Anti-depressant Drug Use in Pediatric Populations

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before

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EXECUTIVE SUMMARY

Depression is a serious mental illness that affects the way nearly 19 million adult Americans feel, think, and interact. In younger populations, depression affects up to 2.5 percent of children and about eight percent of adolescents in the United States. These disorders often go unrecognized by families and physicians because behaviors associated with depressive disorders may be seen as normal mood swings typical of a particular developmental stage. Depression can lead to suicide. Suicide is the third leading cause of death in the U.S. in the 15-19 year-old age group and accounts for more deaths than all other major physical conditions combined.

Older medications are of limited value in the pediatric population because of serious, potentially life–threatening adverse events. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), have fewer side effects than the older drugs, making it easier for people to continue treatment. They have become very widely used to treat depression, especially in the pediatric population. The Food and Drug Administration (FDA or the Agency) approved Prozac, the first SSRI for adults, in December 1987, and for children in January 2003.

Suicidality, in the context of treating patients with depression and other psychiatric illnesses, has been a genuine concern and a longstanding topic of debate. Whether anti-depressant drug use causes suicidal thinking or behavior in adult or pediatric patients is a critically important question that we must answer in a careful, thoughtful manner.

The Agency realizes its responsibility to the public to find the right answer to this question. A premature conclusion that these drugs are harmful (when used in the pediatric population), which does not hold up during a more careful review would be a disservice to the public health given the serious and potentially life-threatening nature of severe depression. This is of particular concern since there are no acceptable therapeutic alternatives for health care providers and their pediatric patients with depression.

FDA has responded to concerns raised by experts about the relationship between anti-depressant drug products and suicidal behavior and suicidal ideation. On March 22, 2004, FDA issued a Public Health Advisory and asked manufacturers of Prozac, Zoloft, Paxil, Luvox, Celexa, Lexapro, Wellbutrin, Effexor, Serzone and Remeron to include a warning statement in their labeling recommending close observation of adult and pediatric patients treated with these drugs for worsening depression or the emergence of

suicidality. On September 13-14, 2004, FDA presented new data to the Agency's Psychopharmacologic Drugs and Pediatric Advisory Committees in a joint meeting. The primary focus of FDA's presentations at the September 2004 meeting was to provide committee members with (1) a detailed description of FDA's approach to evaluating and analyzing the pediatric suicidality data, and (2) the results of this work. The Agency also included presentations on related studies, in particular, several pertinent epidemiological studies and TADS (Treatment of Adolescents with Depression Study). Committee members heard presentations by both FDA staff and experts in pediatric suicidality from the academic community outside of FDA.

The Committee members agreed with FDA's conclusion that the data in aggregate indicate an increased risk of suicidality in pediatric patients and made several recommendations. On September 17, FDA announced that it generally supports these recommendations and has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of anti-depressants and to bolster the information provided to patients when these drugs are dispensed.

While no suicides occurred in pediatric clinical trials, suicides certainly have been reported in treated patients, and the devastating results of these suicides are apparent. FDA realizes the importance of determining whether these terrible events are drug-related. What is very clear, however, is that the period after anti-depressant therapy is started is one in which suicidal behavior and thinking is frighteningly common. While FDA works toward the recommendations made by the Advisory Committees, we will continue to closely examine this very important public health issue.

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Robert Temple, Director, Office of Medical Policy for the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to discuss FDA's review of the safety and efficacy concerns in anti-depressant drugs for use in pediatric populations.

BACKGROUND ON DEPRESSION

Depression is a serious mental illness that affects the way nearly 19 million adult Americans feel, think, and interact. While everyone experiences occasional sadness, particularly in response to loss or adversity, a person with depression has persistent symptoms that can significantly interfere with their ability to function. People with depression cannot merely "pull themselves together" and get better. Depression cannot be willed or wished away.

The two most severe types of clinical depression are major depressive disorder (MDD) and bipolar depression, which is the depressed phase of bipolar disorder. Within these types, patients experience variations in the severity and persistence of mental symptoms associated with these disorders. A person experiencing MDD suffers from, among other symptoms, a depressed mood or loss of interest in normal activities that lasts most of the day and nearly every day, for at least two weeks. Such episodes may occur only once, but more commonly occur several times in a lifetime. People with bipolar disorder cycle between episodes of major depression, similar to those seen in MDD, and highs known as mania.

In a manic phase, a person might act on delusional grand schemes that could range from unwise business decisions to romantic sprees. Both MDD and bipolar disorder can lead to suicide. The treatment of the two conditions is quite different. In general, anti-depressants alone are not an appropriate treatment for bipolar disorder.

DEPRESSION IN THE PEDIATRIC/ADOLESCENT POPULATION

According to a 2000 National Institute of Mental Health (NIMH) Fact Sheet on Depression in Children and Adolescents, depression affects up to 2.5 percent of children and about eight percent of adolescents in the United States. These disorders often go unrecognized by families and physicians because behaviors associated with depressive disorders may be seen as normal mood swings typical of a particular developmental stage. In addition, health care providers may be reluctant to prematurely "label" a young person with a mental illness diagnosis.

At the February 2, 2004, meeting of FDA's Psychopharmacologic Drugs Advisory Committee (PDAC), Dr. Cynthia Pfeffer of Cornell University addressed the issue of pediatric depression and its treatment. She noted that pediatric depression is very common and often recurrent, is often accompanied by very poor psychosocial outcomes for children and adolescents, and is associated with high risk for suicide and substance abuse. She reported that in 2001, about 1,600 15 to 19-year-olds committed suicide in the U.S. Suicide is the third leading cause of death in the U.S. in this age group and accounts for more deaths in this age group than all other major physical conditions combined.

At that meeting, Dr. David Shaffer of Colombia University reported on rates of suicidal ideation (thinking about suicide) and suicide attempts. He obtained his information from large community studies, particularly the Youth Risk Behavior Study (YRBS), a study carried out by the National Center for Health Statistics. In this study, officials from the National Center interviewed a broad population of between 15,000 and 20,000 high school students every two years using self-reporting measures. Based on this data, it was determined that suicidal ideation in high school students is extraordinarily common. Almost 20 percent of American high school students think about suicide. Suicide attempts are also very common. Experts report that the overall rate is about nine percent. Only about a quarter of these attempts are brought to medical attention. It is widely recognized that adolescents are frequently reluctant to disclose suicidal thoughts or even suicide attempts to parents or others. There are about 4,000 female suicide attempts for every female suicide death, and about 400 male attempts for every male death.

Dr. Shaffer also showed rates of pediatric suicide over several decades. The rate has fallen by about 25 percent over the last decade, the period in which the use of anti-depressants has grown steadily. This association does not prove that the increasing use of anti-depressants is the cause of the decline in suicide, but it is at least suggestive.

DRUGS FOR TREATING DEPRESSION

Existing anti-depressant drugs influence the levels of one or both of two neurotransmitters in the brain: serotonin and norepinephrine. Older medications – tricyclic anti-depressants (TCAs) and monoamine

oxidase inhibitors (MAOs) – affect the activity of both of these neurotransmitters. The disadvantage of the older medications is that they can be difficult to tolerate due to significant side effects. MAO use may also be subject to dietary and medication restrictions. TCAs and MAOs are of limited value in the pediatric population because of serious, potentially life–threatening adverse events. These include tachycardia, convulsions, and shock-like coma. Moreover, TCAs are a potential tool for adolescents attempting to commit suicide because overdose can cause serious and protracted cardiac arrhythmias.

Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), have fewer side effects than the older drugs, making it easier for people to continue treatment. They have become very widely used to treat depression, especially in the pediatric population. FDA approved Prozac, the first SSRI, for adults, in December 1987, and for children in January 2003. Experts believe that SSRI drug products work by increasing the level of the hormone serotonin in the brain. There were no approved drugs for the treatment of depression in children before the January 2003 Prozac approval.

ANTI-DEPRESSANT TREATMENT AND SUICIDALITY

Suicidality in the context of treating patients with depression and other psychiatric illnesses has been a genuine concern and a longstanding topic of debate. In fact, for many decades, anti-depressant labeling carried the following standard language under the “Precautions” section of the label alerting clinicians to the need to closely monitor patients during initial drug therapy due to concern for the possible emergence of suicidality:

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for [name of drug] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

This standard precaution statement did not explicitly warn of the possibility that anti-depressant drug products have a causal role in the emergence of suicidality early in treatment. Several mechanisms have been proposed to explain the clinical observation that some depressed patients being treated with anti-depressants, particularly early in treatment, have an increase in suicidality. In September 1991, FDA convened a meeting of the PDAC to discuss this issue. At that meeting, Dr. Martin Teicher, a psychiatrist from Harvard Medical School, proposed various mechanisms to explain the emergence of suicidality early in treatment of depression:

Roll back phenomenon : anti-depressants with prominent energizing effects might actually increase suicidal behavior in severely depressed patients who are suicidal but also have psychomotor retardation and are thus inhibited from acting on their suicidal thoughts.

Paradoxical worsening of depression : in rare cases, the patient’s depressed mood might actually worsen as a result of anti-depressant treatment.

Akathisia (inability to sit still): some anti-depressants are associated with akathisia, which might lead to suicidal behavior in certain depressed patients.

Induction of anxiety and panic attacks : some anti-depressants may induce anxiety and panic attacks, and these might lead to suicidal behavior in certain depressed patients.

Stage shifts : anti-depressants may lead to switching the patient from depression into mixed states in bipolar depressed patients, possibly leading to suicidality.

Insomnia : insomnia associated with certain anti-depressants might lead to suicidal behavior in certain depressed patients.

While all of these theories have some plausibility, it is difficult to know whether these mechanisms are real. In addition, proposing a mechanism is quite different from actually demonstrating that there is a causal association between anti-depressant use and suicidality. It might be possible to demonstrate that anti-depressants cause an increase in suicidality through randomized clinical trials, but these trials would need to be quite large because suicidality is not common. It might be possible to pool results of many trials, but if this involves results from studies of different drugs, the question remains whether some drugs could behave differently from others. Furthermore, assessing this risk in uncontrolled data is particularly difficult because depression itself causes suicidality. In any given case, one cannot usually distinguish whether the suicidality occurred because of the drug or despite it.

ANTI-DEPRESSANT-INDUCED SUICIDALITY IN ADULTS

Thus, the question of whether anti-depressants can provoke suicidality has been the subject of considerable discussion. With regard to the adult population, the debate intensified in 1990 when Dr. Teicher and several colleagues published a paper describing six adult patients with depression who, in their view, became suicidal because of treatment with Prozac. This paper and subsequent discussions led Eli Lilly, the manufacturer of Prozac, to conduct new analyses of data from their controlled trials for Prozac to look for suicidality. These events also led FDA to fully re-evaluate its spontaneous reports database to determine whether we could observe a signal of increased risk.

During a September 1991 PDAC meeting, family members raised concerns about suicide by loved ones whose deaths they attributed to Prozac. Representatives from FDA, NIMH and Lilly also gave presentations. FDA gave an update on the very substantial number of spontaneous reports of suicidality in association with Prozac use, but also noted the marked increase in reporting following the publication of the Teicher paper and the publicity about the paper. A representative from NIMH gave their perspective on the issue, essentially making the case that depression is a serious disorder that itself is associated with suicidality, and arguing that the data available to date did not support the view that anti-depressants further increase the risks of suicidality in this population. Finally, Lilly presented the results of its analysis of data pooled over its extensive clinical trials, revealing no signal of increased suicidality in association with the use of Prozac. Following these presentations, a majority of the

Advisory Committee members concluded that there was no clear evidence of an increased risk of suicidality in association with Prozac, and did not recommend any changes to Prozac labeling.

Over the next several years, researchers accumulated additional data as new anti-depressant drugs came to market. All of these additional data related to the treatment of adults. In recent years, several groups have conducted pooled analyses of data on completed or attempted suicides from these studies in an effort to identify a possible signal of risk from active treatment. They have also searched for risk signals from patients assigned to a placebo group, since some have challenged the use of placebo controls in a disease with potentially serious outcomes. Arif Khan, a psychiatrist from the Northwest Clinical Research Center, and other researchers published a paper in 2000 based on adult data obtained from FDA reviews. Dr. Khan concluded that the risk of completed suicide was the same, regardless of treatment assignment. A similar study reached the same conclusion. FDA researchers also analyzed completed suicides in 234 randomized controlled depression trials of 20 anti-depressant drug products. Based on all our analyses to date of these data, we reached a similar conclusion: there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD.

ANTI-DEPRESSANTS AND AND SUICIDALITY IN PEDIATRIC PATIENTS

Whether anti-depressant drug use causes suicidal thinking or behavior in pediatric patients (or adults) is a critically important question that we must answer in a careful, thoughtful manner. A premature conclusion or emphasis in either direction could have adverse consequences for those who are suffering from depression. Missing or understating a signal of increased risk of suicidality could result in greater reassurance than is warranted about the safety of these drugs, insufficient attention to the patients being treated, and perhaps too casual use of the drugs. On the other hand, overstating the risk could result in overly conservative use of these drugs or excluding their use for the pediatric population, and inadequate treatment of a potentially fatal condition. Below we discuss the origins of the concern that anti-depressants could provoke suicidal ideation in children.

USE OF ANTI-DEPRESSANTS IN PEDIATRIC PATIENTS

Many people have expressed concern about pediatric use of products approved for MDD in adults where clinical trials in children were negative. Prozac is the only product for which efficacy has been established sufficiently to meet FDA's standards for approval in the pediatric population. To date, clinical trials evaluating six other current generation anti-depressants approved for adults have not met FDA's standards for establishing efficacy in the child/adolescent population. Nevertheless, there is widespread belief among treating physicians that these products do in fact work and that the "negative" results are in fact inconclusive. Negative trials are not necessarily informative in MDD trials because they may be an indication of inadequate trials rather than evidence of benefit.

Because Prozac is the only product for which efficacy has been establish for treatment of pediatric/adolescent MDD, it is often the first product prescribed by a physician. However, in 30-40 percent of cases, Prozac does not work for the patient. In such cases, it is standard care for physicians to prescribe one of the other current generation anti-depressants approved for adults. The older medications, tricyclic anti-depressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have not been approved for use in pediatric/adolescent population. Moreover, as noted previously, they are of limited value in the pediatric population because of serious, potentially life-threatening adverse events. They may cause life-threatening arrhythmias in overdose or even at normal doses in individuals who are unable to efficiently metabolize these drugs.

FDAMA AND BPCA STIMULATE NEW PEDIATRIC SUICIDALITY DATA

The question of suicidality arose in the course of FDA's review of clinical trials of anti-depressants in children. When Congress enacted the FDA Modernization Act (FDAMA) in 1997, it provided incentives to manufacturers to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant additional marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of their drugs in pediatric populations. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request from FDA and submit the results of those studies in a new drug application or supplement. Congress renewed this authority in 2002, in the Best Pharmaceuticals for Children Act (BPCA).

BPCA contains important, new disclosure requirements. For studies other than those submitted under the BPCA, the Agency generally may not publicly disclose information contained in investigational new drug applications, unapproved new drug applications, or unapproved supplemental new drug applications. Only after a new drug application or supplemental new drug application is approved can the Agency make public certain summary information regarding the safety and effectiveness of the product for the approved indication. However, section 9 of BPCA regarding the dissemination of pediatric information gives the Agency additional disclosure authority and differs from FDA regulations that generally preclude the Agency from disclosing to the public information in an unapproved application. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request, the Agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether the action taken on the pediatric application is an approval, approvable, or not-approvable action. Thus, although under FDAMA information on pediatric studies conducted in response to Written Requests is not available until after the supplemental application is approved, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies, conducted in response to a Written Request issued under BPCA, is publicly available irrespective of the action taken on the application.

BPCA WRITTEN REQUESTS FOR ANTI-DEPRESSANTS

Prior to the enactment of BPCA, under the pediatric exclusivity authority of FDAMA, FDA issued seven Written Requests to manufacturers of drugs approved for the treatment of depression (Prozac, Zoloft,

Remeron, Paxil, Celexa, Serzone, and Effexor). The sponsors of three of these drugs (Prozac, Zoloft, and Remeron) performed the studies and submitted the reports of their studies before FDAMA expired on January 1, 2002 (and thus, before BPCA took effect). The manufacturers of two of these drugs, Prozac (which has been approved for the treatment of pediatric depression) and Zoloft (which was studied but not approved for the treatment of pediatric depression) received pediatric exclusivity for having conducted studies. The third sponsor, the manufacturer of Remeron, did not receive pediatric exclusivity. Under FDA's general disclosure provisions regarding the availability of data and information in approved applications, information on the approved pediatric use of Prozac is publicly available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/018936s064lbl.pdf1. Just as it has for other product approvals, FDA posted this information because we granted approval for Prozac for use in treating pediatric depression. The pediatric data for Zoloft and Remeron would not normally be available for public disclosure because their pediatric supplements have not yet been approved. However, FDA nonetheless asked the sponsors to allow us to make summaries of these studies public. The sponsors agreed to our request and summaries are now available on FDA's website.

Following enactment of BPCA in January 2002, FDA determined that the provisions of this new law should apply as broadly as possible to outstanding Written Requests for which studies had not yet been submitted. In a July 2002 letter, the Agency notified drug sponsors with outstanding Written Requests issued under FDAMA that FDA considered those Written Requests to be reissued under BPCA. In its July 2002 letter, FDA further advised manufacturers that any studies submitted in response to the reissued Written Requests would be subject to the terms of the BPCA, including, among other things, the provisions governing public availability of study summaries. However, the Written Requests for three anti-depressants (Paxil, Celexa, and Serzone) were not considered as reissued under BPCA in July 2002 because the manufacturers had already submitted their pediatric studies to the Agency before FDA issued its July 2002 letter (albeit after BPCA was enacted). Therefore, FDA considered the studies for Paxil, Celexa, and Serzone, to have been submitted under FDAMA; did not consider their Written Requests to be reissued, and did not apply the public disclosure provisions of BPCA to these studies. Nonetheless, the Agency has received permission from the sponsors of these drugs to post summaries of the safety and effectiveness reviews of their pediatric studies on FDA's website.

Only one of the outstanding and reissued Written Requests under BPCA was for studies relating to the treatment of pediatric depression. This Written Request was for Effexor. FDA granted pediatric exclusivity for this product and posted the study summaries on the FDA Pediatric Summary Review website, according to the requirements of BPCA. No new Written Requests for anti-depressants have been issued since the passage of the BPCA.

We want to emphasize that although these anti-depressants have all been shown to be effective in adults, in its Written Requests FDA asked manufacturers to conduct two pediatric studies because we knew from experience that it is very difficult to show the effectiveness of anti-depressants in children. In all studies submitted in response to Written Requests, no completed suicides occurred in the trials. Nonetheless, FDA reviewers of these Written Requests identified a suicidality concern during the course of their review.

RESULTS OF THE PAXIL WRITTEN REQUEST

FDA has been reviewing the results of anti-depressant studies in children since June 2003 after an initial report on studies with paroxetine (tradename, Paxil) appeared to suggest an increased risk of suicidal thoughts and actions in the children given Paxil, compared to those given placebo. During the review of the supplemental new drug application submitted by GlaxoSmithKline (GSK) for the use of Paxil in children, FDA reviewers noted a greater number of adverse events coded under the term "emotional lability" in patients treated with Paxil compared to the placebo group. FDA reviewers in the Division of Neuropharmacological Drug Products (DNDP) of FDA's CDER noted this in some, but not all, of the Paxil studies. The reviewers also noted that the actual events coded under this term included suicidal thoughts and attempts as well as a wide range of other events.

In an effort to better understand these events and to focus on suicidal thoughts or behavior, DNDP asked the sponsor to reanalyze its data and better characterize the adverse events identified under the term "emotional lability." This FDA request resulted in additional work by GSK and a report on suicidality, submitted first to the UK (UK), and, shortly thereafter, to FDA.

GSK APPROACH TO ACCUMULATING PAXIL SUMMARY DATA

GSK's re-analysis of the Paxil data focused exclusively on placebo-controlled trials (of which there were six). This has been FDA's focus as well. As noted earlier, in their original pediatric supplement, GSK classified adverse events suggestive of suicidality (as well as various other behavioral events) under the general term "emotional lability." In response to our request for a separate approach to better identify events that suggested suicidality, GSK conducted searches to find events of potential interest. GSK's adverse event data was in an electronic file that allowed them to search for text strings that suggested suicidality, e.g. "overdose," "suic," "hung," "cut," etc. The company conducted a blind evaluation of all events detected by this text search to select those considered possibly suicide-related. A subset of these events that could represent self-harm was then classified by GSK as suicide attempts. GSK's examination of events was limited to those occurring within 30 days of the patient's last dose.

GSK submitted its report to FDA on May 22, 2003. This report suggested an increased risk (Paxil vs. placebo) of various thoughts and behaviors coded as events considered "possibly suicide related." In addition, there was a suggestion of increased risk for the subgroup of events that met the sponsor's criteria for "suicide attempts." The signal for increased risk was clearest in 1 of the 3 trials involving pediatric patients with MDD.

It is important to note that these analyses were difficult because investigators used a large variety of terms to describe what might have been suicidal behavior and provided variable amounts of detail when identifying these events. The standard assessments of depression used to evaluate effectiveness all had an item indicating suicidal thoughts, and an evaluation of these scales showed no increased suicidality compared to placebo. However, the trials were not designed to focus on the question of suicide risk with drug treatment. To address this concern, we plan to develop guidance for subsequent trials that will lead to a standard nomenclature and assessment by investigators.

INITIAL RESPONSE TO SIGNAL OF INCREASED RISK OF SUICIDALITY FOR PAXIL

The reaction to the GSK report by the Medicines and Healthcare Regulatory Agency (MHRA) in the UK was to issue a public statement explicitly stating that Paxil "should not be used in children and adolescents under the age of 18 years to treat depressive illness," and to institute a labeling change contraindicating Paxil in pediatric MDD.

On June 6, 2003, Dr. Russell Katz, the director of DNDP, asked the Office of Drug Safety (ODS) to perform a consult review of the newly submitted GSK safety data.

Dr. Katz requested that ODS assign Dr. Andrew Mosholder as the primary reviewer for the consult because Dr. Mosholder had previously been involved in reviewing data on the safety and efficacy of anti-depressants and had generated the original request to GSK. On June 19, 2003, FDA issued a public health advisory stating that: "Although FDA has not completed its evaluation of the new safety data, FDA is recommending that Paxil not be used in children and adolescents for the treatment of [major depressive disorder]."

FDA also requested data similar to that submitted by GSK from the manufacturers of eight other anti-depressant drugs that were studied in children. On July 22, 2003, the Agency sent requests for data to the manufacturers of the following drugs: Prozac, Zoloft, Luvox, Celexa, Wellbutrin, Effexor, Serzone, and Remeron. In those letters, we asked manufacturers to identify suicide-related events for their pediatric studies in a blinded manner using two search strategies. We modeled our request to these manufacturers on the approach used by GSK, and asked manufacturers to conduct an electronic search for text strings relevant to suicidality similar to the approach employed for Paxil. We also asked manufacturers to blindly search narrative summaries for any serious adverse events to identify additional instances of "suicide-related events."

FDA RE-REVIEW OF DATA FROM PEDIATRIC SUPPLEMENTS FOR OTHER ANTI-DEPRESSANTS

While waiting for the various manufacturers of anti-depressants other than Paxil to respond, we went back to the adverse event data in the pediatric supplements for the other eight drugs to re-examine the question of suicidality. Our major question was whether there were other anti-depressants with possible signals of increased risk for suicidality, as was observed for Paxil.

There were several limitations to this re-examination. First, the methods for detecting and coding events were not standard across these studies. Second, because we wanted to have categories similar to those used for the Paxil data for purposes of comparison across drug programs, we classified events described in the adverse event listings for these drug programs into two categories: "possibly suicide-related" and "suicide attempt." One obvious flaw in this approach was that FDA's reviewer was not blinded during this reclassification process. Nevertheless, we believed this re-examination of summary data might shed some light on the possibility of signals emerging from other anti-depressant programs. We discovered that there were signals of increased risk of suicidality for patients assigned to drugs other than Paxil. We also found that the findings were not consistent across the studies, even for individual drugs.

AUGUST 2003 EFFEXOR LABELING CHANGE AND FDA's RESPONSE

While we were beginning to receive responses to our requests for summary data from the sponsors for the other anti-depressants, Wyeth Pharmaceuticals, the manufacturer of Effexor and Effexor XR, decided to make labeling changes for its products to address reports of suicidality and hostility. Sponsors have the authority to make changes to strengthen labeling to address safety issues without prior FDA approval. This action was based on the company's re-analyses of data from the Effexor pediatric trials. The labeling change was the addition of a statement to the "Usage in Children/Pediatric Use" section in the "Precautions" section of the label to note increased reports of hostility and suicidality. This labeling change was accompanied by an August 22, 2003, "Dear Health Care Professional" letter noting the findings and noting that these products are not recommended for use in pediatric patients.

In September 2003, the UK MHRA issued a regulatory response on Effexor similar to its response to the report on Paxil suicidality data. It issued a public statement advising prescribers against the use of Effexor for the treatment of pediatric MDD. This statement was accompanied by a labeling change to contraindicate the products for that pediatric indication. FDA did not take any specific regulatory action on Effexor because we viewed the data as preliminary. Like data for other anti-depressant drug products, it required a more detailed review.

SEPTEMBER 2003 FDA INTERNAL REGULATORY MEETING

An important milestone in our consideration of the pediatric suicidality data was the September 16, 2003, internal briefing for upper level CDER management. This briefing occurred at a time when we only had a preliminary review of the summary data for Paxil and a crude internal re-analysis of suicidality data from the other pediatric supplements. We had not yet received and reviewed the requested new analyses from all the sponsors of pediatric drugs.

There were several agreements reached at this meeting, including two that were of particular importance for our further plans to address this issue. We recognized that we had cast a very broad net to attempt to capture events of potential interest for possible suicidality. This was appropriate, but it meant that individual cases needed closer examination to determine what they actually represented. Our first conclusion was that it would be useful to try to have all events of potential interest blindly reclassified by outside experts in suicidality in order to have greater confidence in what the signals represented. This conclusion eventually led to the Columbia Classification Project, described in greater detail below. Second, because it was apparent that there was inconsistency in the signals of suicidality among the individual studies of the various drugs, we also concluded that it would be useful to attempt to obtain patient-level data sets for all of these trials. This would permit analyses that are more refined and allow adjustments for potentially important covariates. These agreements strongly influenced the subsequent course of our efforts to better understand these data.

RESPONSES TO FDA's REQUEST FOR SUMMARY DATA FOR OTHER ANTI-DEPRESSANTS

The responses to FDA's request for summary data for all of the anti-depressants arrived by late September 2003. These responses were received within DNDP and forwarded to Dr. Mosholder in ODS as they arrived, over roughly a six-week period. Unfortunately, as we began reviewing these responses, it became clear that different sponsors had interpreted the July 22, 2003, request differently. This caused us to doubt whether all eight manufacturers used similar approaches in selecting, classifying, and presenting cases of suicidality for review. There was also a concern, due to the methods used by the manufacturers to search their database, about the possibility that manufacturers had not captured all adverse events of potential interest.

This impression was confirmed when we spoke to individual manufacturers about their approach to our request. In retrospect, the algorithm we had provided to search for potential events and select patients experiencing those events was not sufficiently detailed to result in a common understanding. This discovery presented a major hurdle in our evaluation of these data, because we needed to have confidence in the thoroughness and uniformity of the methods used to gather and classify these cases. We realized that we would need to be more certain that manufacturers captured all relevant cases, and that the relevant cases were appropriately classified.

Greater certainty on this point was necessary to accurately assess the ability of these drugs to provoke suicidality. For example, we did not receive complete descriptions of how manufacturers conducted searches or why manufacturers included or excluded individual cases. In at least one case, the search for and classification of cases was not conducted in a blind manner to avoid bias. In another case, what appeared to be a strong signal in our preliminary analysis of the previously submitted data became a weak signal on re-analysis by the manufacturer. In all, we concluded that we needed to better understand the classification and analysis process.

FDA DECISION ON INDEPENDENT RECLASSIFICATION FOR CASES

FDA also was concerned about case definition and selection by manufacturers in response to our July 22, 2003, letters. We noted substantial differences across different drug products in the selection of cases included as suicide attempts. Some sponsors decided to include essentially all captured events as suicide attempts, even though there was clearly not enough information in some of the cases to justify such a classification.

For example, there was concern about a number of the adverse events classified under the category "possibly suicide related." In one case, a young girl slapped herself on the face and researchers coded this as a suicide attempt. A number of other events coded as "suicide attempts" involved children who had engaged in superficial cutting behavior and children who had ingested small numbers of pills in sight of parents. Such events, while of concern in their own right, would not necessarily be an indication of suicidal behavior.

This confirmed the view reached tentatively at our September 2003 internal regulatory briefing of the need to have potential events blindly reclassified by an independent group. Although we briefly

considered doing this internally, we rejected this idea because FDA did not have the expertise in suicidality to conduct such a large reclassification effort. Furthermore, most employees who might logically participate in such an effort had already seen many of the cases. These reviewers could also be biased because they were aware of the treatment assignment (drug or placebo).

FURTHER REQUESTS FOR DATA/INITIATE THE "COLUMBIA" STUDY

Thus, we began to look outside the Agency and initiated a series of discussions with outside experts. Although we found several experts interested in such an effort, there remained the problem of who could coordinate this work and establish methods and criteria for reclassification.

Columbia University not only had well-recognized expertise in adolescent suicidality, but also had developed an approach to classifying events that possibly were representative of suicidality, and this approach precisely fit our needs. We conducted extensive discussions with this group in order to establish a contract to accomplish this reclassification of cases and to work out the details of a standard approach to finding all relevant cases and setting up categories for the reclassification effort that would meet our needs.

Additionally, as we reviewed the summary data provided by the various sponsors in response to our July 22, 2003, letters, we again noted an inconsistency in results across trials, even within individual programs, that we had observed in our re-review of the pediatric supplements. To further address this issue, on October 3, 2003, DNDP requested patient-level data sets from all manufacturers of the nine anti-depressant drugs. The availability of these more detailed data has permitted FDA to perform a more refined analysis, taking into consideration possible imbalances across study groups in these trials. In order to ensure that we had a complete capture of all relevant events that might possibly be related to suicidality for these trials, we issued follow-up requests to our July 2003 letters; these requests were made on November 24 and December 9, 2003.

This complete set of narratives was sent to Columbia University for review by a panel of international pediatric suicidality experts. This group was assembled to undertake a blinded review of the reported behaviors using a rigorous classification system.

FDA’s OCTOBER 2003 UPDATED PUBLIC HEALTH ADVISORY AND TALK PAPER

FDA issued an updated Public Health Advisory and Talk Paper on October 27, 2003, based on our assessment of the pediatric suicidality data at that time. Although we indicated that preliminary data suggested an excess of reports of suicidality for several anti-depressant drugs, we noted the need for additional data and analysis. We also noted that we intended to bring this issue to an advisory committee meeting. We advised caution in the use of any of these drugs in treating pediatric MDD, and reminded prescribers of the standard language already in anti-depressant labeling alerting clinicians to the need for close supervision of high-risk patients, particularly during initial onset of drug therapy.

DECEMBER 2003 UK MHRA ACTION ON ANTI-DEPRESSANT TREATMENT OF PEDIATERIC MDD

The UK MHRA made a public announcement on December 10, 2003, indicating that, in addition to its earlier statements regarding the contraindications of Paxil and Effexor in pediatric MDD, it was now also contraindicating all SSRI anti-depressants except Prozac for this condition. This announcement noted that the risk to benefit profile could not be assessed for Luvox, and that, the risk to benefit profile is favorable in pediatric MDD for Prozac only. Serzone and Wellbutrin are not approved drug products in the UK. Remeron is an approved product in the UK, but MHRA has offered no specific comment on the pediatric data for this drug.

FDA's FEBRUARY 2, 2004 ADVISORY COMMITTEE MEETING

FDA uses advisory committees to gain expert advice about scientific and public health issues and/or regulatory decisions. In preparing for an advisory committee meeting, scientific team leaders, supervisors and managers – seasoned regulatory scientists with drug development and public health expertise – exercise scientific judgment in synthesizing issues to be brought before advisory committees. This process is designed to ensure that an advisory committee considering an issue is provided with sufficient data and information to fully discuss the issues.

While CDER was conducting its more in-depth review of the data from the pediatric clinical trials, planning was also under way to hold a meeting of the PDAC on February 2, 2004. Because the BPCA mandates a review of the post-marketing safety data for products that have been granted pediatric exclusivity, this meeting was convened to review the post-marketing safety reporting for a number of products (not limited to anti-depressants). One of the drugs scheduled for discussion at the February 2, 2004, Advisory Committee meeting was Paxil.

In planning for the discussion of the safety of the use of Paxil in children, the Agency initially intended to broaden the PDAC meeting to include a discussion of the Agency's review of the safety concerns arising from the data on the use of anti-depressants in children, as these concerns were clearly of public interest. However, as the reviews and meeting planning progressed, it became clear that the additional analyses of the data from the clinical trials of anti-depressants in children, particularly the Columbia analysis, would not be completed in time to present the Agency's final assessment of these data at the Advisory Committee meeting.

The Agency decided to proceed with the plans to discuss the post–marketing safety data for Paxil at the meeting, to brief the Advisory Committee on the Agency's progress in evaluating data from the clinical trials of anti-depressants in children, and to solicit advice and comment regarding the Agency's plans for further analyses. The plan included returning to the Advisory Committee for another meeting once the Agency's more definitive analyses of the clinical trial data were complete. This would allow us to solicit Advisory Committee input before taking further regulatory action.

While CDER was moving ahead with plans for the February 2, 2004, Advisory Committee meeting, Dr. Mosholder was nearing completion of his review of the data from the clinical trials provided in response to our July 22, 2003, request. Based on his review, he believed that the available data were sufficient to reach a conclusion about an association between the use of anti-depressants and suicidality in children and to recommend additional regulatory action, without the need for the more in-depth case classification or analyses that had already been initiated by DNDP. Dr. Mosholder shared his conclusions with his supervisors and with the DNDP/ODE I review team involved in reviewing this issue. The review team and Dr. Mosholder's direct supervisors did not agree that the available data were sufficient to reach a conclusion and believed that definitive action should await the re-analysis by Center staff using the Columbia data. There was a discussion within the DNDP/ODE I review team, as well as higher CDER management including Drs. Katz, Laughren, and Temple, as to whether Dr. Mosholder's scientific and regulatory conclusions on the data should be presented in some form at the February meeting, given that they did not represent the Agency's (but rather an individual staff member's) determination; it was concluded that they should not be.

However, at the February 3, 2004, meeting, Dr. Laughren did present the data that led Dr. Mosholder to his conclusions, although not in detail. These data plainly showed an excess of suicidality in individual studies and across the studies as a group. Dr. Laughren also explained the Agency's reservations about the classification. Dr. Katz also acknowledged in his presentation to the Advisory Committee that some reviewers had reached a conclusion that the data were sufficient to conclude that there was a link between anti-depressant use and suicidality in children. The Agency did not present Dr. Mosholder's conclusion in detail because of concerns that this would have given his determination the appearance of an Agency position before the Agency had made such a determination. This could have been harmful to the public health because it might have led patients who were actually benefiting from the use of these drugs to inappropriately discontinue therapy with potentially dire consequences, or to avoid treatment when it might be the best option.

Senior CDER staff believed that the best way to serve the public health on this very complex and important issue was to: 1) disclose the available publicly releasable safety data during the Advisory Committee meeting; 2) describe the limitations of those data in supporting a definitive conclusion; and, 3) describe the Agency's plans to further evaluate the data. The Agency realized its responsibility to the public to find the right answer to this question. A premature conclusion that these drugs are harmful (when used in the pediatric population) that does not hold up during a more careful review would be a disservice to the public health given the serious and potentially life-threatening nature of severe depression. This is of particular concern since there are no acceptable therapeutic alternatives for health care providers and their pediatric patients with depression.

CDER's DECISION-MAKING PROCESS ON SAFETY ISSUES

CDER's decision-making process is designed to ensure that regulatory actions or policy formulation take into consideration an array of perspectives and concerns designed to advance public health. The process requires that primary reviewers, team leaders, supervisors, and managers work together effectively.

In the free and open discussion of CDER issues within a scientific and regulatory environment, we expect differing professional judgments/opinions. Individual employees are strongly encouraged to discuss their views with co-workers. A number of opportunities are available to discuss and resolve scientific differences and enhance decision-making. These include meetings among review teams, meetings with the supervisory and management chains within the Center and Agency, meetings with sponsors, CDER regulatory briefings and Advisory Committee meetings.

It is never the goal of these discussions to pressure or convince reviewers to reach any particular conclusion, or to reach a different conclusion that they have already reached, but only to provide a forum for a free exchange of views by all. After considering all of the relevant data and arguments, individual reviewers are expected to write reviews that reflect their best judgment. If their supervisor disagrees with their conclusions and/or recommendations, the supervisor documents the disagreement, and the resolution of the disagreement, in the official administrative file on a matter.

FDA's MARCH 2004 ADVISORY: NEW WARNING STATEMENT IN LABELING

At the February 2, 2004, Advisory Committee meeting, experts raised concerns about the possible relationship between anti-depressant drug products and suicidal behavior and suicidal ideation and supported a labeling change to warn of possible suicidality. On March 22, 2004, FDA responded to these concerns by issuing a Public Health Advisory and asked manufacturers of Prozac, Zoloft, Paxil, Luvox, Celexa, Lexapro, Wellbutrin, Effexor, Serzone and Remeron to include a warning statement in their labeling recommending close observation of adult and pediatric patients treated with these drugs for worsening depression or the emergence of suicidality.

In this statement, the Agency informed the public that symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania have been reported in adult and pediatric patients who are being treated with anti-depressants for MDD. We warned that patients who experience one or more of these symptoms might be at an increased risk for worsening depression or suicidality. The Agency pointed out that we did not know whether the drugs increased suicidality but warned that medications may need to be evaluated and perhaps discontinued when symptoms are severe, abrupt in onset, or not part of the patient's presenting symptoms. FDA urged health care providers to instruct patients, their families, and their caregivers to be alert for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality and worsening depression, and to report such symptoms immediately to their health care provider.

"COLUMBIA" STUDY RESULTS

The Columbia group submitted its completed review to FDA in July 2004. FDA then developed its analysis of the pediatric suicidality data based on the case classifications provided by Columbia University. While there were findings among these data suggestive of an increased risk of suicidality for some of these drugs, inconsistencies remained in the results, both across trials for individual drugs and across drugs. Thus, an overall interpretation of these findings represented a substantial challenge to the Agency. The Agency brought these findings to the Psychopharmacologic Drugs and Pediatric Advisory Committees in September 2004 for further consideration.

FDA's AUGUST 2004 ADVISORY: AGENCY PLAN TO PRESENT DATA TO ADVISORY COMMITTEES

As part of its commitment to keep the American public fully informed about the status of its review of data concerning the use of anti-depressants in pediatric patients, on August 20, 2004, FDA informed the public of its detailed plan to present new data to the Psychopharmacologic Drugs and the Pediatric Advisory Committees. This new data, which FDA posted on its website, included the Agency's interpretation and analyses of pediatric suicidality data based on information obtained from the Columbia Study. In addition, the Agency sought advice on appropriate regulatory actions, such as labeling changes to ensure that the labels of anti-depressants used in pediatric patients reflect the most recent information obtained from current studies and analyses.

As we noted previously, FDA also announced that it posted additional summaries on its web site of pediatric efficacy studies for drugs that have been studied for depression in pediatric patients. These summaries are for Paxil, Celexa, Serzone, Zoloft and Remeron. Although specific new labeling language has yet to be developed, FDA will work to assure that the labels of the anti-depressants used in pediatric patients reflect the most recent information obtained from these studies and analyses.

FDA's SEPTEMBER 13–14, 2004 ADVISORY COMMITTEE MEETING

On September 13 and 14, 2004, a joint meeting was held between the Psychopharmacologic Drugs and Pediatric Advisory Committees to consider the occurrence of suicidality in the course of treatment of pediatric patients with various anti-depressants. The primary focus of FDA's presentations at the September 2004 meeting was to provide committee members with (1) a detailed description of FDA's approach to evaluating and analyzing the pediatric suicidality data, and (2) the results of this work. The Agency also included presentations on related studies, in particular, several pertinent epidemiological studies and TADS (Treatment of Adolescents with Depression Study). Committee members heard presentations by both FDA staff and experts in pediatric suicidality from the academic community outside of FDA.

The overall consensus of the committee was an endorsement of FDA's approach to classifying and analyzing the suicidal events and behaviors observed in the controlled clinical trials. Committee

members expressed their view that the new analyses increased their confidence in the results. Further, the committee members concluded that the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (Prozac, Zoloft, Remeron, Paxil, Effexor, Celexa Wellbutrin, Luvox and Serzone) in controlled clinical trials. In addition, the members:

- recommended that the products not be contraindicated in this country because the Committees thought access to these therapies was important for those who could benefit;
- recommended that the results of controlled pediatric trials of depression be included in the labeling for anti-depressant drugs;
- recommended that any warning related to an increased risk of suicidality in pediatric patients should be applied to all anti-depressant drugs, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single medication from an increased risk;
- reached a split decision (15-yes, 8-no) regarding recommending a "black-box" warning related to an increased risk for suicidality in pediatric patients for all anti-depressant drugs; and
- endorsed a patient information sheet ("Medication Guide") for this class of drugs to be provided to the patient or their caregiver with every prescription.

FDA's SEPTEMBER 17 ANNOUNCEMENT REGARDING SSRIs

On September 17, FDA announced that the Agency generally supports the recommendations made to the Agency by the Psychopharmacologic Drugs and Pediatric Advisory Committees regarding reports of an increased risk of suicidality (suicidal thoughts and actions) associated with the use of certain anti-depressants in pediatric patients. FDA has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of anti-depressants and to bolster the information provided to patients when these drugs are dispensed.

EFFECTIVENESS DATA FOR ANTI-DEPRESSANTS IN PEDIATRIC MDD

To date, much of the focus has been on pediatric suicidality and the safety of anti-depressant drug products. However, it is also important to consider the efficacy data for these drugs because a risk-benefit assessment is important to clearly understand the benefit side of this equation. Of the seven products studied in pediatric MDD (Prozac, Zoloft, Paxil, Celexa, Effexor, Serzone and Remeron), FDA's reviews of the effectiveness data resulted in only one approval (Prozac) for pediatric MDD. (In January 2003, FDA approved Prozac for the treatment of children and adolescents ages 7 to 17 for depression and obsessive-compulsive disorder.)

Overall, the efficacy results from 15 studies in pediatric MDD do not support the effectiveness of these drugs in pediatric populations. It is understandable that people might conclude that these data show

that the drugs, except for Prozac, have no benefit in pediatric MDD. We think that conclusion is premature, however.

There are many reasons, other than lack of effectiveness, for studies to fail to show benefit. This phenomenon is a particular problem in depression, and even more so in pediatric depression.

To begin with, in adult MDD programs for drugs approved for this indication, the overall failure rate for studies that appear in every respect to be adequate trials is about 50 percent. This indicates that showing effectiveness in depression is not easy. In fact, because we expected this difficulty, our Written Requests to sponsors asked for two studies, not the one that would have been more typical.

Additionally, the history of pediatric MDD studies with the tricyclic anti-depressants (TCAs) is uniformly negative. This finding may have several possible explanations, including flaws in study design or conduct, or the possibility that TCAs simply do not work in pediatric MDD. It is also possible, however, that there is even greater heterogeneity among pediatric patients who meet criteria for MDD than is true for adults. If true, this would also work against study success in pediatric MDD.

Finally, the context in which sponsors conducted these studies may not have been ideal. Sponsors do not need positive results when conducting a study in response to a Written Request in order to gain exclusivity. The studies simply must be conducted according to the terms of the Written Requests, and the results submitted to meet deadlines specified in those requests. We are not suggesting that sponsors of these studies did not design and conduct them with good intent and according to high standards. We merely point out that the failure of a drug registration trial to show a drug effect represents a more significant loss for the sponsor (i.e., the non-approval of the drug) than the failure of a study in response to a Written Request. We do not know whether this could have influenced the conduct of the study in subtle ways that might have worked against getting a positive result, e.g., in recruitment of patients. As an example of how our thought process has changed since the time we issued the Written Requests, if we were to make a Written Request today for an anti-depressant, we would ask that the trial include a Prozac arm as well as placebo to confirm the ability of the study to demonstrate effectiveness. .

Nevertheless, the failure of most of these programs to show a benefit in MDD heightens the concern about the drugs ability to induce suicidality. The burden is clearly upon those who believe these drugs do have benefits in pediatric MDD to design and conduct studies that are capable of demonstrating such benefits. The problem for practitioners is what to do in the face of the uncertainty. Practitioners must consider the generally negative findings in the context of several other facts.

In all but one of the failed drugs, there were only two studies in pediatric MDD. For the remaining failed drug, there were three pediatric MDD studies. Among the failed drugs, there was one drug where one of the two studies was positive (Celexa), and two others (Zoloft and Serzone) where the results, while negative by our usual standards, were at least trending toward positive in one of the two studies.

It has been observed that the published literature gives a somewhat different perspective, suggesting more positivity in two of these programs. A published paper describes one of the Paxil studies as positive on most of the secondary endpoints, while acknowledging that it failed on the primary endpoint. Another paper describes the Zoloft program as positive, based on a pooling of two similarly designed studies that, when looked at individually, failed. As noted, except for Prozac, we do not believe effectiveness has been shown for any agent in pediatric MDD.

CONCLUSION

FDA was the first to identify a concern about suicidality in several of the submitted pediatric studies. We evaluated the data closely and raised serious questions about its adequacy. We then took the initiative to acquire further relevant data from sponsors and used expertise outside the Agency to access the reports of suicidality thoroughly. FDA's assessment on this issue is designed to achieve the most scientifically rigorous review possible. The Columbia University classification project has provided the Agency with a credible basis for analyzing the risks of these drug products.

The results of pediatric depression studies to date raise very important problems. First, the poor effectiveness results, except for Prozac, make it very difficult for practitioners to know what to do to treat a very serious, life-threatening illness. While we believe that these drugs may be effective in children, studies have not shown this to be true. Second, and of equal importance, the analyses we initiated in 2002 appear to show that the drugs in the pediatric controlled depression trials can lead to suicidal behaviors or thinking. While no suicides occurred in the trials, suicides certainly have been reported in treated patients, and the devastating results of these suicides were a critical part of the February 2, 2004, Advisory Committee meeting.

FDA generally supports the recommendations that were recently made to the Agency by the Psychopharmacologic Drugs Pediatric Advisory Committees regarding reports of an increased risk of suicidality associated with the use of certain anti-depressants in pediatric patients. FDA has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of anti-depressants and to bolster the information provided to patients when these drugs are dispensed.

Thank you for inviting us today to discuss this important subject. We would be glad to answer your questions.