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2157 RAYBURN HOUSE OFFICE BUILDING

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MAJORITY (202) 225-5074
FACSIMILE (202) 225-3974
MINORITY (202) 225-5051
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July 20, 2004

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The Honorable Tommy G. Thompson
Secretary of Health and Human Services
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Mr. Secretary:

I am writing to express concern that neither the pharmaceutical industry nor the U.S. Food and Drug Administration (FDA) has made public important information on medications for children, despite millions of dollars spent by the American public to support their discovery. I urge you to use your existing legal authority to release summaries of this research in a form useful to clinicians and patients.

At issue are industry studies in FDA's possession that were conducted by the pharmaceutical industry in exchange for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act. Section 505A grants pharmaceutical companies six months of exclusive marketing, an extremely valuable incentive, if they conduct FDA-approved clinical trials involving children. Pediatric exclusivity is frequently worth tens or even hundreds of millions of dollars to pharmaceutical companies, much of which is paid for by American consumers who are denied access to lower-priced generic drugs for an additional six months.

Nevertheless, clinicians and patients do not always have access to the results of this pediatric research. For example, seven pharmaceutical companies have been granted pediatric exclusivity in exchange for conducting studies on the safety and effectiveness of antidepressant medications in children. FDA, however, has released detailed results of this research for only two of these drugs. Limited information about the other studies has become available through regulatory proceedings, but only *after* safety concerns about the drugs were raised. The drug industry has published a small number of studies that showed positive results, but has apparently withheld many more studies with negative results. Important drugs used to treat other conditions in children may have also received exclusivity on the basis of unpublished research.

FDA is prevented from disclosing some information on research conducted by pharmaceutical companies. There are, however, at least two avenues through which the agency can make information about industry-sponsored studies available. We strongly urge you to use

them to give clinicians and patients the information they need to make appropriate decisions. It is particularly wrong to permit drug companies to extract huge profits from publicly subsidized research and then conceal the results from the public.

The remainder of this letter explains my concerns in more detail.

Pediatric Exclusivity

Until recently, relatively little research had been done on the safety and effectiveness of drugs in the pediatric setting, leaving children far behind in pharmaceutical advances.¹ Even as late as 1996, only 37% of new FDA-approved drugs with potential uses for children had pediatric labeling.² Pediatricians were left to prescribe needed medicine “off label,” which carried the risk of unstudied adverse reactions.

Efforts in the 1990s to convince pharmaceutical companies to conduct pediatric studies voluntarily failed.³ Between 1991 and 1996, pharmaceutical companies promised to conduct 71 pediatric studies. Only 11 of these were ever completed.⁴ In 1997, Congress decided to provide incentives to conduct pediatric research. FDA was authorized to grant six months of pediatric exclusivity to companies who studied their drugs in children. During those six months, FDA would be barred from approving generic versions of the drug that had been studied, guaranteeing the company monopoly profits for that period.

Pharmaceutical companies responded to the incentive. Between 1997 and 2003, drug companies submitted 364 Proposed Pediatric Study Requests and exclusivity was granted for 73 approved drugs.⁵ From the beginning, however, there has been controversy about the disproportionate profits accrued by companies from the six-month extension when compared to the cost of the clinical trials involved. It has been reported, for example, that while the cost of studies to gain exclusivity can range from \$200,000 to \$3 million, Eli Lilly gained \$831 million

¹Committee on Drugs, American Academy of Pediatrics, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, Pediatrics, 286-295 (Feb. 1995).

²R. Chesney et al., *Changing Requirements for Evaluation of Pharmacologic Agents*, Pediatrics, 1128-1132 (Apr. 2004).

³FDA, *The Pediatric Exclusivity Provision, January 2001 Status Report to Congress*, 3-4 (Jan. 2001).

⁴*Id.* at 8-9.

⁵Terrie Crescenzi, *Statistical Update* (Mar. 3, 2003) (online at www.fda.gov/cder/pediatric/presentation/ac3-03tc/sld001.htm).

from its six-month extension on Prozac.⁶ According to a 2001 FDA estimate, pediatric exclusivity raises the cost of prescription drugs by \$695 million a year, much of which is borne by uninsured Americans.⁷ Pediatric exclusivity also costs generic drug companies and pharmacies \$884 million a year in lost sales.⁸

Yet despite the substantial cost to society of funding pediatric studies, the information collected in these studies frequently fails to get to physicians and patients.

Example: Antidepressant Use in Children

The case of pediatric antidepressant trials illustrates the difficulty physicians and patients can have in gaining access to information about studies conducted for exclusivity at considerable expense to the public. Seven companies have been granted exclusivity for conducting pediatric studies on antidepressants. Together, those companies have gained well over \$3 billion in additional sales revenue in exchange for this research. Yet FDA has only made available the results of studies on two of the drugs.

The prescribing of antidepressants for children has steadily increased in the last several years. One study found that antidepressant use among children tripled between 1987 and 1996.⁹ Another showed an adjusted rate of increase in pediatric antidepressant use of 9.2% each year between 1998 and 2002.¹⁰

This increase has occurred despite the absence of substantial published data available to physicians on a number of the drugs, and despite the fact that many of the prescribed drugs were not approved for use in children. In April 2004, researchers reported in the *Lancet* that only five published trials on the use of one major type of antidepressant in childhood depression were of sufficient quality to include in a meta-analysis.¹¹ For some of the newer drugs used to treat

⁶*Child Play: Pharmaceutical Firms Win Big on Plans to Test Adult Drugs on Kids*, Wall Street Journal (Feb. 5, 2001).

⁷ FDA, *The Pediatric Exclusivity Provision, January 2001 Status Report to Congress*, 16 (Jan. 2001).

⁸ *Id.* at 17–18.

⁹M. Olfson et al., *National Trends in the Use of Psychotropic Medications by Children*, *Journal of the American Academy of Child and Adolescent Psychiatry*, 514–21 (May 2002).

¹⁰T. Delate et al., *Trends in the Use of Antidepressants in a National Sample of Commercially Insured Pediatric Patients, 1998 to 2002*, 387–91 (Apr. 2004).

¹¹C. Whittington et al., *Selective Serotonin Reuptake Inhibitors in Childhood Depression, Systematic Review of Published versus Unpublished Data*, *Lancet*, 1341–5 (Apr. 24, 2004).

childhood and adolescent depression, the medical literature contains no randomized controlled trials at all.¹²

Additional reliable data on the use of antidepressants in children exists, but has not been made available to clinicians. In the course of investigating reports of increased suicidality among children using antidepressants, FDA revealed that the manufacturers of nine antidepressant drugs have submitted to the agency the results of placebo-controlled pediatric studies, many of which have never been published.¹³ The nine drugs for which the FDA currently has unpublished data include five Selective Serotonin Reuptake Inhibitors (SSRIs): citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).¹⁴ Also included are four other antidepressants: bupropion (Wellbutrin), nefazodone (Serzone), venlafaxine (Effexor), and mirtazapine (Remeron).

Most of these studies were submitted to the FDA to gain pediatric exclusivity. All seven of the SSRIs have been granted pediatric exclusivity for conducting studies in children.¹⁵ Of these, only Prozac has updated labeling to inform physicians of the results of the pediatric data it submitted. It is approved for use in children. FDA has released a summary of its review of the data on one additional drug, Effexor.¹⁶ This study failed to show effectiveness. The results of pediatric studies on the remaining five drugs have not been disclosed by the FDA, except for some limited data that was included in FDA's assessment of the potential risk of suicidality.

Consequences of Failing to Disclose Research

Without access to studies conducted to obtain exclusivity, clinicians must rely on the published literature. This literature may be sparse and inadequate. It may also be biased. Published studies, particularly those sponsored by the pharmaceutical industry, may be far more likely to show positive results than are independently-funded studies and the unpublished studies submitted to FDA to gain pediatric exclusivity.

¹² For example: citalopram (Celexa), fluvoxamine (Luvox), and nefazadone (Serzone).

¹³T. Laughren, *Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC)*, 5 (Jan. 5, 2004).

¹⁴GlaxoSmithKline, makers of Paxil, posted unpublished studies on its website in mid-June 2004 after the initiation of a lawsuit from the New York State Attorney General.

¹⁵The list of drugs with pediatric exclusivity is online at <http://www.fda.gov/cder/pediatric/exgrant.htm>. Remeron and Wellbutrin have not been granted pediatric exclusivity.

¹⁶The list of drugs with summaries is online at <http://www.fda.gov/cder/pediatric/Summaryreview.htm>.

The case of pediatric antidepressants is again illustrative. Data indicate that 95.7% of published studies funded by industry show a positive outcome, compared to 63.3% of independently-funded published studies and just 20% of nonpublished studies.¹⁷ Moreover, industry-funded studies may actually fail but be portrayed as successes in the medical literature. For example, in describing two antidepressant studies that were both submitted to FDA and published and which FDA concluded were negative, FDA observed:

Of note, the published literature gives a somewhat different perspective, suggesting more positivity in 2 of these programs than was the conclusion at FDA. One 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 2 similarly designed studies that, when looked at individually, failed.¹⁸

A recent review in the *British Medical Journal* also found that industry-funded studies on antidepressant use in children frequently “exaggerated the benefits, downplayed the harms, or both.”¹⁹

Antidepressants are not the only drugs of concern for children. According to FDA, several drugs have been granted patent extensions without the release of FDA summaries of research data or any changes in labeling. There may also be unpublished data relevant to other drugs, even if changes were made in the drugs’ labeling for children.

¹⁷The Center for Science and the Public Interest recently issued a report analyzing possible bias in published studies on SSRI use in children. The report analyzed 61 efficacy studies on SSRIs in children, including trials that were not randomized and controlled. The authors found that 80% of published studies on this topic had positive results. Among industry-funded studies, fully 95.7% of published studies reported a positive outcome. In contrast, only 63.3% of independently funded studies had positive outcomes. M. Goozner and J. DeViscio, Center for Science in the Public Interest, *SSRI Use in Children: An Industry Biased Record*, 5–6 (Feb. 2004). The comparison between published and unpublished studies is also striking. Of the 15 trials on use of these drugs for pediatric depression reviewed by FDA as part of its analysis of suicide risk, only 20% were found by FDA to be positive. T. Laughren, *Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC)*, 5 (Jan. 5, 2004).

¹⁸T. Laughren, *Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC)* (Jan. 5, 2004).

¹⁹J. Jureidini, *Efficacy and Safety of Antidepressants for Children and Adolescents*, *British Medical Journal*, 879–883 (Apr. 10, 2004).

According to medical experts, the distortion of scientific evidence that results when studies are unpublished or manipulated undermines clinical care. Even professional guidelines that guide clinicians may be assembled based on skewed research data.²⁰

Making Unpublished Data Available

I urge you to make this unpublished pediatric research available to physicians and patients, for whose benefit these data were ostensibly created. In addition, I urge FDA to inform physicians when, as happened with antidepressants, the FDA reaches a different conclusion about what a study actually showed than does a published drug study.

Despite the confidentiality of data submitted to FDA, the agency is authorized to make summaries of pediatric drug studies in its possession available through at least two mechanisms. First, the Best Pharmaceuticals for Children Act, which reauthorized the pediatric exclusivity provision in January 2002, includes a provision requiring FDA to release summaries of studies submitted for pediatric exclusivity within 180 days of the submission of the study.²¹ Among pediatric antidepressant drugs, FDA has released such a summary only for Effexor. If the studies submitted to FDA to gain exclusivity on any of the remaining drugs were submitted to FDA after January 4, 2002, summaries of those studies must be made available to the public.

In addition, FDA is authorized to make summaries of studies submitted in any new drug application available under defined circumstances. First, for applications that have not been approved, "the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue."²² The safety and effectiveness of antidepressants in children is manifestly appropriate for public consideration, as a specific pending issue before FDA. In fact, this authority was already used by FDA to release information about the unpublished

²⁰The authors of the *Lancet* review urged that the unpublished data on antidepressant use in children be disclosed. Emphasizing that treatment guidelines developed for clinicians must be based on complete and unbiased evidence, the authors conclude:

[G]reater cooperation and openness between the pharmaceutical industry and guideline developers, including gaining access to unpublished full trial reports, is clearly a matter of some urgency . . . The fact that the drugs reviewed here have previously been recommended for use in children on the basis of a very restricted published evidence base can only serve to increase that sense of urgency.

C. Whittington et al., *supra* note 11.

²¹Section 505A(m)(1) of the Federal Food Drug and Cosmetic Act, 21 USC §355a(m)(1).

²²21 CFR §314.430(d)(1).

antidepressant data for consideration at the February advisory committee meeting on the risk of suicide. Second, for applications that have already been approved, FDA is authorized to release a "Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process."²³

Conclusion

Congress authorized FDA to grant patent extensions to drug companies in exchange for pediatric studies because of the pressing need to bring reliable information to clinicians and patients about how to use drugs safely and effectively in children. Drug companies reap well over \$1 billion a year from pediatric exclusivity, which Americans pay for in the form of higher drug prices. Despite the high cost of this policy, it is not, in some cases, fulfilling its promise of delivering better pediatric information to those who need it.

Ideally, pharmaceutical companies would publish all clinical research of importance, or release relevant data to expert professional organizations for analysis and dissemination. In the meantime, FDA should take several steps immediately:

1. Make a public acknowledgement of the importance of clinicians having access to all reliable data for clinical care.
2. Use its authority to release summaries of previously withheld data on pediatric antidepressants and other drugs.
3. Inform physicians, through letters to journals where misleading reports appear, whenever FDA concludes that a particular study showed different results than those published by the study sponsor. FDA should start with the misleading studies of pediatric antidepressants.

Without such actions by FDA, pediatricians and other clinicians will not be able to provide the highest level of care for our nation's children. Please respond by August 3 to tell me whether you intend to take the steps I have outlined. You may contact Ann Witt on my staff at (202) 225-3976 if you have any questions.

Sincerely,



Henry A. Waxman
Ranking Minority Member

²³21 CFR §314.430(e)(2)(ii).