ALLIANCE FOR HUMAN RESEARCH PROTECTION
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June 27, 2007
Dr. Andrew von Eschenbach, Commissioner
Food and Drug Administration

Dear Dr. von Eschenbach:

In your testimony before the Senate HELP committee (August 1, 2006) you stated: "Our goal is to streamline our regulatory processes to make them more efficient, rigorous and transparent, in order to ensure the public we serve of the safety and efficacy of those products."[1] And you told the House Oversight & Government Reform committee (May 1,2007): "We have issued guidance designed to make our Advisory Committee operations more consistent, transparent, and predictable…Our goal is to provide CDER with the tools and expertise necessary to create a credible and sustainable environment of open and transparent communication."[2]

Those public statements are largely contradicted by recent a surge of FDA administrative approvals for the expanded use of highly toxic, antipsychotic drugs for children. These approvals were determined after secret deliberations—without disclosure of scientific data, without an advisory panel or open public discussion.

No credible evidence of a clinical benefit has ever been presented by independent non-industry generated studies to offset the documented evidence of the debilitating disabling adverse effects that these drugs produce. Indeed, several authoritative government-sponsored outcome studies[3] [4] [5] all confirm that the $10 billion second generation antipsychotics are no more effective or safe than the cheap earlier drugs.

On October 6, 2006, the FDA approved Risperdal® (risperidone) for the symptomatic treatment of irritability and aggression in autistic children and adolescents. Risperdal, one of the second generation antipsychotics (a.k.a. 'atypical antipsychotics') was approved in 1993 for the treatment of schizophrenia in adults. In 2003, it was approved for adults with bipolar disorder. The expanded license is the first approval of an atypical antipsychotic for use in children and the first drug approved for the treatment of behaviors that are sometimes associated with autism in children. Perhaps, as alarming as the approval of the drug for children, is the methodology and procedure that led to the approval. FDA failed to impose any restrictions on the use of Risperdal for irritability in autistic children—and they conducted their deliberations in secret.

FDA issued the Risperdal marketing license after the company withdrew its

application in the UK on June 8, 2006,[6] following the UK Medicines Authority determination that "safety problems" necessitate strengthened restrictions on conditional approval for: "the short-term treatment of severe aggression and violence whether directed towards self or others in autistic children where available nonpharmacological methods have first been tried and failed." The MHRA further specified monitoring requirements "under black triangle status" and submission of "a full risk management plan with defined milestones for data... which would include a registry of children on risperidone so that the effects of longer term risperidone therapy could be adequately monitored."

Shouldn't concerns about the safety of Risperdal–and the other second generation antipsychotics—for children have compelled the FDA to be especially conservative, and cautious in the transparency of their proceedings?

On April 29, 2007, Dr. Thomas Laughren overruled FDA's team of safety officers and issued an approvable letter to Eli Lilly for pediatric use of Zyprexa (olanzapine) – despite serious concerns about the integrity of the data obtained in Russia.[7]

Clearly encouraged by the approval of Risperdal for children, other competitors filed similar applications. On June 9, 2007, Bristol-Myers announced that FDA granted priority review for its application to market Abilify (aripiprazole) for teenagers;

On June 21, 2007 FDA issued an approvable letter to Johnson & Johnson to expand the use of Risperdal to teens.

On October 20, 2006, the FDA approved AstraZeneca's application for the use of Seroquel® (quietiapine) in the treatment of major depressive episodes associated with bipolar disorder[8]—**despite the fact that a major government review of off-label prescribing of antipsychotics found no evidence demonstrating clinical efficacy for bipolar depression.[9]** Strangely, at the time that the FDA was issuing approvals for use of antipsychotic drugs in children, officials deferred the pediatric study requirements for Abilify until December 2011.

Were these approvals science-based decisions or marketing decisions?

These actions were taken at the time that Congress began to examine the reauthorization of PDUFA (Prescription Drug User Fee Act, 1992) and the cash incentives under FDAMA (FDA Modernization Act, 1997) granting companies a six-month patent extension for testing their drugs in children. All of these administrative approvals were issued without presentation of data to support a clinical justification in spite of the fact that psychiatric diagnoses for which these drugs were approved for adults—i.e., schizophrenia and bipolar disorder—are highly controversial when applied to children. Yet, industry financed consensus panels diluted the bipolar diagnostic criteria for children to include behaviors associated with ADHD.[10] Indeed, a Vanderbilt University study found that 53% of children prescribed antipsychotics are diagnosed with ADHD.[11] With these pediatric approvals, the FDA has sewn the seeds for a catastrophic assault on the health of American children who do not have the debilitating conditions for which they were approved for adults—namely, psychosis—the most toxic drugs carrying a high risk of serious life threatening adverse events.

Dr. von Eschenbach, I doubt that you would sanction the prescribing (or testing) of cancer fighting drugs in children who do not have cancer. Antipsychotics are the equivalent of chemotherapy. Yet, despite these drugs' undisputable debilitating effects, the FDA is endorsing the testing of marketing of antipsychotics for children who are not

psychotic. If allowed to stand, these secretly arrived at decisions will greatly undermine the physical and mental health of thousands of children, not to mention the public's confidence in the competence of the FDA and its ability to ensure safety in the face of strong industry pressure for approval.
It is inconceivable that Congress intended the FDA to award the government seal of approval to market demonstrably unsafe drugs whose severe adverse effects will undoubtedly shorten children's lives!

The Alliance for Human Research Protection urges the FDA to rescind these recent administrative approvals for pediatric uses of antipsychotics inasmuch as they were issued without regard for the evidence of harm these very toxic drugs produce; without convening an advisory committee hearing; and without opportunity for public comment.
FDA's approval process for the atypical antipsychotics warrants investigation:
When approved for marketing (in the 1990s) the new antipsychotics lacked evidence of clinical efficacy.[12] The data submitted included suspect data from investigators whose professional integrity was the subject of civil and criminal investigations:[13] Faruk Abuzzahab, MD,[14] Richard Borison MD,[15] and Bruce Diamond, PhD tested the new SSRI antidepressants and antipsychotics on behalf of the drugs' manufacturers. The fraudulent data was submitted to the FDA with the companies' new drug applications.

According to internal FDA memoranda, premarketing Risperdal trials suffered from a "critical" design flaw:
the trials failed to compare "equieffective" doses of Risperdal and Haldol. Instead, the trials compared multiple doses of Risperdal to a fixed excessively high dose of Haloperidol which increased adverse events—thereby rigging the results in favor of Risperdal. Nevertheless, despite the trials' invalid design; despite the high rate of adverse effects experienced by 75% of patients on Risperdal; and despite the emergence of "serious adverse events" in 1 of 35 patients (defined by the FDA as life-threatening or requiring hospitalization) Risperdal was approved in 1993 without warnings.

FDA documents reveal that Zyprexa premarketing trial designs were also seriously flawed. In a memorandum to Dr. Robert Temple, Director of New Drug Evaluation, Dr. Paul Leber,[16] Director of Neuropharmacology, noted that the trial design was "inappropriate," the selected patient sample was "inappropriate," and the titration schedule was "ill-suited." Even with these biases, "the evidence of efficacy submitted to the FDA provided only 'proof in principle' of the drug's acute antipsychotic action." Furthermore, FDA's data review reveals that even during short 6-8 week premarketing trials, there were 27 deaths—15 suicides—among 3,546 patients testing Zyprexa; 20 deaths—12 suicides—among 3,423 patients on Risperdal; and 14 deaths—4 suicides—among 3,013 patients on Seroquel. That means that **1 in 163 adult patients who entered an antipsychotic drug trial died—half had committed suicide.**[17]

But these deaths were never acknowledged in the scientific literature or in the drugs' labels. FDA's loosened standards for drug approval prompted Dr. Leber to state in memoranda addressed to Dr. Robert Temple (August 1996) that an FDA "determination that a drug is 'safe for use' is not a finding of fact, but an opinion." He noted that "risks have not been reliably assessed" because FDA safety standards fail to detect rare but severe adverse effects. Indeed, at the time of approval, **Dr. Leber warned that if Zyprexa becomes a widely used drug: "no one should be surprised if, upon**

marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use."

Dr. Leber's warning has been validated by four major government sponsored controlled antipsychotic outcome evaluation studies: Veterans Affairs (2003),[18] **CATIE** (2005),[19] **CUtLASS** (2006)[20] and **AHRQ** (2007).[9] **These authoritative studies all document post-marketing evidence of failed efficacy and "staggering" adverse effects produced by the second generation antipsychotics**.[21]
But a decade of aggressive marketing propaganda, promotional "positive" reports by industry-financed influential psychiatrists, and the tacit endorsement of high ranking FDA officials, submerged these drugs' toxic effects and life-threatening endocrine-metabolic risks under a sea of false and misleading claims about their "safety and efficacy." FDA's failure to provide accurate risk / benefit information resulted in widespread misprescribing of antipsychotics in the U.S. Children and the elderly who are especially vulnerable to the severe toxic effects are being prescribed antipsychotics as chemical restraints to curb their behavior—not as a legitimate medical treatment.

On April 29, 2007, the FDA once again accepted Zyprexa data whose integrity is seriously in doubt. Adolescents who are prescribed psychotropic drugs are expected to take them for years. Yet, Dr. Thomas Laughren,[22] FDA's Director of the division of Psychiatry Products, accepted as evidence of Zyprexa safety and efficacy from a three-week bipolar study in 161 adolescents, and a six-week schizophrenia study in 107 adolescents. Close to half of the pediatric schizophrenia data (47%) submitted by Eli Lilly in support of its Zyprexa pediatric label application came from pediatric trials conducted in Russia. **FDA medical reviewers noted that the Russian findings—"highly favorable" for Zyprexa—are inconsistent with all other trials,** and they raised concerns about Russia's patient recruitment "success." **All three FDA medical officers rejected the Russian data as likely to be fraudulent.** Even during these short 3-week and 6-week trials, 44% of children on Zyprexa gained more than 7% of their body weight, exhibited increased prolactin levels, trigycerides, glucose, and of particular concern, 12% had increased liver enzymes (Transaminase) signaling possible liver damage.

No other regulatory agency in the world has approved Zyprexa for the treatment of schizophrenia or bipolar disorder in adolescents. **Incredibly, Dr. Laughren acknowledged "some differences in magnitude" in the adverse events suffered by adolescents in these very short trials, but overruled safety review team which recommended "nonapproval action" for Zyprexa pediatric use.**

One can legitimately raise questions about the sources of influence that induced senior FDA officials to overrule a full safety review team's recommendations and to ignore a body of authoritative clinical evidence of drug-induced harm from long-term controlled studies.[3 4 5] Much closer Congressional oversight and direct intervention, if there is evidence of conflict of interests in this regard, is needed.

Overwhelming clinical evidence documented in the 18-month randomized, comparative antipsychotic drug outcome study, CATIE, published in the *New England Journal of Medicine* (2005), refutes claims about the "improved safety and efficacy" of the new drugs over the old. It demonstrated that there is no difference in the incidence of extrapyramidal adverse symptoms (EPS). Patients on the new antipsychotics scored --13%- 17%--on the abnormal involuntary movement scale (AIMS) which measures

tardive dyskinesia (TD): severely disabling, usually irreversible disfiguring movements affecting the face and tongue; 5% - 9% experienced excruciating restlessness (akathisia); and 8% of patients on Zyprexa and Risperdal exhibited EPS. These adverse effects are indicators of neurological (brain) damage. Indeed, clinicians acknowledge[23] that the clinical consequences of EPS extend beyond motor manifestations and include:

- worse cognition
- worse negative symptoms (*neuroleptic-induced deficit syndrome*)
- worse depression and suicidality (*neuroleptic dysphoria*) higher risk of tardive dyskinesia

Approximately 65% of the patients in the 18 months CATIE[19] study suffered "moderate or severe adverse events." The vast majority dropped out—between 64% (Zyprexa) and 82% (Seroquel); 30% of patients on Zyprexa gained more than 7% of their body weight; and 18% of suffered intolerable adverse effects. After randomization, 9% of Zyprexa patients experienced measurable acute increases in glucose, cholesterol, and triglycerides—which, the authors acknowledge, "may have serious implications with respect to medical comorbidity" and "are consistent with the potential development of the metabolic syndrome."

Patients prescribed Risperdal (9%) had measurable abnormal increased prolactin levels. In clinical practice increased prolactin caused boys to grow breasts (gynocomastia) and some boys had to undergo bilateral breast reduction surgeries. The indisputable clinical evidence from CATIE and comparative effectiveness analysis by AHRQ revealed that there is no measurable difference in efficacy or safety between the first generation antipsychotic drug, perphenazine, and the second generation atypical antipsychotics—Zyprexa®, Seroquel®, Risperdal®, and Geodon® (ziprasidone).

The CATIE study results prompted an editorial in *The New York Times*[24] to chastise the FDA: "A government-financed study has provided the strongest evidence yet that the system for approving and promoting drugs is badly out of whack. The study compared five drugs used to treat schizophrenia and found that most of the newest, most heavily prescribed drugs were no better than an older drug that is far cheaper. The nation is wasting billions of dollars on heavily marketed drugs that have never proved themselves in head-to-head competition against cheaper competitors."

CUtLASS (2006)[20] a U.K. government -sponsored year long, randomized controlled study found no advantages either in the quality of life or discontinuation rate among 227 schizophrenia patients randomly prescribed either an old (cheap) antipsychotic or one of the new (expensive) antipsychotics. The results showed no difference—other than the cost of the drugs. These three large studies overturned the rationale for current schizophrenia treatment practice guidelines favoring the new, very expensive antipsychotics over the old drugs. The evidence prompted prominent schizophrenia researchers who had conducted commercially sponsored antipsychotic drug trials, and had believed in their safety and effectiveness, to acknowledge "an institutional gap" between psychiatry's practices and the evidence. [25]

Robert Rosenheck, MD of Yale University stated: "It should not have needed 10 years to get three government studies." And **Jeffrey Lieberman, MD** of Columbia University acknowledged that psychiatry's claims of these drugs' superiority "were greatly exaggerated;" that "aggressive marketing" "in the absence of empirical information" resulted in "this enhanced perception of their effectiveness."[25] The influence of

unsubstantiated claims made about the drugs' safety and efficacy by their manufacturers—Eli Lilly, AstraZeneca, Janssen, and Pfizer—by influential, industry supported psychiatrists; and by FDA officials, can be measured in widespread prescribing of antipsychotics by U.S. clinicians who prescribe these drugs mostly for off-label uses.

A **Vanderbilt University study by Cooper et al[11] found that 2.5 million U.S. children are being exposed to antipsychotics,** though these toxic drugs had not been approved for use in children. The number of children prescribed an antipsychotic increased from 8.6 per 1,000 in the 1990s to 40 per 1,000 children in 2001-2002. An analysis by Medco Health Solutions26 of outpatient prescriptions found that in a sampling of about 2.5 million, the rate of U.S. children under 19 prescribed at least one atypical antipsychotic jumped 80% from 2001 to 2005. Both analyses reported that these toxic drugs are not being prescribed for their approved use in adults—i.e., psychosis in schizophrenia and bipolar disorder. Antipsychotics are prescribed primarily to control children's behavior, as in ADHD (53%, Cooper)[11]**.** (43%, Medco).[26] Earlier analyses show that antipsychotics are prescribed for children on Medicaid and in foster care in even greater numbers.[27] [28]

Pediatric data analysis[29] confirm that "children and adolescents appear to be at higher risk than adults for antipsychotic induced hyperprolactinemia, weight gain, and possibly, associated metabolic abnormalities, which is of particular concern." Indeed, these drugs damage the central nervous system, the endocrine system triggering hyperglycemia and diabetes in some cases. Cardiac arrests have occurred as has cognitive impairment. These drugs diminish the quality of these children's lives, possibly forever. Black Box labels warn about strokes and cardiac arrest in the elderly.

The lack of clinical justification for exposing children to these drugs' severe adverse effects is underscored by a recent report by the American Psychological Association:[30] "For most of the disorders reviewed... there are psychosocial treatments that are solidly grounded in empirical support as stand-alone treatments. The preponderance of available evidence indicates that psychosocial treatments are safer than psychoactive medications. Therefore the working group recommends that in most cases psychosocial interventions be considered first."

A surge of back-door FDA approvals sacrifice children's welfare to protect profitmargins:

FDA officials disregarded children's best interests when they recently issued a surge of administrative approvals for use of these drugs in children without providing medical or scientific justification for their actions, and without convening an advisory committee hearing. These back door approvals disregarded the body of evidence showing the drugs produce irreversible harm, and ignored recommendations by medical and psychotherapeutic experts. The approvals appear to be intended to protect industry profits now and in the future by legitimizing current, widely criticized, irresponsible prescribing practices.27 [31] FDA's administrative approval is intended to encourage more doctors to prescribe these toxic drugs for children—thereby putting more children at risk of potentially life-threatening events. This administrative action will protect industry from legal actions by the Department of Justice seeking to recover taxpayer money for illicit marketing for off-label uses, and it will shield physicians who prescribe these drugs irresponsibly, for unapproved uses for toddlers, such as Rebecca Riley.[31] [32]

At the time of FDA's approval of Risperdal for autistic children (October, 2006), **Dr. Steven Galson,** director of the FDA's Center for Drug Evaluation and Research (CDER), issued the following misleading statement: "This approval should benefit many autistic children as well as their parents and other caregivers. Our agency strongly encourages the development of appropriate pediatric labeling for adult drugs, and Risperdal is a welcome addition to the growing number of such products that have been shown to have an appropriate risk-benefit profile when tested in children."

Dr. Galson's statement is refuted by an overwhelming body of evidence from both controlled clinical trials and clinical practice. The evidence shows that an alarming proportion of children who were exposed to Risperdal for just 8 weeks suffered serious adverse events compared to children on placebo.[33] [34] The makers of Risperdal, Janssen / Johnson & Johnson, concealed those risks for years.[35] Some of the most serious irreversible adverse effects linked to Risperdal are listed on the drug's revised label which now includes Black Box warnings about deaths and strokes in the elderly.[36] The primary, most prominent treatment emergent adverse effect of antipsychotic drugs is somnolence–affecting 57% to 72.5% of children. The next prominent adverse drug effect in children is acute increase in prolactin levels (hyperprolactinimia, 49%) with 2.3% of boys or girls developing enlarged breasts (gynecomastia).

The drug is also associated with high incidence of acute rapid weight gain, which triggers debilitating neurological, metabolic, hormonal, cardiovascular, and respiratory diseases that pose life-threatening risks. These adverse effects are followed by high incidence of serious neurological adverse effects, signaling brain damage: tremor, dystonia, dizziness, confusion, Automatism (psychosis) involuntary movements, Parkinsonism, and tardive dyskinesia—all occurred at a high disproportionate rate in children exposed to the drug for only 8 weeks. Of note: since antipsychotics both CAUSE and MASK tardive dyskinesia,[35] [36] the risk is higher than recorded in short trials—and likely to be detected too late to be reversible. Other risks include heart rate disturbance, respiratory infection, and reports of sudden deaths.
The somnolence effect is an adverse effect which some may conceivably regard as a benefit for a few children. To achieve a clinically appropriate calming effect demands that an evidence-based approach from clinically meaningful long-term studies must be sought—rather than the latest metabolically toxic drug. Given the overwhelming evidence of drug induced debilitating adverse effects confirmed by authoritative long-term studies and decades of clinical experience, why does the FDA encourage wide use of metabolically toxic and costly second generation antipsychotics rather than recommending safer and cheaper alternatively available drugs, such as low doses of conventional antipsychotics [e.g., Moban (molindone) or Trilafon (perphenazine)], lithium, certain non-benzodiazepine sedatives-or short-term use of benzodiazepines for emergency treatments? Additionally, nonpharmacological methods such as those recommended by the American Psychological Association [30] should be re-examined. Indeed, the U.K. Medicines and Healthcare Agency[6] required—as a condition for approval of Risperdal "for severe aggression and violence" in autistic children—the use of non-pharmacological methods first.

National press reports describe severe adverse effects suffered by children prescribed antipsychotic drugs off-label:
USA Today (May 2006)[37] and ***The New York Times*** (November 2006)[38](2007)[39] published a series of reports about children and psychotropic drugs. *USA Today* analyzed adverse event data from FDA's MedWatch database documenting 1,373

reports of severe side effects (estimated as representing 1% to 10% of actual adverse drug events).[40] There were at least 45 deaths among children—six were related to diabetes. Other causes of death ranged from heart and pulmonary problems to suicide, choking and liver failure. Furthermore, among the adverse events reported to MedWatch, 41 children nearly died of a drug-induced toxic reaction--neuroleptic malignant syndrome (NMS). NMS is life-threatening and can kill within 24 hours of diagnosis. It's been linked to drugs that act on the brain's dopamine receptors—including the atypicals.

USA Today described the agonizing effect these drugs had on children: **"**After one month on Risperdal, Rex started having tremors; within a few months, his hands shook so severely that he could barely write at school, and I'd have to guide the cup of milk to his mouth in the morning." The boy then developed tardive dyskinesia.
When confronted with children's drug-related death toll, Dr. Thomas Laughren stated: "We haven't been alerted to any particular or unusual concern. The effects (in kids) are similar to what we're seeing in adults." In adults the effects include DEATH. Yet, Dr. Laughren blithely acknowledges: "We have not systematically looked at the data for children" because the drugs aren't approved for them."

When confronted with the evidence of harm, numerous leading child psychiatrists have disavowed current prescribing practices, including the loose labeling of children as "bipolar:" **John March, MD,** chief of child and adolescent psychiatry at Duke University School of Medicine, prescribes the drugs to kids in some cases of serious illness when he thinks the benefits outweigh the risks. But he says prescribing them for behavior problems alone may be a mistake. "We have no evidence about the safety of these agents or their effectiveness in controlling aggression," he says. "Why are we doing this?" Dr. March went to say, "We're conducting a very large experiment on our children."
Dr. Cynthia Kuhn, a Duke University pharmacologist stated: "The brain system that the drugs work on develops through childhood and adolescence. We really don't know the impact of chronically perturbing that system in childhood."
Peter Jensen, MD, head of Columbia University's Center for Advancing Children's Mental Health, expressed concern about over-diagnosis: "We are jumping to this (bipolar) label too quickly."
Barbara Geller, MD, one of the major proponents of diagnosing and medicating children for bipolar, made an astounding acknowledgment about the absence of science in psychiatry: "The science is nowhere near where it is in other branches of medicine."

FDA's administrative approvals to expand the use of antipsychotics in children will increase the number of children who will be harmed by these drugs. It is inconceivable that Congress intended the cash incentives provided under the FDAMA —i.e., a six month patent extension—to prompt the FDA to issue pediatric approval for unsafe drugs that will shorten children's lives!

When confronted in May 2006, by *USA Today* reporter, Marilyn Elias, with the severe effects suffered by children prescribed antipsychotics, drug makers emphasized that their products are not approved for children—as did Dr. Laughren who responded: "The FDA does not regulate the practice of medicine." As will be shown below, this FDA official has actively shaped the prescribing practices in psychiatry. **Dr. Laughren failed to tell the reporter** that he was in the process of approving expanded use of antipsychotics in children. Six months later, Dr. Laughren approved Risperdal for

"irritability" in autistic children--even after Johnson & Johnson withdrew its U.K. application "for short-term use in the treatment of severe aggression and violence" in autistic children.[6] In the U.S. Risperdal was approved for use as a chemical restraint for behavior without restrictions or safeguards.

Appearance of Conflict of Interest:
Throughout his tenure as team leader of FDA's Psychiatric Drug Products Division of Neuropsychopharmacology (1983-2005), and since his appointment as the director of the Psychiatry Products division, Dr. Thomas Laughren has maintained close ongoing collaborative ties with pharmaceutical industry officials and industry financed psychiatrists in academia and professional associations. Dr. Laughren has participated in influential industry sponsored consensus panels convened by the American Academy of Child and Adolescent Psychiatry (AACAP) that recommended expanded use of psychotropic drugs—primarily the expensive patented SSRI antidepressants and antipsychotics—for unapproved, off-label uses in children.

Dr. Laughren was a panel participant (with Pfizer and Hoffman LaRoche officials) at the **Fourth International Bipolar conference which has been promoting bipolar disorder and the use of multiple psychotropic drugs (polypharmacy).[41]**
He has authored / co-authored more than a dozen articles with some of industry's highest paid opinion leaders whose promotion of these drugs influenced others to prescribe them widely, catapulting antidepressants and antipsychotics to blockbuster sellers. **Dr. Laughren has penned a disingenuous disclaimer[42]on his 'unofficial' publications while closely collaborating with industry and its contracted authors.**

His participation in forums whose purpose is to influence regulatory policy and /or expanded use of psychotropic drugs exerted influence on policy and practice guidelines. His co-authors include Eli Lilly's chief medical officer,[43] and unabashed industry-subsidized drug promoters[44]—even a convicted felon. For more than a decade Dr. Laughren endorsed industry's denials of an increased suicide risk for consumers of SSRI antidepressants. He dismissed safety concerns raised by FDA medical reviewers, including a reviewer who reported a seven-fold greater incidence of suicidality in children prescribed sertraline (Zoloft®). Dr. Laughren stated in a memo dated October 25, 1996: "I don't consider these data to represent a signal of risk for suicidality for either adults or children." In 2004, Zoloft—and all antidepressants—were required to add a black box label warning about a twofold increased suicidality risk for children.

Dr. Laughren's disclaimer notwithstanding, his status as FDA's highest authority on psychotropic drugs carries enormous influence. He has been lending the appearance of credibility and regulatory legitimacy by participating in numerous industry-funded conferences, co-authoring articles and consensus statements under the direct influence of industry. In 2000, following revelations in the *Journal of the American Medical Association* that a high number of US preschool children (aged 2 to 5) were being prescribed powerful psychotropic drugs,[45] a public furor erupted.[46] Psychiatrists, the drug industry, and government officials responded to public concerns by convening meetings—but adopted no policy to curtail or restrict the use of drugs known to pose serious risks of harm for children.

Dr. Laughren participated in a consensus panel[47] convened by the AACAP with funding from industry. Its stated aim was "To identify the obstacles and special challenges—ethical, practical, scientific, and regulatory—faced by investigators who

attempt to conduct psychopharmacological studies in preschoolers." In 2002, Dr. Laughren served on the "development panel" for the "Mood Disorders in the Medically Ill" conference[48] underwritten by major pharmaceutical companies. The report, published in *Biological Psychiatry*, endorsed "depression assessments" in ALL medically ill patients—a thinly veiled market expansion ploy. The report, co-authored by Dr. Laughren, recommended the use of SSRI antidepressants for patients whose conditions[49]—ranging from cardiovascular disease, cancer, Parkinson's to AIDS—were said to have "benefited" or "were much improved." Underscoring the fact that this report is an example of propaganda masquerading as science, is the claim that "SSRIs may be cardioprotective."[50]

Even the most ardent supporter of Dr. Laughren must question the integrity of a high ranking FDA-CDER official who endorses claims contradicted by the FDA-approved product label which warns that SSRIs are associated with increased cardiovascular risks.[51]

Dr. Laughren has provided industry invaluable ongoing support for its expansive offlabel marketing goals which are prohibited under law. For example, he co-authored a consensus conference report (2003)10 financed by industry [52] that endorsed expanded enrollment of children and adolescents (10 to 17) in clinical trials testing drugs for the treatment of manic psychosis in bipolar disorder. The consensus report endorsed broadened criteria for juvenile bipolar eliminating the core symptom for diagnosing mania in bipolar disorder and the core condition for which antipsychotics were approved—namely, psychosis.[53]

Dr. Laughren, a co-author of the consensus report, recommended replacing psychosis with "irritability and aggression" lasting one week or less. **The effect of this recommendation was enormous as it helped propel the epidemic mislabeling of children as "bipolar."** The panel also recommended including children with ADHD and "conduct disorder" in "bipolar" clinical trials—thereby further diluting the criteria for juvenile bipolar. The panel ignored the observation by a European participant that inclusion of ADHD children will undermine the integrity of the trial findings because it will not be possible to distinguish between manic symptoms and ADHD.

In essence, these consensus panels acted in a result-oriented manner, deciding first on the desired outcome, then promoting promoted research aimed at legitimizing off-label prescribing practices. The endorsement by Dr. Laughren, FDA's most authoritative official on psychotropic drug safety issues, surely carried enormous weight. It communicated a reassuring message to clinicians that powerful antipsychotic drugs posed no inherent risk for children, and their use need not be restricted to their approved uses in psychotic adults.

Such reassurance had considerable financial value for manufacturers of antipsychotics. As the Vanderbilt**Error! Bookmark not defined.** and Medco2626 reports confirm, these toxic drugs are being prescribed for children who do not meet the criteria of severe psychosis for which the drugs were approved. **A child prescribed an antipsychotic is essentially condemned to lifelong debilitating drug-induced diseases.**

Steven Hyman, MD, the former director of the National Institute of Mental Health, and current Provost of Harvard University, who is also a neurobiologist severely criticized the abusive use of antipsychotics for children:

"Bipolar disorder in children represents the intersection of two great extremes of ignorance: how to best treat bipolar disorder and how to treat children for anything. It's really important that we define the kids with bipolar disorder and treat them, but it's also important that we not begin to diagnose kids with excess exuberance or moodiness as having the disease. We have to realize that we are risking treating children who could turn into obese diabetics with involuntary movements. There is something very real about the kids with devastating and disruptive symptoms, but the question is still the boundaries. You can do more harm than good if you treat the wrong kid."[54]

Dr. Hyman notes that the diagnosis, juvenile bipolar, is a pretext for prescribing drugs: **"The diagnosis has spread too broadly, so that powerful drugs are prescribed too widely. We are going to have hell to pay in terms of side effects."**

Dr. Laughren's written endorsement of industry-influenced consensus statements broadening the bipolar diagnosis in children to "irritability" contributed to the overprescribing of antipsychotics for children and led to irresponsible antipsychotic drug trials in preschool children—such as those conducted by Dr. Joseph Biederman[55] [56] at Massachusetts General Hospital.[31]

Would children who do not have cancer be subjected to cancer fighting drugs? The psychiatrist who prescribed multiple psychotropic drugs—including the antipsychotic, Seroquel—for Rebecca Riley from the tender age of 28 months, insists that she followed highest practice guidelines. Four- year old Rebecca and the other child casualties of psychiatry's assaultive prescribing practices are the sacrificial lambs whose lives are being forfeited by a subverted profession lacking rudimentary medical competence, and a derailed watchdog agency—both dominated by a rapacious industry.

Dr. Laughren used his inordinate official FDA authority to provide the government seal of approval for expanded marketing of antipsychotics for highly controversial uses. He signed off approval, without review by an advisory committee, on the expanded use of Seroquel for depression in bipolar disorder, despite the fact that a major government analysis found no scientific evidence of efficacy.[9] He approved Risperdal for "irritability" and aggression in autistic children despite documented evidence—noted on the label—that the drug induces extreme mental and physical restlessness (called akathisia), agitation and insomnia—all of which increase the propensity toward violence. Indeed, hospital records document[57] increased incidence of violent and aggressive behavior by patients prescribed atypical antipsychotics—including Risperdal.

In his "private capacity" Dr. Laughren co-authored a consensus report[58] in March, 2007 broadening the definition of "aggression" across all diagnoses—an effort to legitimize the abusive use of antipsychotics as chemical restraints for bad behavior. I doubt that Dr. Laughren's participation[10] [43] [44] [48] [52] in industry-dominated consensus panels that sought to establish research and treatment guidelines to facilitate expanded use of psychotropic drugs in children; adding his name to promotional articles penned by industry-contracted psychiatrists whose task is to influence clinician prescribing practices, and reimbursement policies; or that co-authoring a book chapter with Eli Lilly's chief science officer, were performed gratis. Whether or not a financial conflict of interest is documented, the appearance of a conflict of interest exists when a senior FDA

administrator with authority to grant marketing approval, is collaborating "privately" with those stakeholders who seek agency approval for new drugs; or seek to expand the market by gaining approval for additional uses for patented drugs; or who seek six-month patent exclusivity extensions under FDAMA (FDA Modernization Act) for drugs with annual sales in the $2 to $4 billion bracket.

Our public health policy has been derailed:
Today's medico-industrial complex has much in common with the military-industrial complex that President Dwight D. Eisenhower warned the nation to guard against.[59] The unwarranted influence of a "scientific-technological elite" financed by the pharmaceutical industry has derailed America's healthcare policy—its expenditure and treatment paradigm. Since antipsychotics are being prescribed primarily for unapproved, off-label uses, it is a national scandal the Medicaid pays for 70% to 80% of all U.S. sales of antipsychotics.[60] Indeed expenditures for antipsychotics are bankrupting public health budgets.[61] In a bizarre twist, even as Eli Lilly paid more than $1 billion to settle lawsuits by consumers (and surviving relatives) for failure to warn about the Zyprexa's diabetes risk; and even as Lilly's illegal marketing tactics are the subject of numerous lawsuits by the US Attorney and State Attorneys General;[62] two dozen states have contracted with Eli Lilly ostensibly "to save costs" on psychotropic drugs. Lilly sub-contracted with Comprehensive NeuroScience to operate a "physician monitoring" program since 2003. However, Medicaid officials in Georgia, Kentucky and Tennessee, say "Lilly tied the program to unrestricted access to Zyprexa and the company's other mental health drugs."[63] Lilly's profits from Zyprexa more than off-set any expenditure for "physician monitoring."

FDA's failure to carry out its mission of ensuring safety first can be measured in preventable human casualties[64] and the history of governmental investigations.

The marketing of antipsychotics documents a pattern of deception:

- **January 2004** – The Office of the Inspector General for the U.S. Office of Personnel Management asked J&J for documents related to payments made to doctors in connection with sales, marketing and clinical trials for Risperdal®.
- **November 3, 2005** – Eli Lilly reported to the Securities and Exchange Commission that the U.S. attorney's office in Massachusetts subpoenaed the company, seeking documents on Lilly's business relationship with an unnamed long-term care pharmacy related to some of the company's drugs, including the antipsychotic drug Zyprexa®.
- **November 2005** – J&J's Janssen unit received a subpoena from the U.S. Attorney's Office in Philadelphia seeking information about marketing and adverse side effects of Risperdal®, according to an October 2006 regulatory filing.
- **December 21, 2006** – Bristol-Myers Squibb reported that it reached a tentative agreement to pay $499 million to settle a federal investigation into illegal sales and marketing activities from the late 1990s through 2005. The United States attorney's office in Boston, which first subpoenaed the records of Bristol-Myers in the matter in 2003, declined to confirm the announcement, saying it did not comment on such negotiations unless a final settlement has been signed. Jeff Macdonald, a company spokesman, confirmed previous reports that one product involved was the antipsychotic drug Abilify®.
- **March 1, 2007** – Congressman Henry A. Waxman, Chairman of the House

Committee on Oversight and Government Reform, requested information relevant to Seroquel® from AstraZeneca: “Allegations have been raised that AstraZeneca inappropriately marketed Seroquel.”

- **March 1, 2007** – Congressman Henry A. Waxman, Chairman of the House Committee on Oversight and Government Reform, requested information relevant to Zyprexa® from Eli Lilly: “Allegations have been raised that Eli Lilly misled physicians and inappropriately promoted off-label uses of Zyprexa.”
- **March 12, 2007** – Johnson & Johnson said that it had received subpoenas from U.S. attorneys in Philadelphia, Boston and San Francisco over allegations the company marketed schizophrenia drug Risperdal® for unapproved uses.

We believe that further investigation will reveal a concerted effort by industry and its academics, government regulators, and patient advocacy groups—all of whom industry funds—to promote expanded use of these very profitable, but dangerous drugs. Congress has recently heard a great deal about FDA’s mishandling of safety concerns about the suicide risk posed by SSRI antidepressants; the risk of cardiac arrest from Vioxx® and Avandia.® However, the catastrophic multiple damaging effects posed by the antipsychotics, Zyprexa®, Seroquel® and Risperdal® which are widely and irresponsibly prescribed to our children—even toddlers—and the elderly have yet to be addressed.64 The number of unsafe FDA-approved drugs that were subsequently pulled from the market for safety reasons rose from 1.56% (1989-1991) to 5.34% from 1997-2006.

We urge the FDA to take the following actions:

- Withhold any pending approvals relating to the anti-psychotics until an independent, transparent data review is conducted at an open public hearing;
- Rescind the recent administrative approvals awarded to Janssen (Risperdal), Astra-Zeneca (Seroquel); Bristol-Myers (Abilify), Eli Lilly (Zyprexa).
- Before the FDA considers approving any new indications or uses for anti-psychotics, data and FDA safety reports should be provided to an advisory committee with ample time to review the data prior to an open public hearing, providing opportunity for the public to be heard and testify.
- Consider contraindicating the use of second generation antipsychotics for children, or, at a minimum:,
- Adopt the British safety requirements for conditional approval of Risperdal for all these drugs for children.6

The case of the antipsychotics encapsulates FDA’s irresponsible approval process providing a picture window into FDA’s culture of ineptitude and corruption that prevents it from meeting its primary mission of protecting the public health. The case provides further confirmation that the FDA is an agency mired irrevocably in a culture that promotes alignment with an industry that has grown intoxicated by the pursuit of profits causing them to overlook the safety of patients. The agency’s misdirected focus has resulted in loss of trust and loss of respect by the American people.

Dr. von Eschenbach, in your June 6, 2007 testimony before Congress you affirmed “FDA’s role as a public health agency is to protect and promote the nation’s health by assuring that patients and health care providers have access to safe and effective drugs

along with accurate benefit and risk information to make informed choices."[65]
We respectfully submit that the time has come for you to deliver on this promise, and restore the FDA to the safety function and independence for which it was created.

Sincerely,

Vera Hassner Sharav
President
Alliance for Human Research Protection

cc: Senate Finance Committee:
Senator Max Baucus, Senator Charles Grassley
Testimony, June 6, 2007: http://www.fda.gov/ola/2007/Avandia060607.html

Senate HELP Committee: Senator Edward Kennedy, Senator Mike Enzi
Senator Hillary Clinton, Senator Charles Schumer
Subcommittee on Federal Financial Management
Senator, Tom Coburn, MD

House Energy and Commerce Committee:
Chairman, John Dingell, Cong. Joe Barton
------- Sub-Committee Oversight & Gov. Reform:
Cong. Henry Waxman, Chairman
Cong. Tom Davis, Cong. Tom Lantos, Cong. Dan Burton, Cong. Carolyn Maloney
Cong. Dennis Kucinich, Cong. Edward Markey
------- Sub-committee on Oversight & Investigations:
Cong. Bart Stupak, Chairman
Cong. Edward Whitfield, Cong. Diana DeGette, Cong. Mike Furgeson
------- Sub-committee on Health:
Cong. Frank Palone, Chairman, Cong. Nathan Deal
Cong. Maurice Hinchey
Cong. Carolyn Maloney
Daniel Levinson, HHS Inspector General
Lewis Morris, Chief Counsel to the IG
Mark Cohen, Government Accountability Project

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