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Pediatric Clinical Trials for Anti-depressant Drug Products

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before

the Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Acting Deputy Commissioner for Operations at the U.S. Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding publication and disclosure issues in pediatric clinical trials for anti-depressant drug products.

On September 23, 2004, the Committee will hold a hearing regarding FDA's process for review of anti-depressants for pediatric use. Today, I will focus on the disclosure and publication of information regarding clinical trials under the Food and Drug Administration Modernization Act (FDAMA) of 1997 and the disclosure and dissemination of pediatric information under the Best Pharmaceuticals for Children Act (BPCA) in general, and in the context of anti-depressant pediatric clinical trials in particular. I will also provide a status report on the Agency's review of selective serotonin reuptake inhibitors (SSRIs) for pediatric use.

It is generally agreed upon in the biomedical community that results of trials involving human subjects should be made available to the public after completion of the trial and data analysis. This is especially important for studies of marketed products, surgical interventions, and other medical treatments where a bias toward publication of positive results may distort the community's overall understanding of an intervention's effectiveness or risk profile. Government, academic, or industry groups, may sponsor human trials and each of these sponsors has a role in making clinical trial results available.

FDA MA: CLINICAL TRIALS DATA BANK

Section 113 of FDAMA amended the Public Health Service Act to require the Department of Health and Human Services (HHS or the Department), acting through the National Institutes of Health (NIH) and in consultation with FDA and the Centers for Disease Control and Prevention, to establish, maintain and operate a data bank of information on clinical trials for treatments for serious or life-threatening diseases and conditions. The goal of section 113 was to improve access to information that would

enable the public to learn about opportunities to participate in clinical trials of promising new treatments. FDAMA specifies that the data bank must contain information about clinical trials, whether Federally or privately funded, that are conducted under an investigational new drug (IND) application if the drug under study is to treat a serious or life-threatening disease or condition and the trial is testing the drug's effectiveness.

Working together with FDA and other sister agencies in the Department, NIH implemented section 113 by establishing the ClinicalTrials.gov1 website in February 2000. The information in the data bank must include, for each trial, a description of the purpose of each experimental drug, patient eligibility criteria, the location of the clinical trial sites, and a point of contact for patients seeking to enroll in the trial. Information about other clinical trials, such as those treating non-serious diseases or for trials that are not designed to assess effectiveness, may be included, but sponsors are not required to submit this information. Additionally, the law authorizes but does not require that the data bank include information about the results of clinical trials of such treatments, but only with the consent of the sponsor.

CLINICAL TRIALS.gov

Today, ClinicalTrials.gov2 contains information on more than 11,000 publicly and privately funded trials, of which over 4,000 are open for recruitment. Most of the trials are safety efficacy studies (Phase II, III, and IV) for treatments for serious or life-threatening diseases or conditions. However, sponsors can and have voluntarily listed some Phase I (safety) studies and studies for conditions not classified as serious. In addition, for some of the completed studies in ClinicalTrials.gov3 links are also provided to publications or abstracts describing the study's outcome. Information on studies that are no longer recruiting patients or that are completed is retained in the database and available to the public.

Recent public attention on increasing the availability of clinical trial information has made pharmaceutical companies more aware of their responsibility to list clinical trials in ClinicalTrials.gov4. In fact, non-Federal sponsors listed 80 new trials last month--two times the average monthly listing for 2003. Additionally, companies that previously listed "pharmaceutical company" as the drug sponsor now list the specific company name.

Section 113 of FDAMA does not authorize NIH to require that sponsors submit all clinical drug trial information to ClinicalTrials.gov5. However, NIH does include non-mandatory information in the database when the sponsor voluntarily provides this information. For example, sponsors can include information about trial design.

FDA DISCLOSURE OBLIGATIONS UNDER BPCA

When Congress enacted FDAMA in 1997, it also 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 BPCA.

BPCA contains important, new disclosure requirements. Outside of 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 our action 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 is publicly available irrespective of the action taken on the application. Since 2002, FDA has posted the summaries of these reviews of 41 products submitted in response to a Written Request on FDA's website6.

DISCLOSURE OF INFORMATIUON RELATED TO PEDIATRIC SSRI CLINICAL TRIALS

Prior to the enactment of BPCA, using 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 and Zoloft, received pediatric exclusivity for doing those studies. The third sponsor, the manufacturer of Remeron, did not receive pediatric exclusivity. Under FDA's general disclosure provisions regarding the availability of information in approved applications, pediatric anti-depressant data on Prozac are publicly available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/018936s064lbl.pdf7

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 website8.

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 also considered those Written Requests to be reissued under the BPCA. In its July 2002 letter, FDA further advised manufacturers that any studies submitted in response to the Written Requests would be subject to the terms of 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 and 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 website9.

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 BPCA.

STATUS OF SSRIs AND SUICIDALITY IN THE PEDIATRIC POPULATION

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. Later reports on studies of other drugs supported the possibility of an increased risk of suicidal thoughts and actions in children taking these drugs. There were no suicides in any of the trials.

FDA has closely examined the studies of the anti-depressants because of the potential public health impact of a link between the drugs and suicidality and the importance of these drugs in treating depression and other serious mental health conditions. After examining the initial reports of suicidality, it was unclear whether some of the identified suicidal behaviors reported in these studies represented actual suicide attempts or self-injurious behavior that was not suicide-related. FDA therefore arranged with Columbia University suicidality experts to review these reports.

Meanwhile, FDA brought available information on this issue to its Psychopharmacologic Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees on February 2, 2004. The advisory committee members advised FDA that even before the Columbia analysis was complete, the labeling should draw more attention to the need to monitor patients closely when anti-depressant therapy is initiated. Based on this recommendation, FDA asked manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for

worsening of depression and the emergence of suicidality, whether such worsening represents an adverse effect of the drug or failure of the drug to prevent such worsening. The new warning language has now been added to the labels for seven of these products. Sponsors for the other three drugs have also agreed to adopt the language.

The "Columbia" Study

Because of concerns about whether the varied events identified by sponsors under the broad category of "possibly suicide-related" could all reasonably be considered to represent suicidality, FDA asked Columbia University to assemble an international panel of pediatric suicidality experts to undertake a blinded review of the reported behaviors using a rigorous classification system. The Columbia group submitted its completed review to FDA in June 2004.

FDA has analyzed the pediatric suicidality data, based on the case classifications provided by Columbia University, and has posted the analysis on its website10. While there are findings among these data suggestive of an increased risk of suicidality for some of these drugs, there remain inconsistencies in the results, both across trials for individual drugs and across drugs. Thus, an overall interpretation of these findings remains a substantial challenge.

The September 2004 FDA Advisory Committee Meeting

As a public health agency, FDA must weigh the possibility of an increased risk of suicidality in young patients taking these drugs against the known risk of suicide in patients whose depression goes untreated. FDA's next step, as we announced in

March 2004, will be to update the Psychopharmacologic Drugs and the Pediatric Advisory Committees about the results of these reviews and to seek assistance from the committees in interpreting the data and in considering what additional regulatory actions may be needed to promote the safe use of these drugs. This meeting will be held in Bethesda, Maryland on September 13 and 14, 2004.

CONCLUSION

FDA and NIH will continue to work with individual sponsors to put required information into the registry. Also, FDA is reviewing sponsor listings in ClinicalTrials.gov11 to assess whether additional FDA action is warranted. FDA will continue to actively provide summaries of pediatric trials in a timely manner. FDA welcomes a continued dialogue regarding the kind of information from clinical trials that would be useful to providers, patients, and families so they can make more meaningful treatment decisions. Finally, FDA will carefully consider what further action may be required for the safe use of anti-depressant drugs in children.