs include: PSYCHOTIC DISORDER, HALLUCINATION, MANIA, PARANOIA

<**PROVIGIL (modafinil)**[48]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[49]> Received from January 1, 2000 through June 30, 2005 (n = 18)

		Number of Reports
Country of Origin	USA	15
	United Kingdom	2
	France	1
Reporter Type	Health Professional	14
	Consumer	4
Age	11-20	1
	21-30	3
	31-50	7
	NR	7
Sex	Male	4
	Female	10
	NR	4
Total Daily Dose (mg/day)	≤ 100	2
	>100 and ≤ 200	4
	>200 and ≤ 400	1
	>400	1
	NR	10
Exacerbation of pre-existing condition?	Yes	3
	No	6
	NR	9
Psychiatric history other than ADHD?	Yes	8
	NR	10
History of seizure disorder?	No	17
	NR	1
Drug Abuse?	Yes	1
	No	16
	NR	1
Overdose?	Yes	4
	No	13
	NR	1
Serious criteria (if any)	Death	3
	Life-threatening	2
	Hospitalization	5
	Medically Important	1
	Non-serious	9
Positive Dechallenge	Yes	7
	No	1
	NA	5
	NR	5
Positive Rechallenge	No	1
	NA	12
	NR	5
Concomitant medications	None reported	13

[48] The indication for modafinil use in most cases was narcolepsy

[49] Most frequent MedDRA PTs include: SUICIDE ATTEMPT, DEPRESSION SUICIDAL, COMPLETED SUICIDE, SUICIDAL IDEATION

1.3.5 <RITALIN[50]>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[51]>
Received from January 1, 2000 through June 30, 2005 (n = 130)

		Number of Reports
Country of Origin	USA	43
	JAPAN	23
	Other	64
Reporter Type	Health Professional	97
	Consumer	32
	Other	1
Age	1-10	34
	11-20	34
	21-30	11
	31-50	13
	>50	9
	NR	29
Sex	Male	87
	Female	34
	NR	9
Total Daily Dose (mg/day)	≤10	11
	>10 and ≤20	17
	>20 and ≤40	16
	>40	5
	NR	81
Exacerbation of pre-existing condition?	Yes	13
	No	116
Psychiatric history other than ADHD?	Yes	40
	No	90
History of seizure disorder?	Yes	3
	No	127
Drug Abuse?	Yes	14
	No	116
Overdose?	Yes	13
	No	117
Serious criteria (if any)	Death	2
	Life-threatening	2
	Hospitalization	29
	Disability	1
	Medically Important	69
	NR	27
Positive Dechallenge	Yes	32
	No	3
	NA	91
	NR	4
Positive Rechallenge	Yes	1
	No	2
	NA	123
	NR	4
Concomitant medications	None reported	90

[50] Brand of methylphenidate (summary data from Sponsor includes both immediate release and long acting formulations, as well as a few dexmethylphenidate cases)
[51] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, MANIA

<**RITALIN**[52]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[53]> Received from January 1, 2000 through June 30, 2005 (n = 67)

		Number of Reports
Country of Origin	USA	18
	JAPAN	18
	GERMANY	10
	Other	21
Reporter Type	Health Professional	50
	Consumer	16
	Other	1
Age	1-10	11
	11-20	18
	21-30	6
	31-50	13
	>50	2
	NR	17
Sex	Male	43
	Female	18
	NR	6
Total Daily Dose (mg/day)	≤20	4
	>20 and ≤40	9
	>40 and ≤60	1
	>60	14
	NR	39
Exacerbation of pre-existing condition?	Yes	3
	No	63
	NR	1
Psychiatric history other than ADHD?	Yes	20
	No	47
History of seizure disorder?	Yes	0
	No	67
Drug Abuse?	Yes	21
	No	46
Overdose?	Yes	44
	No	23
Serious criteria (if any)	Death	7
	Life-threatening	4
	Hospitalization	24
	Medically Important	16
	NR	16
Positive Dechallenge	Yes	11
	No	1
	NA	50
	NR	4
Positive Rechallenge	Yes	0
	NA	63
	NR	4
Concomitant medications	None reported	42

[52] Brand of methylphenidate (summary data from Sponsor includes both immediate release and long acting formulations, as well as a few dexmethylphenidate cases)

[53] Most frequent MedDRA PTs include: SUICIDAL IDEATION, COMPLETED SUICIDE, SUICIDE ATTEMPT

6.0.0 <STRATTERA (atomoxetine)>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[54]> Received from January 1, 2000 through June 30, 2005 (n = 992)

		Number of Reports
Country of Origin	USA	919
	UK	41
	Other	32
Reporter Type	Health Professional	382
	Consumer	590
	Other	18
	Literature	1
	Legal	0
Age	1-10	464
	11-20	297
	21-30	22
	31-50	39
	>50	17
Sex	Male	752
	Female	184
	NR	56
Total Daily Dose (mg/day)	≤20	164
	>20 and ≤40	428
	>40 and ≤60	114
	>60 and ≤80	72
	>80	1
	NR	210
Exacerbation of pre-existing condition?	Yes	92
	No	887
	NR	12
Psychiatric history other than ADHD?	Yes	368
	No	20
	NR	604
History of seizure disorder?	Yes	19
	No	3
	NR	970
Drug Abuse?	Yes	12
	No	979
	NR	1
Overdose?	Yes	41
	No	950
	NR	1
Serious criteria (if any)	Life-threatening	1
	Hospitalization	33
	Medically Important	36
	Non-serious	922
Positive Dechallenge	Yes	132
	No	25
	NA	484
	NR	351
Positive Rechallenge	Yes	13
	No	11
	NA	942
	NR	26
Concomitant Medications	None	232
	NR	301

[54] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOMICIDAL IDEATION

<**STRATTERA** (atomoxetine)>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[55]> Received from January 1, 2000 through June 30, 2005 (n = 360)

		Number of Reports
Country of Origin	USA	340
	UK	12
	Other	8
Reporter Type	Health Professional	250
	Consumer	107
	Literature	3
Age	1-10	134
	11-20	130
	21-30	14
	31-50	37
	>50	9
Sex	Male	236
	Female	99
	NR	25
Total Daily Dose (mg/day)	≤20	34
	>20 and ≤40	130
	>40 and ≤60	25
	>60 and ≤80	40
	>80	9
	NR	119
Exacerbation of pre-existing condition?	Yes	31
	No	323
	NR	6
Psychiatric history other than ADHD?	Yes	157
	No	16
	NR	187
History of seizure disorder?	Yes	5
	No	1
	NR	354
Drug Abuse?	Yes	17
	No	343
Overdose?	Yes	14
	No	346
Serious criteria (if any)	Life-threatening	1
	Hospitalization	57
	Medically Important	10
	Non-serious	295
Positive Dechallenge	Yes	95
	No	25
	NA	82
	NR	158
Positive Rechallenge	Yes	1
	No	4
	NA	340
	NR	15
Concomitant Medications	None	77
	NR	112

[55] Most frequent MedDRA PTs include: MANIA, HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA

<**STRATTERA** (atomoxetine)>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[56]> Received from January 1, 2000 through June 30, 2005 (n = 399)

		Number of Reports
Country of Origin	USA	373
	UK	13
	Other	13
Reporter Type	Health Professional	220
	Consumer	132
	Other	4
	Literature	42
Age	1-10	84
	11-20	157
	21-30	24
	31-50	30
	>50	11
Sex	Male	260
	Female	122
	NR	17
Total Daily Dose (mg/day)	≤20	24
	>20 and ≤40	108
	>40 and ≤60	57
	>60 and ≤80	53
	>80	26
	NR	119
Exacerbation of pre-existing condition?	Yes	28
	No	313
	NR	58
Psychiatric history other than ADHD?	Yes	129
	No	56
	NR	214
History of seizure disorder?	Yes	7
	No	3
	NR	389
Drug Abuse?	Yes	12
	No	348
	NR	39
Overdose?	Yes	219
	No	180
Serious criteria (if any)	Death	7
	Life-threatening	5
	Hospitalization	51
	Medically Important	33
	Non-serious	293
Positive Dechallenge	Yes	69
	No	12
	NA	251
	NR	67
Positive Rechallenge	Yes	3
	No	9
	NA	339
	NR	48
Concomitant Medications	None	113
	NR	122

[56] Most frequent MedDRA PTs include: SUICIDAL IDEATION, ACCIDENTAL OVERDOSE, OVERDOSE, INTENTIONAL SELF INJURY, SUICIDE ATTEMPT, COMPLETED SUICIDE, SELF INJURIOUS IDEATION

5.0 ATTACHMENT 5

TABULAR SUMMARIES

OF POSTMARKETING SAFETY DATA

FROM FDA AERS SAFETY DATABASE

1.3.6 <AMPHETAMINE / DEXTROAMPHETAMINE[57]>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[58]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 28)

		Number of Reports
Country of Origin	USA	26
	Germany	1
	NR	1
Reporter Type	Health Professional	11
	Consumer	16
	Legal	1
Age	1-10	10
	11-20	9
	21-30	1
	31-50	7
	NR	1
Sex	Male	19
	Female	9
Total Daily Dose (mg/day)	1-10	4
	11-20	5
	21-30	4
	31-50	1
	>50	3
	NR	11
Duration of Therapy (time to onset of adverse event)	Days	4
	Weeks	7
	Months	8
	Years	3
	NR	6
Exacerbation of pre-existing condition?	Yes	3
	No	14
	NR	11
Psychiatric history other than ADHD?	Yes	12
	No	7
	NR	8
History of seizure disorder?	Yes	1
	No	18
	NR	9
Drug Abuse?	Yes	1
	No	20
	NR	7

[57] Searches of the FDA AERS safety database included all brands and formulations
[58] Most frequent MedDRA PTs include: AGGRESSION, ANGER, HOSTILITY

AMPHETAMINE / DEXTROAMPHETAMINE and AGGRESSION (continued)

Overdose?	Yes	1
	No	20
	NR	7
Serious criteria (if any)	Death	1
	Hospitalization	10
	Medically Important	16
	Non-serious	1
Positive Dechallenge	Yes	11
	No	5
	NA	2
	NR	10
Positive Rechallenge	Yes	1
	NA	21
	NR	6
Family History of psychiatric illness	Yes	4
	No	1
	NR	23
Concomitant medications	None	5
	NR	12

<AMPHETAMINE / DEXTROAMPHETAMINE[59]>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[60]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 77)

		Number of Reports
Country of Origin	USA	67
	Australia	6
	Canada	3
	NR	1
Reporter Type	Health Professional	27
	Consumer	36
	Legal	2
	Literature	9
	NR	2
Age	1-10	23
	11-20	23
	21-30	10
	31-50	14
	>50	1
	NR	6
Sex	Male	47
	Female	28
	NR	2
Total Daily Dose (mg/day)	1-10	16
	11-20	13
	21-30	5
	31-50	10
	>50	7
	NR	26
Duration of Therapy (time to onset of adverse event)	Minutes	1
	Hours	3
	Days	9
	Weeks	8
	Months	21
	Years	8
	NR	27
Exacerbation of pre-existing condition?	Yes	10
	No	44
	NR	23
Psychiatric history other than ADHD?	Yes	27
	No	22
	NR	28
History of seizure disorder?	Yes	1
	No	38
	NR	38
Drug Abuse?	Yes	2
	No	50
	NR	25

[59] Searches of the FDA AERS safety database included all brands and formulations
[60] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, MANIA

AMPHETAMINE / DEXTROAMPHETAMINE and PSYCHOSIS or MANIA (continued)

Overdose?	Yes	3
	No	52
	NR	22
Serious criteria (if any)	Death	4
	Life-threatening	1
	Hospitalization	40
	Disability	1
	Medically Important	31
Positive Dechallenge	Yes	45
	No	10
	NA	6
	NR	16
Positive Rechallenge	Yes	2
	NA	54
	NR	20
Family History of psychiatric illness	Yes	6
	No	1
	NR	70
Concomitant medications	None	17
	NR	38

<AMPHETAMINE / DEXTROAMPHETAMINE[61]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[62]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 29)

		Number of Reports
Country of Origin	USA	27
	NR	2
Reporter Type	Health Professional	13
	Consumer	15
	Legal	1
Age	1-10	9
	11-20	10
	21-30	5
	31-50	4
	NR	1
Sex	Male	19
	Female	10
Total Daily Dose (mg/day)	1-10	7
	11-20	4
	21-30	3
	31-50	4
	>50	4
	NR	8
Duration of Therapy (time to onset of adverse event)	Minutes	1
	Hours	1
	Days	2
	Weeks	5
	Months	4
	Years	4
	NR	12
Exacerbation of pre-existing condition?	Yes	6
	No	8
	NR	15
Psychiatric history other than ADHD?	Yes	13
	No	3
	NR	13
History of seizure disorder?	NR	19
	No	10
Drug Abuse?	Yes	1
	No	17
	NR	11

[61] Searches of the FDA AERS safety database included all brands and formulations
[62] Most frequent MedDRA PTs include: COMPLETED SUICIDE, SUICIDE ATTEMPT

AMPHETAMINE / DEXTROAMPHETAMINE and SUICIDALITY (continued)

Overdose?	Yes	5
	No	16
	NR	8
Serious criteria (if any)	Death	6
	Life-threatening	2
	Hospitalization	9
	Disability	3
	Medically Important	9
Positive Dechallenge	Yes	10
	No	3
	NA	10
	NR	6
Positive Rechallenge	Yes	1
	NA	20
	NR	8
Family History of psychiatric illness	Yes	3
	NR	26
Concomitant medications	None	6
	NR	15

2.0.0 <ATOMOXETINE>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[63]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 566)

		Number of Reports
Country of Origin	USA	552
	United Kingdom	10
	Other	4
Reporter Type	Health Professional	194
	Consumer	367
	Other	2
	Literature	3
Age	1-10	268
	11-20	192
	21-30	11
	31-50	31
	>50	8
	NR	56
Sex	Male	435
	Female	104
	NR	27
Total Daily Dose (mg/day)	≤20	34
	>20 and ≤40	160
	>40 and ≤60	47
	>60 and ≤80	22
	>80	8
	NR	295
Duration of Therapy (time to onset of adverse event)	Minutes	2
	Hours	35
	Days	93
	Weeks	69
	Months	72
	Years	6
	NR	289
Exacerbation of pre-existing condition?	Yes	110
	No	52
	NR	404
Psychiatric history other than ADHD?	Yes	175
	No	9
	NR	382

[63] Most frequent MedDRA PTs include: AGGRESSION, ANGER, AGITATION, PHYSICAL ASSAULT

ATOMOXETINE and AGGRESSION (continued)

History of seizure disorder?	Yes	15
	No	25
	NR	526
Drug Abuse?	Yes	5
	No	153
	NR	408
Overdose?	Yes	28
	No	314
	NR	224
Serious criteria (if any)	Non-serious	243
	Life-threatening	2
	Hospitalization	32
	Disability	76
	Medically Important	62
	NR	151
Positive Dechallenge	Yes	96
	No	26
	NA	248
	NR	196
Positive Rechallenge	Yes	16
	No	8
	NA	117
	NR	425
Family History of psychiatric illness	Yes	8
	No	3
	NR	555
Concomitant medications	None	7
	NR	108

<ATOMOXETINE>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[64]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 292)

		Number of Reports
Country of Origin	USA	284
	United Kingdom	4
	Other	4
Reporter Type	Health Professional	194
	Consumer	95
	Literature	3
Age	1-10	105
	11-20	118
	21-30	13
	31-50	26
	>50	4
	NR	26
Sex	Male	204
	Female	73
	NR	15
Total Daily Dose (mg/day)	≤20	20
	>20 and ≤40	69
	>40 and ≤60	13
	>60 and ≤80	18
	>80	7
	NR	165
Duration of Therapy (time to onset of adverse event)	Minutes	3
	Hours	16
	Days	43
	Weeks	56
	Months	35
	Years	2
	NR	137
Exacerbation of pre-existing condition?	Yes	27
	No	41
	NR	224
Psychiatric history other than ADHD?	Yes	98
	No	6
	NR	188
History of seizure disorder?	Yes	6
	No	10
	NR	276
Drug Abuse?	Yes	5
	No	72
	NR	215

[64] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

ATOMOXETINE and PSYCHOSIS or MANIA (continued)

Overdose?	Yes	9
	No	157
	NR	126
Serious criteria (if any)	Life-threatening	1
	Hospitalization	47
	Disability	21
	Medically Important	84
	Non-serious	76
	NR	22
Positive Dechallenge	Yes	96
	No	17
	NA	59
	NR	120
Positive Rechallenge	Yes	4
	No	5
	NA	60
	NR	223
Family History of psychiatric illness	Yes	15
	No	4
	NR	273
Concomitant medications	None	56
	NR	95

<**ATOMOXETINE**>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[65]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 214)

		Number of Reports
Country of Origin	USA	199
	United Kingdom	10
	Other	5
Reporter Type	Health Professional	132
	Consumer	80
	Literature	2
Age	1-10	49
	11-20	97
	21-30	19
	31-50	19
	>50	4
	NR	26
Sex	Male	147
	Female	57
	NR	10
Total Daily Dose (mg/day)	≤20	5
	>20 and ≤40	27
	>40 and ≤60	15
	>60 and ≤80	9
	>80	16
	NR	142
Duration of Therapy (time to onset of adverse event)	Minutes	2
	Hours	22
	Days	21
	Weeks	32
	Months	37
	Years	5
	NR	95
Exacerbation of pre-existing condition?	Yes	42
	No	30
	NR	142
Psychiatric history other than ADHD?	Yes	62
	No	3
	NR	149

[65] Most frequent MedDRA PTs include: SUICIDAL IDEATION, INTENTIONAL SELF INJURY, SUICIDE ATTEMPT, COMPLETED SUICIDE, OVERDOSE, SELF INJURIOUS IDEATION

History of seizure disorder?	Yes	3
	No	13
	NR	198
Drug Abuse?	Yes	26
	No	47
	NR	141
Overdose?	Yes	49
	No	75
	NR	90
Serious criteria (if any)	Death	12
	Life-threatening	7
	Hospitalization	43
	Disability	7
	Medically Important	92
	Non-serious	27
	NR	26
Positive Dechallenge	Yes	65
	No	4
	NA	57
	NR	88
Positive Rechallenge	Yes	9
	No	1
	NA	50
	NR	154
Family History of psychiatric illness	Yes	3
	No	7
	NR	204
Concomitant medications	None	43
	NR	76

1.3.7 <METHYLPHENIDATE[66]>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[67]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 110)

		Number of Reports
Country of Origin	USA	78
	United Kingdom	14
	Other	18
Reporter Type	Health Professional	61
	Consumer	42
	Literature	7
	Legal	2
Age	1-10	49
	11-20	40
	21-30	3
	31-50	5
	>50	4
	NR	9
Sex	Male	89
	Female	18
	NR	3
Total Daily Dose (mg/day)	≤ 18	18
	>18 and ≤ 36	33
	>36 and ≤ 54	18
	>54	12
	NR	29
Duration of Therapy (time to onset of adverse event)	Minutes	1
	Hours	15
	Days	19
	Weeks	10
	Months	14
	Years	4
	NR	47
Exacerbation of pre-existing condition?	Yes	10
	No	9
	NR	91
Psychiatric history other than ADHD?	Yes	26
	No	2
	NR	82

[66] Searches of the FDA AERS safety database included all brands and formulations

[67] Most frequent MedDRA PTs include: AGGRESSION, HOMICIDAL IDEATION, HOSTILITY, AGITATION, MURDER,

METHYLPHENIDATE and AGGRESSION (continued)

History of seizure disorder?	Yes	1
	No	1
	NR	108
Drug Abuse?	Yes	2
	No	2
	NR	106
Overdose?	Yes	6
	No	53
	NR	51
Serious criteria (if any)	Death	1
	Life-threatening	3
	Hospitalization	21
	Disability	1
	Medically Important	64
	Non-serious	16
	NR	4
Positive Dechallenge	Yes	57
	No	3
	NA	20
	NR	30
Positive Rechallenge	Yes	6
	No	2
	NA	57
	NR	45
Family History of psychiatric illness	Yes	5
	NR	105
Concomitant medications	None	11
	NR	58

<**METHYLPHENIDATE**[68]>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS OR MANIA[69]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 148)

		Number of Reports
Country of Origin	USA	93
	United Kingdom	20
	Other	35
Reporter Type	Health Professional	100
	Consumer	43
	Literature	11
Age	1-10	71
	11-20	38
	21-30	3
	31-50	8
	>50	9
	NR	19
Sex	Male	103
	Female	36
	NR	9
Total Daily Dose (mg/day)	≤ 18	31
	>18 and ≤ 36	45
	>36 and ≤ 54	15
	>54	13
	NR	44
Duration of Therapy (time to onset of adverse event)	Minutes	2
	Hours	17
	Days	24
	Weeks	15
	Months	17
	Years	11
	NR	62
Exacerbation of pre-existing condition?	Yes	11
	No	8
	NR	129
Psychiatric history other than ADHD?	Yes	36
	No	2
	NR	110
History of seizure disorder?	Yes	2
	No	1
	NR	145

[68] Searches of the FDA AERS safety database included all brands and formulations
[69] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

METHYLPHENIDATE and PSYCHOSIS or MANIA (continued)

Drug Abuse?	Yes	5
	No	45
	NR	98
Overdose?	Yes	9
	No	65
	NR	74
Serious criteria (if any)	Death	2
	Life-threatening	3
	Hospitalization	42
	Disability	4
	Medically Important	72
	Non-serious	13
	NR	12
Positive Dechallenge	Yes	71
	No	8
	NA	24
	NR	45
Positive Rechallenge	Yes	4
	No	2
	NA	69
	NR	73
Family History of psychiatric illness	Yes	8
	No	3
	NR	135
Concomitant medications	None	7
	NR	62

<**METHYLPHENIDATE**[70]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[71]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 100)

		Number of Reports
Country of Origin	USA	58
	Germany	10
	Other	31
Reporter Type	Health Professional	68
	Consumer	27
	Literature	15
	Legal	2
Age	1-10	23
	11-20	42
	21-30	3
	31-50	15
	>50	4
	NR	12
Sex	Male	64
	Female	28
	NR	7
Total Daily Dose (mg/day)	≤ 18	10
	>18 and ≤ 36	29
	>36 and ≤ 54	11
	>54	10
	NR	39
Duration of Therapy (time to onset of adverse event)	Minutes	2
	Hours	3
	Days	16
	Weeks	5
	Months	10
	Years	6
	NR	57
Exacerbation of pre-existing condition?	Yes	8
	No	8
	NR	83
Psychiatric history other than ADHD?	Yes	29
	No	1
	NR	69

[70] Searches of the FDA AERS safety database included all brands and formulations

[71] Most frequent MedDRA PTs include: SUICIDAL IDEATION, INTENTIONAL SELF INJURY, SUICIDE ATTEMPT, COMPLETED SUICIDE

METHYLPHENIDATE and SUICIDALITY (continued)

History of seizure disorder?	Yes	0
	No	1
	NR	98
Drug Abuse?	Yes	9
	No	26
	NR	64
Overdose?	Yes	25
	No	32
	NR	42
Serious criteria (if any)	Death	15
	Life-threatening	6
	Hospitalization	27
	Disability	1
	Medically Important	49
	Non-serious	1
Positive Dechallenge	Yes	38
	No	2
	NA	14
	NR	45
Positive Rechallenge	Yes	2
	NA	43
	NR	54
Family History of psychiatric illness	Yes	1
	NR	98
Concomitant medications	None	10
	NR	44

1.3.8 <MODAFINIL[72]>

Tabular Summary of Spontaneous or Literature Reports for <AGGRESSION[73]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 8)

		Number of Reports
Country of Origin	USA	4
	France	2
	Other	2
Reporter Type	Health Professional	7
	Legal	1
Age	1-10	1
	11-20	0
	21-30	2
	31-50	3
	>50	1
	NR	1
Sex	Male	4
	Female	4
Total Daily Dose (mg/day)	≤ 200	3
	>200 and ≤ 400	2
	>400	1
	NR	2
Duration of Therapy (time to onset of adverse event)	Hours	1
	Weeks	3
	Months	2
	Years	1
	NR	1
Exacerbation of pre-existing condition?	Yes	3
	No	1
	NR	4
Psychiatric history other than ADHD?	Yes	5
	No	1
	NR	2
History of seizure disorder?	NR	8
Drug Abuse?	Yes	3
	NR	5
Overdose?	Yes	3
	No	3
	NR	2
Serious criteria (if any)	Death	1
	Life-threatening	1
	Hospitalization	5
	Non-serious	1
Positive Dechallenge	Yes	3
	No	3
	NA	1
	NR	1
Positive Rechallenge	No	2
	NA	4
	NR	2
Family History of psychiatric illness	Yes	1
	NR	7
Concomitant medications	None reported	3

[72] The indication for modafinil use in most cases was narcolepsy
[73] Most frequent MedDRA PTs include: AGGRESSION, AGITATION, ANGER, MURDER (1)

<**MODAFINIL**[74]>

Tabular Summary of Spontaneous or Literature Reports for <PSYCHOSIS or MANIA[75]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 43)

		Number of Reports
Country of Origin	USA	39
	France	2
	Other	2
Reporter Type	Health Professional	38
	Consumer	4
	Legal	1
Age	1-10	3
	11-20	4
	21-30	5
	31-50	17
	>50	10
	NR	4
Sex	Male	19
	Female	23
	NR	1
Total Daily Dose (mg/day)	≤ 100	9
	>100 and ≤ 200	17
	>200 and ≤ 400	9
	>400	2
	NR	6
Duration of Therapy (time to onset of adverse event)	Hours	3
	Days	6
	Weeks	16
	Months	7
	Years	5
	NR	6
Exacerbation of pre-existing condition?	Yes	13
	No	8
	NR	22
Psychiatric history other than ADHD?	Yes	26
	No	2
	NR	15
History of seizure disorder?	Yes	2
	NR	41
Drug Abuse?	Yes	5
	NR	38
Overdose?	Yes	6
	No	33
	NR	4
Serious criteria (if any)	Life-threatening	2
	Hospitalization	20
	Medically Important	4
	Non-serious	16

[74] The indication for modafinil use in most cases was narcolepsy

[75] Most frequent MedDRA PTs include: HALLUCINATION, PSYCHOTIC DISORDER, PARANOIA, MANIA

MODAFINIL and PSYCHOSIS or MANIA (continued)

Positive Dechallenge	Yes	26
	No	9
	NA	4
	NR	4
Positive Rechallenge	Yes	4
	No	4
	NA	27
	NR	8
Family History of psychiatric illness	Yes	2
	No	1
	NR	40
Concomitant medications	None	2
	NR	10

<**MODAFINIL**[76]>

Tabular Summary of Spontaneous or Literature Reports for <SUICIDALITY[77]> Received by FDA from January 1, 2000 through June 30, 2005 (n = 18)

		Number of Reports
Country of Origin	USA	16
	France	2
Reporter Type	Health Professional	16
	Consumer	2
Age	1-10	1
	11-20	1
	21-30	2
	31-50	7
	>50	4
	NR	3
Sex	Male	8
	Female	9
	NR	1
Total Daily Dose (mg/day)	≤ 200	9
	>200 and ≤ 400	2
	>400	1
	NR	6
Duration of Therapy (time to onset of adverse event)	Hours	1
	Days	3
	Weeks	5
	Months	4
	Years	1
	NR	4
Exacerbation of pre-existing condition?	Yes	7
	No	2
	NR	9
Psychiatric history other than ADHD?	Yes	13
	No	1
	NR	4
History of seizure disorder?	Yes	2
	NR	16
Drug Abuse?	Yes	6
	NR	12
Overdose?	Yes	6
	No	9
	NR	3
Serious criteria (if any)	Death	3
	Life-threatening	2
	Hospitalization	7
	Medically important	2
	Non-serious	3
	NR	1

[76] The indication for modafinil use in most cases was narcolepsy

[77] Most frequent MedDRA PTs include: SUICIDAL IDEATION, SUICIDE ATTEMPT, SELF MUTILATION, COMPLETED SUICIDE, OVERDOSE

MODAFINIL and SUICIDALITY (continued)

Positive Dechallenge	Yes	11
	No	1
	NA	5
	NR	1
Positive Rechallenge	No	4
	NA	13
	NR	1
Family History of psychiatric illness	Yes	2
	NR	16
Concomitant medications	None reported	7