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Global Research & Development

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Dear Dr. Temple:

This letter responds to the arguments set out in Dr. David Healy's letter to the Food and Drug Administration ("FDA"), through Peter J. Pitts, dated February 19, 2004. As described in detail in this response, we are gravely concerned that the many erroneous statements, unsupported contentions, and data distortions in Dr. Healy's letter will, if not examined, exposed, and rejected by the FDA, endanger large numbers of citizens suffering from serious, often life-threatening mental disorders and illnesses.

Overview

We at Pfizer believe that discussions of important medical issues benefit the public the most when they are driven by valid science and by patients' best interests. Unfortunately, we do not believe that the contentions made by Dr. Healy—and several other detractors of selective serotonin reuptake inhibitor medications ("SSRIs")—are so driven. We are concerned that writings like the February 19 Healy letter may mislead at least some members of the Psychopharmacological Drugs Advisory Committee ("Advisory Committee") and some FDA officials, unduly frighten the health-care community and the public, misinform legislators with oversight responsibilities for health-care matters, and, as a result, severely harm the patient community.

It is with this in mind that we now write to ensure that you and the members of the Advisory Committee are aware of at least the most significant errors in Dr. Healy's letter. To that end, we request that you provide a copy of this response to each member of that committee and to any other advisory personnel who may be participating in the ongoing review of SSRI safety and efficacy.*

In considering his letter, we hope you will take into account the following facts:

- Zoloft has been tested in thousands of patients during the past two decades in randomized, blinded, placebo-controlled trials. Patients with depression, obsessive-compulsive disorder, panic disorder, post-traumatic distress syndrome, and other disorders have been studied in these clinical trials—more than 5,000 patients in depression trials alone. This testing has shown no increased risk of suicidal behavior.

- In addition, more than 800 healthy volunteers have been studied in Pfizer's Zoloft clinical trials, and none of those subjects reported or showed any suicidality;

- Dr. Healy has little scientific experience in conducting and interpreting the results of controlled clinical research. In fact, in one suit involving Zoloft, a federal court excluded Dr. Healy's testimony as unreliable and scientifically invalid, and then dismissed the case. In that case, two **court-appointed** experts were asked to examine Dr. Healy's opinions and reasoning, and they concluded that his claims and reasoning were unscientific and unreliable in numerous respects, many of which apply equally to his February 19 letter;

- Dr. Healy has distorted and mischaracterized the 1982 "Hindmarch study" of sertraline in healthy volunteers by erroneously asserting that the study proves that SSRI's "induc[e] agitation, or an activation syndrome, that can include suicidality and homicidality." The study's principal investigator, Professor Ian Hindmarch, has refuted that assertion;

- Dr. Healy has distorted and mischaracterized the results of a healthy-volunteer study by Dr. B. Saletu and others, calling that study one "in which there has been a dose dependent induction of agitation in healthy volunteers," when, in fact, the study does not even mention agitation as a side effect, much less as a dose-dependent side effect.

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* For your convenience, we are sending under separate cover a binder containing copies of the materials cited in the end-notes to this letter that are not already in the FDA'.

- Dr. Healy has misrepresented the actual facts about his own so-called healthy-volunteer study by, for example, erroneously asserting that his volunteers had all been determined to have been healthy as required by the approved protocol and by neglecting to describe conduct that effectively unblinded the medications given during the study;

- Pfizer's September 1990 report to the FDA in connection with Pfizer's then-pending new-drug application for Zoloft in depression demonstrated lower rates of suicidal behavior and thinking among sertraline subjects than among placebo controls. Contrary to Dr. Healy's assertion, the FDA has neither criticized these data or the report as "inappropriate" nor required additional analyses;

- Though he chose to criticize—albeit inappropriately—the 1990 report, Dr. Healy chose not to cite an even more extensive, May 1992 analysis that also evinced a negative association between exposure to sertraline and suicide attempt or ideation;

- Dr. Healy erroneously asserts that "only positive" data were published about the Alderman study, when in fact the study's safety section spans three pages and describes in detail all the adverse events. Moreover, after reviewing the report detailing all suicide-related events in the pediatric OCD development program, the FDA concluded that the data did not suggest any causal relationship to sertraline therapy, and Dr. Healy has not identified any Pfizer data that had not been provided to the FDA in that regard; and

- Dr. Healy purports to construct a statistical model showing that the SSRIs Paxil, Prozac, and Zoloft caused "excess suicides" in the United States. In fact, however, careful analysis of his "model" reveals that it is based on a combination of unsupported and unrealistic assumptions, speculations, and internal inconsistencies.

David Healy

Dr. Healy has been hired, by lawyers representing civil-litigation plaintiffs and criminal defendants, to criticize SSRIs in at least eight cases. Although he is a psychiatrist and reader at the University of North Wales, he is primarily known for his work as a medical historian. He has little scientific experience in conducting and interpreting the results of controlled clinical research.[1]

Dr. Healy's early thinking. Before becoming a litigation expert witness testifying against SSRI manufacturers, Dr. Healy published views opposite to those that he now espouses on the question whether SSRIs induce suicide. For example, in 1994 he wrote an article titled *The Fluoxetine and Suicide Controversy: A Review of the Evidence*, 1 CNS Drugs 223 (1994). In that article he conceded that the 1990 report by Teicher *et al.* that had started the controversy was unreliable, and he listed several factors indicating its unreliability, including the following: "no patients were treated with fluoxetine alone"; "all patients were or had recently been receiving other medications"; and "all patients had a history of suicide ideation or attempted suicide."[2] Since becoming involved in litigation, however, he has made a practice of approvingly characterizing the Teicher report as a "controlled case study" and suggesting that the "criticisms" to which the report was subjected were in some sense unfair.[3]

Similarly, before becoming a litigation expert witness, he wrote: "In reply to the case reports of fluoxetine induced suicidality, Beasley and colleagues scrutinized the Eli Lilly database for evidence of increased suicidality in patients receiving fluoxetine. No such evidence has been found. These data from several thousand patients, and the evidence that fluoxetine reduces suicidal ideation, must on any scientific scale outweigh the dubious evidence of a handful of case reports."[4] He did not refer to case reports, as he now does, as "controlled case

studies."[5] He did not suggest that Dr. Beasley should have used some other means of analysis.[6] He did not criticize the FDA's reliance on the Beasley study or the method of analysis it used to reject the claims of the Scientologists and other 1990s SSRI critics.[7] In fact, he characterized the collection of published case reports—abbreviated versions of which were relied on at the February 2 Advisory Committee meeting by lawyers and litigants with whom Dr. Healy is now affiliated—as "dubious evidence."[8]

Since his involvement in litigation began in 1998, Dr. Healy has worked to persuade regulators, courts, and the public to conclude that SSRIs cause suicide and other violent behavior. His efforts include an intense regulatory campaign directed at U.K. authorities since late 1999. He personally sent the Medicines Control Agency (now the Medicines and Healthcare Products Regulatory Agency, or "MHRA") more than 25 letters critical of, and often threatening to, MHRA officials, sometimes sending copies to members of Parliament.[9]

The *Miller* litigation. In his February 19 letter to the FDA, just as in other forums, Dr. Healy has made assertions and purported analyses that are unscientific and misleading, as well as potentially dangerous to the public health. Most instructive is a review of his claims that were examined and criticized by court-appointed experts and by the federal court in *Miller v. Pfizer Inc.*

In that case, Mr. Mark Miller and his wife sued Pfizer, claiming that their 13-year-old son had committed suicide as a result of six days' use of Zoloft.[10] Dr. Healy, who was offered as the Millers' expert witness on general and specific medical causation,[11] claimed that suicide was a "vanishingly rare" phenomenon in 13-year olds,[12] purported to "reanalyze" Pfizer data much as he does here, and purported to apply the causal-analysis criteria commonly called "Koch's postulates" to reach the conclusion that Zoloft caused the Miller youth's suicide.[13]

Among the facts that he ignored, however—and that Mr. Miller himself withheld from the FDA, the Psychopharmacological Drugs Advisory Committee, and everyone else when he spoke at the Advisory Committee meeting on February 2, 2004—were these undisputed facts about the Miller youth:

- Before first ingesting Zoloft or any other antidepressant, he had discussed suicide every day for six months with his sole close male friend.[14]

- Before first ingesting Zoloft or any other antidepressant, he had developed academic and behavioral problems in school that were so serious and so protracted as to result in repeated disciplinary actions, assignment to special classes for children with emotional problems, and special meetings among his parents, faculty members, school administrators, and the school psychologist.[15]

- Before first ingesting Zoloft or any other antidepressant, he had been diagnosed with depression by a board-certified child psychiatrist.[16]

- Before first ingesting Zoloft or any other antidepressant, he had physically attacked other students and destroyed their property.[17]

- Before first ingesting Zoloft or any other antidepressant, he had manifested such severe agitation in school that his teachers had observed and recorded in a written report that he "constantly move[d] his feet around," "g[ot] up and walk[ed] around" at inappropriate times, and exhibited "extreme" and "obvious agitation."[18]

- Before first ingesting Zoloft or any other antidepressant, he had drawn violent pictures and made violent comments about killing himself and his parents to his peers.[19]

- Before first ingesting Zoloft or any other antidepressant, he had threatened to his teacher to kill himself.[20]

- Before their son had ingested Zoloft or any other antidepressant, both Mr. and Mrs. Miller had completed behavioral assessment surveys at the request of the school's psychologist. They had stated on those surveys that their son had sometimes said, "I want to kill myself," and that they, the parents, had observed evidence of hyperactivity, aggression, conduct problems, depression, atypicality, withdrawal, and attention problems.[21]

After years of litigation, the federal court, advised by independent, highly qualified, court-appointed experts, expressly found that Dr. Healy's testimony in support of the Millers' claims was unscientific and unreliable, that his purported figures and calculations could not be replicated, and that he had failed in numerous respects to apply proper scientific methodology.[22] Consequently, the court dismissed the case on summary judgment.[23]

In *Miller*, as in his February 19 letter to the FDA, Dr. Healy couched his opinions in terms of a scientific analysis of the issues.[24] He opined on the prevalence and etiology of suicide; purported to reanalyze Zoloft clinical trial data; purported to apply epidemiological analysis to the claimed causal relationships between the use of Zoloft and akathisia, and between akathisia and suicide; and criticized the clinical data and testing methods employed in the development of Zoloft. Pfizer challenged the scientific reliability of his opinions, reasoning, and data, and sought to exclude his testimony from evidence.[25]

To resolve the issue, the United States District Judge took the unusual step of appointing two independent experts to examine Dr. Healy's opinions and reasoning and to advise the court on their scientific reliability.[26] The court appointed Dr. John Davis, an esteemed neuropsychopharmacologist from the University of Illinois Medical Center, and Dr. John Concato, an esteemed physician-epidemiologist from the Yale University Medical Center.[27] Drs. Davis and Concato examined all of the voluminous reports and other materials submitted by Dr. Healy before the hearing that the court held to determine whether his testimony was sufficiently reliable to be admissible.[28] At that hearing, which lasted for two days, both Dr. Healy and the Millers' lawyer were permitted to ask the court-appointed experts questions (as was Pfizer's lawyer), and Dr. Healy was permitted to answer various questions posed by the

independent experts.[29] The court did, however, preclude him from springing new "reanalyses" that he had not provided in the numerous reports he had submitted before the hearing.[30]

Drs. Davis and Concato set out their conclusions on the scientific unreliability and invalidity of Dr. Healy's methodology in their Report of Independent Experts, which is publicly available in full on the Internet through the Westlaw judicial reporting service.[31] They concluded that Dr. Healy's claims and reasoning were unscientific and unreliable in numerous respects, many of which apply equally to his recent publications, to his numerous letters to MHRA, and to his February 19 letter to you. They found, for example, the following:

- His "methodology for determining medical causation has not been accepted in the relevant scientific community."[32]
- His "heavy reliance on case reports" was not accepted methodology for determining the strength of a posited association between a drug and suicidality. "[L]ack of a comparison group would still make a series of case reports unsuitable for determining the quantitative strength of an association, regardless of other attributes."[33]
- His failure to discuss other research and demonstrate consistency with other research pertaining to his posited associations between sertraline and "akathisia" and between akathisia and suicide constituted misapplication of the scientific method.[34]
- His failure to "rule out alternative explanations" for suicides temporally associated with therapy violated "a fundamental tenet of scientific reasoning."[35]
- His reliance on certain factual evidence and "exclusion of evidence from other sources which suggest the possibility of suicidal thoughts and behavior" that preceded and were independent of use of sertraline was "not generally accepted practice."[36]
- His "manner of finding a causal association between use of SSRIs and akathisia, and akathisia and suicide," was not "generally accepted by the scientific community."[37]
- "A threshold for level of proof [about causal relationships] is often established only after deliberation by selected members of the scientific field, as when scientific panels reach consensus. Regarding the question of SSRIs and suicide,

such panels have not found the level of proof to be reached. Dr. Healy . . . holds a minority opinion in this matter. We acknowledge that a minority view (proposing causality) at one point in time may later become the majority view (that establishes causality), but that phenomenon has not, to date, occurred with regard to an association of sertraline and suicide."[38]

- "We cannot replicate the calculations of relative risk (with a value of 2.19) provided by Dr. Healy[.]"[39]

- "The data related to Dr. Healy's healthy volunteer study, as well as data from the so-called Hindmarch study, do not produce statistically significant results."[40]

- "Randomized, controlled trials are very pertinent to determining the relative risks of a potential sertraline-suicide association . . . . [T]he available evidence does not show an increased rate of suicidal acts [or ideation] associated with SSRI agents. The rate of suicide on SSRIs is actually decreased by approximately one-half."[41]

- Regarding Jick (1995), relied on by Dr. Healy in the *Miller* litigation and here in his February 19 letter to the FDA: Based on the reduction in initial calculations of a higher relative risk for fluoxetine to take into account certain factors leading to confounding caused by selection bias, "it is plausible that additional confounding factors (e.g., physicians' suspicion of suicide risk), if they had been available for this analysis, would have decreased the relative risk even more towards 1.0." [42]

- Dr. Healy's methods rely on unpublished data and "do not conform to generally accepted methodology" because "the numbers of patients in each group are not reported, and the statistical significance of the results . . . are not provided."[43]

- His "healthy volunteer study [discussed below] is not a sufficient basis for calculating any statistically significant relative risk, due to issues involving study design and sample size."[44]

- Regarding Donovan *et al.* (2000), relied on by Dr. Healy in *Miller*: "As noted by the study authors, however, available data suggested that three possible confounding factors (age; antidepressant prescription switches; prior history of deliberate self-harm) contributed to an increased unadjusted relative risk [for SSRIs relative to other antidepressants]. . . . Thus, the study does not provide strong evidence for or against a possible sertraline-suicide association."[45]

- His "'lines of evidence' only partially satisfy Koch's postulates . . . [and] 'confounding' has not been excluded as an alternative explanation for an apparent sertraline-suicide relationship."[46]

Having examined Dr. Healy's written submissions and heard his attempt to answer the criticisms of the two court-appointed experts, the court excluded his testimony as unreliable and invalid and dismissed the case. The court concluded (i) that Dr. Healy's opinions were a "moving target"—*i.e.*, his tactic, as in his February 19 letter to the FDA, was to throw up unsupported assertions about purported data and, when his assertions were shown to be erroneous, to throw up new assertions in the hope that they would not be scrutinized sufficiently to show their flaws; (ii) that Dr. Healy did not use scientific methods and reasoning; and (iii) that Dr. Healy's opinions were political and rhetorical, not scientific.[47]

Earlier this year, the United States Court of Appeals for the Tenth Circuit affirmed that ruling.[48]

As shown below, Dr. Healy's claims in his February 19 letter to the FDA, like his similar claims in litigation, are based on serious errors, unsupported (and often unstated) assumptions, and unscientific rhetoric.

Healthy Volunteer Studies

Contrary to Dr. Healy's claim, the studies conducted on healthy volunteers do not support his contentions. He claims in his February 19 letter to the FDA that if the "details [of healthy volunteer studies] were made public in this case I believe that it would be clear that the induction of agitation, or an activation syndrome, that can include suicidality and homicidality was a recognized class effect of SSRI medication in the early 1980s." (Healy Letter at 4.) In fact, however, examination of the details of those studies shows that his claims are unsupported and erroneous.

Hindmarch Study. Here, as he has in litigation, Dr. Healy has distorted and misstated the results of the 1982 "Hindmarch study" of sertraline in healthy volunteers in multiple respects.

As an initial matter, he claims that, when he began corresponding with the MHRA about these issues in the late 1990s, "it became clear that MHRA at least initially did not have access to and had no awareness of the Hindmarch study . . . ." (Healy Letter at 4.) That is untrue. In fact, in September 1988 Pfizer submitted to the British agency (then called the Medicines Control Agency, or "MCA"), as part of the International Registry Dossier ("IRD") for sertraline,[49] a 34-page study report for the Hindmarch study. In addition, of course, the agency had access to any additional information about the study that it may have thought it should consider.

Dr. Healy also claims that "MHRA appeared to have operated on the basis of a four-page summary of the study prepared for them by Pfizer."* That, too, is untrue. As just noted, Pfizer submitted to the MCA in September 1988 a 34-page study report.[50] In 1984[51] and 1988[52] Pfizer also submitted to the FDA reports for the Hindmarch study (Protocol 206), with the latter version being 99 pages long.

The Hindmarch study was a Phase I dosage study conducted by Professor Ian Hindmarch in 1982, early in the development of sertraline. It was a double-blind, placebo-controlled study designed to determine the effects of non-titrated 150 mg sertraline (three times the normal starting dose) on psychomotor performance and subjective feeling states. Five patients were randomized to sertraline 150 mg, seven to placebo. All patients were adult females. The study

* Dr. Healy's use of the suggestive term "appeared to have" is typical of the type of innuendo he regularly employs in his writings critical of SSRIs and their manufacturers. For example, his February 19 letter to the FDA includes, in the space of only about four pages, equally evasive phrases such as "there would appear to be," "may in fact," "will commonly give enough doubt," "it is highly likely," "may be considerably worse," "it seems clear," "can be expected to yield," "many observers . . . will guess that it is highly likely," and "may well be in error." This tactic cannot disguise his lack of hard data to support his contentions.

was terminated on day 4 due to complaints of side effects by 1 placebo volunteer and 5 sertraline volunteers.

Neither the FDA nor the MHRA ever suggested that the Hindmarch study showed any significant safety issue for sertraline, much less the phenomenon that Dr. Healy claims the study shows. Review of the details of the adverse events recorded in the actual study report demonstrates why not.

By design specified in the protocol, "subjects were to be asked to complete side-effect questionnaires at the same time points as psychomotor tests were performed. All reported side-effects were to be recorded together with details of time of onset, duration, and the investigator's opinion of relationship to treatment. Leading questions were not permitted."[53]

Tables 9 and 10 in the Hindmarch study report submitted to the FDA 16 years ago detail, among other things, each of the adverse events and their severity reported by subjects in the Hindmarch study.[54]

- There was no report of any suicidal idea or act by any subject.
- The report submitted to the FDA summarized the adverse events reported in the study and its associated termination as follows: "Due to intolerable side effects in 6 subjects (five found to be on sertraline) the study was terminated on day 4 and thus no subjects were assessable for effects on psychomotor performance, mood or sleep. The most frequently reported side-effects in the sertraline regimen were tremor, insomnia, nausea, asthenia and agitation (all volunteers), dizziness, sweating, dry mouth, and anxiety (4/5 volunteers), headache, somnolence, cold clammy skin, hypertonia (stiff jaw) and vision abnormalities (3/5 volunteers), all of which were reported from the first dosing day."[55]
- No side effects required treatment.[56]
- "Some side effects caused concern and may have resulted in over-reporting of symptoms."[57]

- "[T]he reason for the high frequency of side-effects in this study remains unknown. Most importantly, it is not reflective of the overall side-effect experience with sertraline."[58]

- "One volunteer in the placebo regimen complained of a variety of side effects—of similar type to the sertraline group—all of mild to moderate degree, but which necessitated withdrawal from the study."[59]

- "Aggressive reaction" on placebo: one subject on placebo reported "aggressive reaction," compared with none on sertraline.[60]

Professor Hindmarch's testimony to the court in *Miller* further explained the true nature of the "agitation" reported among sertraline and placebo patients in his study. Dr. Healy was present and is fully aware of this information, and yet withheld it from the FDA in his February 19 letter. Professor Hindmarch testified that he and Pfizer had canceled the study because the non-titrated study dose of 150 mg caused "profound physical effects." These adverse events, and the circumstances producing them, included

> nausea, gastrointestinal side effects, insomnia, and . . . dry mouth. There was a whole raft of other very, very physical reports. There were also two volunteers who reported feelings that they couldn't cope. . . . [T]hey were all female, they were all homemakers, and they all had responsibilities for husbands and children and things like that. And what they were complaining about was that they were unable to continue with their normal daily routines . . . [b]ecause they had such awful physical effects of this drug. . . . And this was causing these volunteers, well, a lot of stress. They were not sure how they could cope with doing their domestic tasks. And on the first day there were only two volunteers that complained of this. And then on the second or third day, the rest, there was another four volunteers that complained of this sort of anxiety. . . . So I decided to stop the study . . . for these primarily physical effects. . . . But these in my mind certainly, I would never have classified what we'd seen as agitation or anxiety. . . . Well, an unfortunate feature of this study in the sense that all of our volunteers were actually bussed into the unit every morning together, well, there were two mini-busses . . . . So there was a tremendous amount of discussion amongst these volunteers about who's had what side effect and a lot of gossiping. We do know that the volunteers were actually telephoning each other at night . . . . And this is why I'm convinced we had the proliferation of these side effects, which were only reported after the first dose by two of the volunteers, proliferate to another four volunteers, [including] one that was actually on placebo. So she

did not actually experience any drug, and yet she had exactly almost word-for-word exactly the same description of the side effects.[61]

This testimony by the study's principal not only shows that Dr. Healy's description of the study is erroneous, but also shows why, in addition to the reasons that caused the court-appointed experts to conclude that the study did not produce statistically significant results,[62] the study cannot properly be relied on for any conclusion about any adverse psychiatric effects—namely, several study subjects were heavily influenced by conversations with other study subjects during the study.

Professor Hindmarch later conducted a second, similar study in healthy volunteers, using lower starting doses of sertraline. He found that none of the subjects in the second study experienced the substantial physical effects, or the resulting agitation or anxiety, reported by the subjects in the first study, which had used initial, non-titrated 150 mg doses.[63]

Professor Hindmarch conducted a third, similar study in elderly volunteers using rising, rapidly titrated dosing from 100 mg to 200 mg. Again, none of the subjects experienced the substantial physical effects, or the resulting agitation or anxiety, reported in the first study.[64]

The Hindmarch study thus provides no basis for Dr. Healy's claim that SSRIs "induc[e] agitation, or an activation syndrome, that can include suicidality and homicidality[.]" (Healy Letter at 4.) The phenomenon he advocates in his litigation work and in his February 19 letter is completely fabricated and has been denied by the study's principal, Professor Hindmarch, both in writing and in testimony under oath. Nor, as described below, has that purported phenomenon been observed in <u>any</u> of the more than 800 healthy volunteers treated with sertraline in some 50 separate studies sponsored by Pfizer.

Zoloft Healthy-Volunteer Studies. Dr. Healy ignores the complete absence of any reported instance of suicidality in any of more than 800 subjects exposed to sertraline in Pfizer's clinical studies of healthy volunteers.

As he knows, but did not disclose in his February 19 letter, on May 24, 2000, the British MCA sent Pfizer a copy of Dr. Healy's then-recently-published article in which he misrepresented the nature and results of what he falsely called a "healthy volunteer study" titled *Emergence of Antidepressant Induced Suicidality*, 6 Primary Care Psychiatry 23 (2000), and asked Pfizer to submit information on all healthy-volunteer studies conducted with sertraline and adverse effects reported during those studies.[65] Pfizer submitted its report on June 12, 2000, providing detailed summaries of study designs and adverse events reported in more than 800 healthy volunteers treated with sertraline in 50 separate studies, including Protocol 206, the Hindmarch study discussed above.[66]

In those 50 studies, any observed or subject-reported undesirable event that occurred, regardless of treatment group or causal relationship, was required to be recorded as an adverse event. There was no reported instance of suicidal ideation, suicide attempt, or completed suicide in any of the 800-plus healthy volunteers in any of the 50 studies.[67] Having reviewed these healthy-volunteer data, the British regulators responded to Dr. Healy in a July 2000 letter and stated:

> In studies contained in the sertraline hydrochloride International Registry Dossiers (IRD-1 and -2), Oral Concentrate IRD, and Renal/Hepatic Supplement, there have been over 50 studies in normal healthy volunteers involving over 800 subjects, the majority of subjects were male, although some studies did include females. The sertraline dose range was generally 50 to 200 mg and sertraline was administered in both single and multiple doses. The duration of multiple dose studies was normally less than 30 days. There was no incidence of suicidal ideation, suicide gesture or attempt or completed suicides. There are a few reports of agitation, anxiety, nervousness, abnormal thinking and hyperkinesia

among the safety data collected in these studies. These were described as mild or moderate in all cases. No serious psychiatric events were reported. (Emphasis added.)[68]

In a letter to Pfizer dated August 14, 2000, the British regulators concluded that "the available study data did not support a causal association between SSRIs and suicidal behavior." (Emphasis added.)[69]

Thus, Dr. Healy's contention that healthy-volunteer studies support his claims is wrong. In addition, in his February 19 letter to the FDA he withheld from the agency his knowledge that the MHRA had considered his erroneous claim and had expressly rejected it.

Dr. Healy also mischaracterizes the results of a healthy-volunteer study by Dr. B. Saletu and others, "On Central Effects of Serotonin Re-uptake Inhibitors: Quantitative EEG and Psychometric Studies with Sertraline and Zimelidine," 67 J. Neural Transm. 241 (1986). Dr. Healy characterizes that study as one "in which there has been a dose dependent induction of agitation in healthy volunteers." (Healy letter p. 3.) In fact, the Saletu article does not even mention agitation as a side effect, much less as a dose-dependent side effect. The only listed side effect bearing any reasonable relationship to agitation is restlessness. Even as to that, the article shows that two subjects experienced restlessness on placebo, 3 on Zoloft 200 mg, and 5 on Zoloft 400 mg. It is to be expected that some subjects would experience restlessness when exposed to highly elevated, non-titrated dosages of Zoloft, given the marked uncomfortable physical side effects that often occur in those circumstances. For example, at Zoloft 400 mg, 10 of 10 subjects reported nausea, 4 reported dizziness, 4 reported tremor, 2 reported dry mouth, 2 reported vomiting, 3 reported trismus, and 1 or more reported headache, diarrhea, coldness, tiredness, muscle tension/weakness/twitching, paresthisia, photophobia, or pollakiuria.

Making Dr. Healy's mischaracterization even more improper is his failure to acknowledge that the Saletu study was one in which the study subjects received, in random order in weekly intervals, single oral doses of placebo, 100 mg Zoloft, 200 mg Zoloft, 400 mg Zoloft, and 100 mg zimelidine as a reference drug. Thus, the administration of Zoloft did not commence at the recommended dosage of 50 mg; was not titrated; when randomly administered at 400 mg, was administered at twice the maximum recommended dosage; and was randomly administered in a manner such that in many instances it was administered within 24 hours of the administration of zimelidine, an early SSRI that was briefly marketed in Europe before being taken off the market because of an apparent association with Guillain-Barre Syndrome and that, as Dr. Healy himself elsewhere states, had "a greater number of suicide attempts than expected" during clinical trials and post-launch studies. David Healy, Let them eat Prozac 61 (2003 Canadian. ed.).*

Dr. Healy's Own "Healthy Volunteer" Study. In his February 19 letter to the FDA, Dr. Healy refers to "a healthy volunteer study, involving Zoloft, in which two volunteers had become suicidal, that had been undertaken by my group in North Wales." (Healy Letter at 3.)

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* It also is worth noting that in a recently published article, David J. Nutt, University of Bristol, Psychopharmacology Unit, School of Medical Sciences, University of Walk, Bristol, United Kingdom, stated: "My own group has conducted many volunteer studies with SSRIs and other antidepressants. Our total volunteer exposure to SSRIs is of the order of 650 volunteer days with one study of fluoxetine for 5 weeks (Wilson *et al.*, 2002). We have not seen alterations in mood or other measures such as anxiety or being relaxed on rating scales. Furthermore, we have had no spontaneous reports of suicidal thoughts. Other psychopharmacology groups, such as Cowen's in Oxford, have similar experiences (P. J. Cowen, personal communication)." Journal of Psychopharmacology 17(4) (2003) 355-364.

He has mischaracterized his own purported "healthy volunteer" study in much the same way that he has mischaracterized Pfizer healthy-volunteer data.

The study to which he refers was conducted in October-November 1999, about a year after he had first been hired to testify against SSRI manufacturers in litigation. In 2000 he published, in a journal titled "Primary Care Psychiatry," an article in which he purported to describe the study protocol and results. In the article he claimed:

> Twenty healthy volunteers aged between 28 and 52 . . . were recruited to a study comparing reboxetine with sertraline on a range of personality, self-report and quality of life measures. The study was aimed at establishing the effects of antidepressants on levels of well-being in subjects not currently depressed. There were 9 males and 11 females recruited from the administrative, medical, and nursing members of the North West Wales district general hospital psychiatric unit. . . . All volunteers were free of medical conditions. None were on concurrent drug treatment. None had a history of previous psychiatric illness.
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>
> The cases described in this paper [two patients who reportedly experienced brief suicidal thoughts] appear to have become suicidal on sertraline with no easy means of explaining what happened other than by invoking an SSRI-induced suicidality. [Emphasis added.][70]

In fact, to this day Dr. Healy has concealed from the medical profession and regulatory authorities the actual facts about his patients and their experiences. We discovered the truth when he was forced to produce the underlying data in litigation. The documentation reveals that (i) his claims about the supposed "healthy volunteer" nature of his subjects were untrue; (ii) the protocol on which permission to conduct the study was based was violated multiple times; (iii) the two purportedly "suicidal" subjects never manifested any intention to harm themselves or committed any "suicidal" act; and (iv) rather than there being, as he asserted, "no easy means" of explaining his reported two cases of suicidal ideation other than "SSRI-induced suicidality," it is clear that relationships between the subjects and Dr. Healy, biases on the part of Dr. Healy and

the two subjects involved, and information provided to the subjects that effectively unblinded the medications given during the study, can, in fact, easily account for their reported instances of "suicidal ideation."

Dr. Healy's unpublished study records showed several misstatements in his published article and methodological defects in his study. In the first place, no baseline measure of suicidality was made for any subject entering his study. Furthermore, no measures were taken to ensure that there had been a return to baseline during crossover (both "suicidal" subjects took reboxetine first). Indeed, no validated rating instrument for assessing suicidality was used at any point during his "study"—not the HAMD, not the Beck scale, and not any other instrument. Dr. Healy faults the SSRI depression studies and FDA analyses of SSRIs and suicide during the past decade for having used HAMD Item 3 (suicidality) scores as <u>one</u> endpoint for examination, yet in his own study he used no scale at all.

Another serious flaw in Dr. Healy's study and his account of it is his insufficient diagnosis of subjects as "perfectly normal" or "healthy," including his erroneous descriptions of subjects as not taking concurrent medications and having no previous psychiatric histories.[71] His unpublished study records show that, to determine the status of a subject's mental health, some of the subjects were merely asked whether their "current mental status" was normal or abnormal. Those records further reveal that even that single inadequate question about "current mental status" was left blank or marked "Not done" for 12 of the 20 subjects (60%), including each of the two who purportedly experienced suicidal thoughts.[72]

Still further, Dr. Healy's unpublished study records showed that <u>four</u> subjects (20%) <u>were</u> taking concomitant medications,[73] contrary to Dr. Healy's representations, in his published

article, in documents filed in court under penalty of perjury, and in other contexts, that none of the subjects was taking concomitant medication.[74]

One of Dr. Healy's subjects affirmatively recorded a history of depression only two years before the study, yet Dr. Healy published that there was no history of depression in any of the subjects.[75] Even when confronted with this discrepancy during cross-examination in the *Miller* case, he further misstated to the court that the patient had been depressed five years earlier.[76] Only when confronted with his own study records did he admit that the depression had occurred just two years earlier.[77]

Examination of Dr. Healy's unpublished study records also reveals the misleading nature of his descriptions of the two purportedly "acutely suicidal" subjects in his study, as well as the absence of any basis for his assertion that "no easy means" other than exposure to Zoloft could have caused the events. One of the two purportedly "suicidal" subjects was unable to say whether her supposed suicidal thoughts had occurred while she was awake.[78] The other reportedly had a momentary thought of suicide that evaporated when the telephone rang.[79] For both cases, Dr. Healy's unpublished study records reveal that obvious explanations do exist for why the two subjects reported those thoughts.

The first is simple information and reporter bias. Dr. Healy's subjects were familiar with his views on SSRIs when they entered the study.[80] Most of his subjects, including both of those who reported suicidal ideation, were employees within the same hospital department of which he was a director and senior figure.[81]

Compounding this flaw was the compromised "blinding" of the study. More than half of the subjects, including one of the two who he says became "suicidal," were physicians or nurses who had prescribed or administered the study drugs and would have been familiar with the

common, expected side-effect profiles of the two drugs (*e.g.*, nausea and gastrointestinal problems on sertraline).[82] Moreover, as Dr. Healy was forced to admit on cross-examination in *Miller*, his subjects were informed before the study began that (i) his position was that SSRIs cause akathisia and suicide and (ii) while taking the SSRI, they might experience "classic SSRI side effects like nausea and vomiting," and while taking Reboxetine, they might, in contrast, experience sleeplessness and urinary hesitancy.[83]

Dr. Healy also has withheld from the MHRA, the FDA, and the medical community that one of the subjects who purportedly experienced suicidal thoughts was, even before entering the study, "prone to lucid dreaming, including both sleepwalking and sleeptalking"; that during the first phase of the study (on Reboxetine), she experienced extreme stress after the death and burial of her grandmother, inability to sleep, and inability to have a normal diet; and that she felt annoyed, miserable, unhappy, and angry, and experienced nausea, lethargy, and uncomfortable symptoms while taking Zoloft during the second phase.[84]

He likewise has withheld from the MHRA, the FDA, and the medical community that the other of the two patients who purportedly experienced suicidal thoughts, a physician, reported having consumed two pints of alcohol weekly before entering the study and that, during the first phase of the study (on Reboxetine), she experienced cold and flu-like symptoms, and that while taking Zoloft during the second phase, she experienced inability to sleep, appetite problems, nausea, and constipation and nausea, anxiousness, and agitation, and "a cracking migraine headache."[85]

Thus, both of those two subjects would have been likely to be able to discern which medication they were taking merely by comparing the symptoms they experienced to the descriptions at the beginning of the study of the likely side effects of the respective drugs, and

therefore whether or not they were taking the one that Dr. Healy wanted to show caused akathisia and suicide. The court-appointed experts in *Miller*, in commenting on Dr. Healy's study, specifically mentioned "the significance that a number of the people in this study were mental health professionals or involved and might have some knowledge of the drugs."[86]

Examination of the undisclosed study records also shows the degree to which Dr. Healy embellished descriptions of the two subjects' experiences in a manner that supports his litigation-driven theories. In the article to the medical and scientific community, he said they manifested "clear" and "extremely serious" suicidality.[87] In fact, one of the subjects had only a passing suicidal thought that she could not recall whether she had had while awake or dreaming. The other reported a suicidal thought or impulse that was so ephemeral that it was interrupted by a ring of the telephone. In addition, Dr. Healy "elicited" some of the descriptions of the subjects' symptoms in "post study focus groups" and private conversations, which indicates that he may have suggested some of the details.[88]

Neither of the two subjects "actively" did anything that harmed them or that required any intervention. Both continued on sertraline for the duration of the study.[89]

Placebo-Controlled Studies

Dr. Healy's reliance on erroneous characterizations of healthy-volunteer studies apparently results from the fact that the voluminous data that could provide valid scientific evidence of a positive association, if one existed, between sertraline and suicidal behavior provide no support for his claims. Instead, they substantially refute those claims. The FDA long ago examined all pertinent data related to suicidality from the Zoloft depression development program and concluded—we believe correctly—that those data evinced a <u>negative</u> association between sertraline and suicidality.

The 1990 Report. Pfizer's September 1990 report to the FDA in connection with Pfizer's then-pending New Drug Application for approval of Zoloft as a treatment for depression demonstrated lower rates of suicidal behavior and thinking among sertraline subjects than among placebo controls.[90] This report is the source of the suicide attempt data that Dr. Healy purports to include in his "reanalysis" set out in Table 1 of his February 19 letter. In fact, that data set is the same data set that has been the basis of his recent publications,[91] Dr. Khan's publications,[92] and Drs. Laughren and Mosholder's recent publication.[93]

Suicide ideation analyses in the 1990 report were prescribed by the FDA and have been explained in the public scientific writings of, among others, Dr. Laughren of the FDA, who was involved in the agency's study of SSRI safety at all pertinent times.[94] Those analyses examined comparative rates of improvement in preexisting suicidal ideation, various degrees of worsening ideation, and "emergence of substantial suicide ideation," which focused on patients in placebo-controlled trials whose HAMD Item 3 scores progressed from 0 or 1 at baseline to 3 or 4 at any time during a clinical trial. Those analyses consistently showed less risk of suicidal thinking worsening or emerging in sertraline-treated patients than in placebo controls.[95]

Suicide attempt analyses were also conducted, as set out in Table 1 of the 1990 report.[96] Suicide attempts (including both completed and uncompleted suicidal acts) are outcomes that are not subject to the criticisms of the "sensitivity" of the HAMD scale to detect suicidal ideation that Dr. Healy espouses. Pfizer submitted analyses to FDA of both absolute rates of suicide attempts (unadjusted for the substantially greater exposure time for patients randomized to sertraline) as well as rates adjusted to account for duration of therapy (*i.e.*, rates calculated on a patient-exposure-year ("PEY") basis). These analyses also showed less risk of suicidal behavior among sertraline patients than among placebo controls.[97] Narratives of each of the patients who

attempted suicide were also provided to the FDA with the 1990 report; the narratives included available information on other adverse events, time on therapy, concomitant medications and illnesses, and similar medical information.[98] The patient narratives do not suggest any connection between suicidal acts and "akathisia," other psychiatric adverse events, dose increases, time on therapy, or any other aspect of the supposed "drug-induced suicide" phenomenon that Dr. Healy advocates.[99] Both quantitatively and qualitatively, the suicide-related adverse events described in the 1990 report are consistent with a depressed adult clinical trial population, not a population that has been randomized to placebo or a suicide-causing new agent.

With respect to sertraline, Dr. Healy is wrong when he claims that "run-in phase" suicide-related events were improperly attributed to placebo, and therefore improperly suggest placebo suicide-attempt rates larger for placebo than for sertraline patients. Dr. Healy claims, "Despite FDA recognition that these procedures are inappropriate, Glaxo SmithKline and Pfizer have also filed under the heading of placebo suicidal acts that did not happen in the randomized phase of their respective trials." (Healy Letter at 9.) The truth, as Pfizer's 1990 report to FDA plainly shows, is that the report specifically identified certain events (3 placebo attempts) as having occurred during single-blind placebo phases. Table 1, note 1 explicitly stated that the total of suicide attempts on placebo "includes 145.8 patient-years of double-blind placebo and 63.2 patient-years of single-blind placebo exposure." (Emphasis added.)[100] Furthermore, the case-specific patient narratives appended to the report for each of the suicide attempts specifically identified 3 placebo attempts as having occurred during single-blind placebo exposure (what Dr. Healy calls "run-in" and claims should not be counted as placebo-group

attempts).[101] Contrary to Dr. Healy's assertion, the FDA has neither criticized these data or the report as "inappropriate," nor required additional analyses.

The above data were provided to and reviewed by the FDA and the Advisory Committee before Zoloft's approval. The analyses were carried out pursuant to methods prescribed by FDA officials. Neither the FDA nor any Advisory Committee member criticized these data or the analyses in any respect. Dr. Laughren authored a book chapter in 1994 describing the methods used in analyzing SSRI suicidal ideation data and explaining how and why those analyses reassured the agency that no subgroup of patients was subject to drug-induced suicidality.[102] The data provided to and reviewed by the FDA in this 1990 report were subsequently summarized in detail in the FDA's Summary Basis of Approval ("SBA") for Zoloft.[103]

The May 1992 Report. Dr. Healy has been provided and cross-examined about, but has chosen not to cite, a later and larger analysis of suicide attempts and ideation in the sertraline development program prepared in May 1992 (and publicly presented at the Collegium Internationale Neuro-Psychopharmacologicum convention in that same year). That analysis refutes his claim that inclusion of placebo "run-in" phases improperly results in rates favorable to sertraline.[104] In the May 1992 report, placebo "washout" or "run-in" suicide attempts (*i.e.*, attempts occurring during single-blind placebo washout phases preceding randomization to placebo or study drug) were excluded from the pooled analysis of suicide attempts in sertraline and placebo in randomized head-to-head trials—as Dr. Healy now claims should be done.[105] Further, the May 1992 report's analysis did not adjust for differential duration of exposure (an adjustment that Dr. Healy criticizes when it tends to disprove his contentions), but instead calculated incidence based on absolute numbers.[106]

The result—even with the exclusion of the 3 patients who attempted suicide while taking a placebo during single-blind placebo phases of sertraline depression trials—was a suicide attempt rate of 0.28% (4/1424) (95% CI 0-0.7%) for sertraline and a numerically higher rate, 0.32% (3/936) (95% CI 0-0.8%), for placebo.[107] Dr. Healy is fully aware of these sertraline data refuting his claims, has been cross-examined about them in open court, and yet chose not to refer to them in his February 19 letter to the FDA.[108]

The May 1992 report was completely consistent with the 1990 report; it evinced a negative association between exposure to sertraline and suicide attempt or ideation. Looking at all of the data available to Dr. Healy, instead of only the subset on which he chooses to rely, the rates of suicidal behavior were lower for patients taking sertraline than for patients taking placebo controls, whether or not the several attempts during "run-in" placebo phases are included in the placebo numerator. The court-appointed experts in the *Miller* case, having reviewed Pfizer's September 1990 and May 1992 reports, similar reports on suicidality in the adult and pediatric OCD clinical trial programs, and numerous other published analyses of SSRI suicide data, stated:

> Among almost 10,000 patients taking an SSRI drug (fluoxetine, sertraline, paroxetine) or placebo in these studies, approximately 0.7% had suicidal acts with the active agent vs. approximately 1.4% with placebo. Thus, the available evidence does not show an increased risk of suicidal acts associated with SSRI agents. (The rate of suicide on SSRIs is actually decreased by approximately one-half.)[109]

"Miscoding" Allegations Are Inapplicable to Sertraline Data. Dr. Healy's claims about purported coding of suicide attempts and ideation as "emotional lability" are inapplicable to sertraline. Pfizer sertraline data, regulatory submissions, and labeling have been governed, consistently and properly, by the WHO-ART terminological dictionary.[110] "Emotional lability,"

under WHO-ART, is the preferred term for dozens of verbatim (reporter) terms, including crying, emotional distress, and mood change, but not suicidality of any kind. Instead, "suicidal ideation," "suicide attempt," and "suicide gesture" are the WHO-ART preferred terms for events in which reporters refer directly or indirectly in their verbatim descriptions of adverse events to any form of suicidality (*e.g.*, "thoughts of suicide," "suicide ideas," "attempted self-hanging," or "possible suicide attempt").[111]

Dr. Healy has had the same kind of access (via litigation) to sertraline-related documents that he claims to have had for other companies' documents, and he has never identified any instance in which a sertraline patient in a Pfizer-sponsored clinical trial manifested suicidal behavior and Pfizer coded the event as "emotional lability."

Pfizer's submissions of its pediatric data on September 12, 2003, and January 16, 2004, confirm that no miscoding of suicide events as "emotional lability" affects its data. Both of the terminological analyses prescribed by FDA produced exactly the same set of cases.[112]

"Crisis in the Scientific Literature"

With respect to sertraline, Dr. Healy's contention that there is a "crisis in the scientific literature" publicizing clinical trials of SSRIs is unsupported and wrong. He claims that "[t]here is probably no other area of medicine in which the academic literature is so at odds with the raw data." (Healy Letter at 11.) His February 19 letter is at odds with both the raw data and the academic literature he criticizes.

He contends: "In other Zoloft trials (Alderman et al.) the rate of suicidality on the Zoloft was 9% in depressed children. The published article on this latter study reports on adverse events that occurred at a 10% rate or more and hence it fails to mention that there was any issue with suicidality in these children." (Healy Letter at 11.) Alderman *et al.* (1998) is the published

report on a forced-titration study of the pharmacokinetics and tolerability of sertraline in children and adolescents with depression, OCD, or both, conducted as part of the pediatric OCD development program in the mid-1990s.[113]

While the published Alderman study report does contain one table (Table 2) that used a 10% incidence cutoff for tabulating certain events, Dr. Healy misleadingly withholds other facts that undercut his allegation. For instance, he fails to mention that the same article's "Safety" section, spanning three published pages, describes in detail adverse events reported in the study, including specific reference to the 3 of 56 total patients, all depressed males, who discontinued for adverse events.[114] The section includes (i) a specific description of a 7-year-old who discontinued after 24 days for moderate hyperactivity; (ii) a specific description of a 13-year-old who discontinued after 22 days for "moderate nervousness attributed to family stress," and (iii) a specific description of an 8-year-old who "was hospitalized and discontinued on study day 36 after an episode of severe self-mutilation that included razor lacerations of his feet."[115] A mere reading of the material that Dr. Healy describes belies his claim that "only positive" data are published in the literature, and further reveals that it is Dr. Healy himself who is being deliberately and unfairly selective.

Further, as the FDA knows, the agency requested, and Pfizer provided, a detailed analysis of all suicide-related events (ideation and attempts) that had occurred in the study reported in the Alderman *et al.* publication, as well as in other protocols in the pediatric OCD development program.

- As reported to FDA in 1996, in placebo-controlled phases of these trials, there was no instance of suicidal behavior or ideation among 92 sertraline subjects, and one such event (suicidal ideation) in the placebo controls.[116]

- As reported to FDA in 1996, in open, uncontrolled phases of these trials, 6/220 (2.7%) of sertraline subjects manifested suicide ideation or behavior. The majority of these 6 patients had a primary diagnosis of depression, and each of the 6 had multiple risk factors for suicidal behavior.[117]

The FDA reviewed the report detailing all suicide-related events in the pediatric OCD development program and concluded that the data did not suggest any causal relationship to sertraline therapy.[118]

Dr. Healy's unsupported assertion of a 9% "rate of suicidality on the Zoloft" is fabricated and bears no relationship to the Alderman publication to which he refers, or to the underlying data from that study, or to the underlying data from the entire pediatric OCD program, or to any of the publications or clinical trial data from any aspect of any Zoloft clinical trial programs. Like the purported figures that he advanced in the *Miller* litigation, his numbers cannot be replicated; they are concocted and thrown up as purported support for his claims.[119]

Dr. Healy also contends: "A further article on Zoloft by Ambrosini et al, which reports on a 5.7% rate of suicidality on Zoloft, says that 'Sertraline is effective, safe and well-tolerated.'" (Healy Letter at 10.) Again, examination of the material he refers to belies his assertions. The publication, Ambrosini *et al.* (1999), reported on an uncontrolled (open) study of sertraline (Study No. R-0246) in 53 adolescents with major depression. The article does not say, and cannot properly be read to support a contention that, "suicidality" manifested in 5.7% of these patients; rather, it says, "Three subjects were discontinued secondary to worsening of their depression and/or suicidality." (Emphasis added.)[120] The actual rate of suicide attempt (1/53) and ideation (1/53) combined was 3.7% (2/53), not the "5.7%" Healy claims. The article also says, carefully, scientifically, and appropriately, "This open label study of sertraline in adolescent MDD suggests that this selective serotonin reuptake inhibitor is an effective, safe, and

well-tolerated antidepressant for use in adolescents in doses up to 200 mg/day. However, the lack of a placebo comparison group limits the conclusions that can be drawn." (Emphasis added.)[121] The article also explicitly reports that "one patient discontinued treatment because of a drug-related adverse event (akathisia)" and that "[n]o subjects developed manic-like activation or mania."[122] Thus, far from Dr. Healy's demonstrable mischaracterization of the data from the study and what he claims the published article says, the article evinces no "crisis."

The data on suicide-related events from the pediatric depression trials now being reviewed by the FDA and the Advisory Committee show rates that are

- consistent with rates of these behaviors that have been reported in the published literature (which includes published reports on all Pfizer-sponsored sertraline trials in pediatric and adolescent patients), *i.e.*, on the order of 2% to 3%, as opposed to the fabricated "9%" and "5.7%" rates put out by Dr. Healy in his letter;
- consistent with rates of these behaviors that were reported to FDA in Pfizer's 1996 report on its pediatric OCD program (2.7%), and that were then determined by FDA to evince no sign of a causal relationship to therapy; and
- not statistically different from comparative rates among placebo controls.

Dr. Healy makes similarly unscientific, erroneous, and misleading assertions about the recent ACNP Task Force's report, which, in the case of sertraline, is based on the very same pediatric and adolescent depression data that FDA is currently reviewing. He claims in his letter that the ACNP Task Force authors "claimed that they might be mistaken in that they had not seen the raw data." (Healy Letter at 10.) In fact, he has distorted and overstated the ACNP Task Force's careful caveat.

The ACNP Task Force's preliminary report did not say that its authors "might be mistaken in that they had not seen the raw data." Instead, the report cautioned that "its findings

and recommendations are preliminary because it did not have access to all the data held by regulatory agencies and pharmaceutical companies." (Emphasis added.)[123]

Dr. Healy also wrongly contends that certain of the authors of the ACNP report—Emslie, Wagner, and Ryan—"are authors on almost all of the randomized trials on SSRIs" and they therefore have no "basis" to "claim not to have seen the raw data." (Healy Letter at 10.) In other words, he accuses those authors of lying to the medical community about the state of their knowledge. The accusation is false.

If there was even one study as to which these three authors did not see all the data held by the sponsor or FDA, the ACNP Task Force's caveat, as actually written, would be entirely accurate and appropriate. Since there are numerous SSRI studies as to which none of the three was an author, the ACNP statement is accurate and Dr. Healy wrong.

Dr. Healy asserts, at page 11 of his letter to FDA: "Portraying positive only results as science, in other settings, has been called fraud." He thus implies that scientific publications on SSRI trials in pediatric and adolescent patients are fraudulent, and that each of the sponsors, authors, and reviewers responsible for those publications are scientific frauds. It is Dr. Healy, however, who, in his February 19 letter, misrepresents the materials he cites and purports to summarize, concocts numbers that appear nowhere in the underlying data and that cannot be replicated, and presents what, to use his terminology, are "negative only results." His tactics here are the same as those he employed in his discredited assertions in the *Miller* litigation and in the errors in his article about his misnamed "healthy volunteer study," as discussed above.

Dr. Healy's Flawed Estimate of "Excess" U.S. Suicides from 1988-2002

Dr. Healy estimates that Paxil, Prozac, and Zoloft actually caused 21,900 excess suicides in the U.S. in 1988-2002.[124] His figures, however, are based on unsupported and unrealistic assumptions, speculation, and internal inconsistencies.

Dr. Healy arrives at this estimate from the rates of suicide for two groups of SSRI patients: "depressed" patients and "anxious" patients. For depressed patients he uses a suicide rate of "100 per 100,000 exposures to active treatment." He provides no supporting calculation for this number, but simply asserts that "it is clear" from the data in Table 1 of his letter.[125]

His Table 1 shows 8 (5+1+2) suicides among 6,443 patients who received Paxil, Prozac, or Zoloft in clinical trials, which yields a combined rate of approximately 124 [(8/6,443) × 100,000] suicides per 100,000 SSRI "exposures." His Table 1 also reports 2 suicides among 4,879 placebo patients, including 3,140 placebo patients in clinical trials of all SSRIs (not limited to Paxil, Prozac and Zoloft). These numbers yield rates of approximately 41 [(2/4879) × 100,000] and 64 [(2/3,140) × 100,000] suicides per 100,000 placebo "exposures." The differences between these rates suggest, in Dr. Healy's terminology, "excess" suicide rates among SSRI recipients of 85 (124-41) or 60 (124-64) suicides per 100,000 SSRI "exposures." Thus his value of 100 per 100,000 appears to be inconsistent with his own Table 1, which summarizes the data from which he claims it follows.[126]

Participants in trials listed in Dr. Healy's Table 1 typically suffered from depression, but SSRIs are prescribed in practice for various conditions other than depression, and the rate of suicide among these other patient populations receiving SSRIs is lower than that among the depressed. Dr. Healy attempts to account for this mismatch between trials and practice by inventing his calculation for a miscellany of "anxious" patients (as opposed to "relatively severely depressed" patients) to which he assigns a different, lower excess suicide rate of 32 per

100,000. He identifies no data or reference to support this lower rate; rather, it simply materializes where he states that his "grid" calculation "assumes ... a rate as low as 32/100,000 suicides if all patients were anxious."[127]

Dr. Healy's "grid" is an array of alternative assumptions about the percentage of patients receiving SSRIs in practice who under his characterization are "anxious," as opposed to "depressed," with the percentage ranging from 0% to 100%. The rest of the calculation consists, apparently, of partitioning an assumed number, X, of "exposures to active treatment" in the U.S. in 1998-2002 into his "depressed" and "anxious" categories, and multiplying the numbers of exposures in these categories by excess suicide rates of 100 and 32, respectively. This results in estimates ranging from 70,290 excess suicides (based on an assumption that 100% of exposures were among "depressed" patients) to 21,900 excess suicides (based on an assumption that 100% of exposures were among "anxious" patients).[128]

Dr. Healy's Final Estimate Is a Product of His Subjective Judgment. Dr. Healy neither reports nor cites any data on the relative proportions of his categories of "depressed" and "anxious" patients in practice. After recognizing that factors not accounted for in these crude estimates likely affect the rate of suicide among SSRI recipients in practice, however, he simply "suggest[s] using our baseline estimate – that is 21,900,"[129] *i.e.*, the estimate corresponding to the extreme assumption of 0% "depressed" and 100% "anxious" patients.

Thus, Dr. Healy's final estimate of U.S. excess suicides is completely independent of and unaffected by the input value of 100 suicides per 100,000 exposures among the "depressed," a value that he claims to have derived from actual data on suicides in clinical trials. Instead, his final estimate is determined solely by the unexplained input value of 32 suicides per 100,000 exposures among the "anxious." Accordingly, his estimate of U.S. excess suicides is a product

of his own *speculation*, for which his letter offers no factual basis at all. The letter reports no supporting calculation based on data and assumptions that can be subjected to scientific scrutiny. He could have made this estimate smaller or greater merely by speculating differently and landing on a purported excess rate among the "anxious" either smaller or greater than 32 per 100,000.

Dr. Healy Improperly Finds a Marked Elevation of Suicidality Rate Among SSRI Patients. The reason for the radically different findings of Dr. Healy and the manufacturers is that he and the manufacturers use qualitatively different metrics to measure suicidality risk. The manufacturers measure suicidality risk in terms of the comprehensive rate ("R(.)") averaged (in effect) over the full duration of treatment in the clinical trials:

R(Drug X) =

[total suicide events, during any phase of the trial, among patients then on Drug X] /

[cumulative duration of patient-time, during any phase of the trial, on Drug X], and

R(placebo) =

[total suicide events, during any phase of the trial, among patients then on placebo] /

[cumulative duration of patient-time, during any phase of the trial, on placebo].

R(.) as defined here is a well-defined, widely used, and well-accepted measure of risk. In particular, it is widely used in risk analyses prepared by and for the FDA, including the SSRI manufacturers' submissions to FDA on the risk/benefit profiles of SSRIs.

Nevertheless, Dr. Healy deems R(.) "inappropriate" for characterizing the risk of suicide associated with SSRIs. His letter does not explain the basis for his contention, but elsewhere he asserts that there is an elevated suicide risk associated with SSRIs that is "clearly linked to the

first weeks of active therapy. An analysis of suicidal acts on the basis of duration of exposure systematically selects patients who do not have the problem under investigation, because those with the problem often drop out of the trial, whereas others who do well are kept on treatment ...."[130] Thus, Dr. Healy objects to measuring risk in terms of R(.) on the ground that the manner in which R(.) aggregates patient time obscures a transient elevation of risk concentrated during the "first weeks"—a period that he fails to specify and that he could intend to mean any number of weeks greater than one—of treatment. Under Dr. Healy's premise, however, this could occur even if there were no dropouts, because the majority of patient time monitored during a trial lasting 8 weeks occurs outside "the first weeks of active therapy."

The dropout phenomenon magnifies the problem because potentially suicidal SSRI patients are more likely to drop out, Dr. Healy suggests, than are non-suicidal patients. This, he further suggests, creates a selection bias that causes non-suicidal patient time at risk to be overrepresented in R(.) based on clinical trials of SSRIs when compared to the mix of patient time at risk during the first week of therapy before the dropouts occur. In effect, he suggests, the comprehensive incidence rates R(.) conceal a needle in a haystack by pooling the brief, unfavorable experience of those patients who drop out after doing poorly during the initial period of transient high risk of suicide with the more extensive, favorable experience of those who do well and stay on. He provides and cites no data, however, supporting his assumption that the patients who drop out would have experienced a higher suicide rate had they not dropped out, much less any data or calculation showing any such difference to be significant. Indeed, as described below, our data do not support the conjecture of a transient elevation of suicide risk upon starting active therapy.

In any event, an obvious response to Dr. Healy's conjectural premise would be simply to calculate R(.) using data limited to "the first weeks of active therapy" and to compare this result to R(.) calculated using data from later weeks of therapy. Such an analysis of the relation of rates to time on drug should reveal directly any pattern of declining risk of suicide, starting with a transient, high level of risk during "the first weeks of active therapy."

Dr. Healy, however, eschews the obvious response. Instead, he contrives a measure of risk ("Hrisk(.)") that counts patients and outcomes, but simply ignores the variation in duration of treatment among patients. This risk metric is the simple proportion of suicides among subjects commencing the double-blind phases of trials following run-in washout:

HR(Drug X) =

[total suicides, during or after double-blind phase of the trial, among patients then on Drug X] /

[total patients commencing double-blind phase of the trial on Drug X], and

HR(placebo) =

[total suicides, during or after double-blind phase of the trial, among patients then on placebo] /

[total patients commencing double-blind phase of the trial on placebo].

Dr. Healy's risk construct HR(.) is certainly is not an obviously "appropriate" choice for accommodating his stated objections to R(.). First, HR(.) is incapable of detecting whether a transient, high-level of risk during "the first weeks of active therapy" is actually reflected in these data; Dr. Healy simply assumes such a risk . Second, given his concern about the supposed

transiently elevated risk of suicide during the unspecified "first weeks of therapy," there is no principled justification for his failure to limit the numerators of HR(.) to events during whatever he means by the "first weeks of therapy," and for instead including events during *all* weeks of therapy. In this respect his numerators are not properly matched to his denominators in Hrisk(.). This is so because all patients who enter the double-blind phase of a trial contribute at least some person-time to week 1 of the trial. Thus, Dr. Healy's denominators—numbers of patients—are approximately proportional to the "cumulative duration [in weeks] of patient-time, during week 1 of the trial, on Drug X" (or, alternatively, on placebo). This is true to a lesser extent for weeks 2 and 3, and to a still lesser extent subsequently. Thus, Dr. Healy's patient-count denominators are roughly proportional to cumulative patient exposure during the "first [3] weeks" of a trial, but his numerators are not correspondingly limited to events during those weeks.

A third anomalous feature of Dr. Healy's risk construct is its exclusion of placebo-patient suicide attempts during run-in washout. There is no obvious reason in the present context for treating differently a suicide attempt by a placebo patient on, say, the first day of double-blinded "treatment" (*i.e.*, the first day after the end of the run-in period during which the same patient received the same placebo) from a suicide attempt by a similar patient during run-in washout on the day before the start of double-blinded "treatment." Moreover, Dr. Healy's stated objections to R(.) do not justify this distinction in any obvious way, and he offers no adequate explanation.

The consequences of these anomalous features of the risk measure chosen by Dr. Healy are clear: they unjustifiably create the appearance of a large, statistically significant elevation of suicide risk among SSRI patients where the manufacturers, upon analyzing the same data, had found none. (In the case of sertraline, for example, compare rows [15] and [17] of Table 1 below.) He has offered no principled basis for the choices that produce the anomalies. Absent a

compelling explanation from Dr. Healy, his "finding" of an elevated suicide risk is unsupported and unreliable. This would be so even if he were correct in his assertion that the R(.) metric is "inappropriate" for characterizing SSRI suicide risk due to the transience of the elevated suicide risk. As we now show, based on available data for sertraline, he is not.

The Sertraline Data Do Not Support Dr. Healy's Conjecture of a Transient Elevation of the Risk of Suicide upon Starting Active Therapy. Table 1 below shows the timing within clinical trials of the 9 attempted and 2 completed suicides recorded during the clinical trials of sertraline for the treatment of major depressive disorder addressed by Dr. Healy (see columns [b] and [c] at rows [2] through [12] for sertraline events).[131] There is no indication in this table of a transient elevation of risk during the early—*i.e.*, the first three—weeks of therapy. Compared to three suicide attempts during the first three weeks of the trials, there also were three suicide attempts after the end of the placebo-controlled trials (see column [b] at rows [3]-[5] and [11]). Statistical tests confirm that there is no significant tendency for attempts to occur earlier rather than later.[132] Based on the sertraline data, Dr. Healy's transient-risk premise is simply wrong.

Table 1 below also serves to illustrate the anomalous features of his HR(.) metric outlined above. The denominators of HR(.)—numbers of patients—are essentially a proxy for patient-years exposed very early in the trial, during weeks 0, 1, and 2, say, as indicated by the box enclosing rows [2]-[4].[133] The table illustrates, then, the bizarre mismatch of numerator and denominator of HR(.) produced by both *excluding* from the numerator of HR(.) the events on row [2] (suicide attempts by placebo patients just days before the start of double-blind treatment) and *including* in the numerator of HR(.) the events on rows [6]-[11] (including 3 suicide attempts by sertraline patients at more than 8 weeks after the start of double-blind treatment). This

mismatch imparts a dramatic upward bias to Dr. Healy's estimate of excess risk and any projection of excess suicides based on it.

Dr. Healy's Flawed Conclusion. Dr Healy's claim that approximately 21,900 "excess" suicides were induced by SSRIs in the U.S. from 1988-2002 rests not on a scientifically rigorous, testable analysis, but, instead, on a set of unsupported and arbitrary judgments. A critical assumption made by Dr. Healy—the concentration of suicide risk early in the exposure—is inconsistent with the sertraline data analyzed by him. The clinical trials data, properly interpreted, do not support his conclusion of a highly elevated rate of suicide among SSRI patients or, consequently, his projection of large numbers of excess suicides in the U.S. since 1988.

Conclusion

We appreciate the serious responsibility you have in sifting through the data to arrive at a decision that serves the public health. We hope our response to Dr. Healy's letter helps you in distinguishing fact from fiction and scientific analysis from faulty reasoning based on unsupported assumptions, invalid statistical modeling, and misstatements of fact. In the end, we hope your analysis will help to ensure that the patient population is neither unduly frightened by the publicity that has been generated by advocates such as Dr. Healy nor discouraged from taking their prescribed medication.

Sincerely,

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Table 1

Incidence of Suicide Attempts in Sertraline Clinical Trials Addressed by Dr. Healy

	[a]	[b]	[c]	[d]	[e]
	Trial Period	**Treatment**			
[1]		**Sertraline (N=2,053)**		**Placebo (N=786)**	
		Suicides Attempted	**Suicides Completed**	**Suicides Attempted**	**Suicides Completed**
[2]	Washout (Week 0)	N/A	N/A	3	
[3]	Week 1	2			
[4]	Week 2	1	1	1	
[5]	Week 3				
[6]	Week 4	2			
[7]	Week 5				
[8]	Week 6				
[9]	Week 7	1			
[10]	Week 8				
[11]	Beyond Completion	3	1	1	
[12]	**Total**	9	2	5	0
[13]	**Patient-Years Exposed**	507.9		209.0	
[14]	**Incidence of Suicide Attempts** (= [12] / [13])				
[15]		1.77/PEY		2.39/PEY	
		(Rate difference not statistically significant)			
[16]	**Proportions of Trial Subjects Attempting Suicide** (= {[12]-[2]} / [1])				
[17]	Post-Washout	0.44%		0.25%	
		(Rate difference not statistically significant)			

Source: Report to FDA by Pfizer Inc, September 14, 1990.

ENDNOTES

[1] *See* Healy *Miller* Deposition 202:13-203:19, 332:1-337:10.

[2] David Healy, *The Fluoxetine and Suicide Controversy: A Review of the Evidence*, 1 CNS Drugs 223, 224 (1994).

[3] *See Lines of Evidence on the Risks of Suicide with Selective Serotonin Reuptake Inhibitors*, 72 Psychotherapy & Psychosomatics 71 (2003).

[4] David Healy, *The Fluoxetine and Suicide Controversy: A Review of the Evidence*, 1 CNS Drugs 223, 227 (1994).

[5] *Id.*

[6] *Id.*

[7] *Id.*

[8] *Id.*

[9] *See* http://www.healyprozac.com/MCA.

[10] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1095, 1097 (D. Kan. 2002), *aff'd*, 356 F.3d 1326 (10th Cir. 2004), *petition for cert. filed* (U.S. June 4, 2004).

[11] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1066 (D. Kan. 2002), *aff'd*, 356 F.3d 1326 (10th Cir. 2004), *petition for cert. filed* (U.S. June 4, 2004).

[12] *Id.* at 1086.

[13] *Id.* at 1077-85.

[14] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1095, 1098 & n.3 (D. Kan. 2002); Deposition of Chad Brownell, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 46:1-47:11 (D. Kan. Apr. 24, 2000).

[15] 196 F. Supp. 2d 1095 at 1098 n.2; Deposition of Robert Kreifels, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 33:19-34:23 (D. Kan. Jan. 24, 2000) [hereinafter "Kreifels Deposition"]; Deposition of Roxana Rogers, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 3:15-4:17, 8:19-9:13, 26:8-20, 39:3-10 (D. Kan. Jan. 18 & 24, 2000) [hereinafter "Rogers Deposition"].

[16] 196 F. Supp. 2d 1095 at 1099.

[17] Kreifels Deposition 22:24-23:24; Deposition of Dale Bergerhoffer, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 29:23-31:9 (D. Kan. Feb. 29, 2000).

[18] Rogers Deposition 75:1-79:18.

[19] *Id.* at 51:3-22, 148:4-152:14, 87:5-21, 54:22-56:20, 88:17-89:24, 182:2-183:19, 186:9-21, 187:8-15.

[20] *Id.* at 54:22-56:20, 87:5-21.

[21] Deposition of Lisa Sonsthagen, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 44:17-45:1, 90:20-91:6, 75:14-77:2 (D. Kan. Jan. 18, 2000).

[22] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1077-85 (D. Kan. 2002) ("[T]he flaws in Dr. Healy's methodology – particularly his Healthy Volunteer Study, his Meta-Analysis of Pfizer data and his application of Koch's Postulates – are glaring, overwhelming and unexplained[.]").

[23] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1095 (D. Kan. 2002), *aff'd*, 356 F.3d 1326 (10th Cir. 2004), *petition for cert. filed* (U.S. June 4, 2004).

[24] *See Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1066-72 & n.10 (D. Kan. 2002).

[25] *Id., passim.*

[26] *Id.* at 1065.

[27] *Id.*

[28] *Id.* at 1065-66.

[29] *Id.*; *see* Transcript, *Miller v. Pfizer Inc*, No. 99-2326-KHV, *passim* (D. Kan. Nov. 19-20, 2001).

[30] 196 F. Supp. 2d at 1090-92.

[31] Report of Independent Experts, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 2001WL 1793169 (D. Kan. Sept. 4, 2001) [hereinafter "Report of Independent Experts"].

[32] *Id.* at *2.

[33] *Id.* at *2-3.

[34] *Id.* at *2-4.

[35] *Id.* at *4.

[36] *Id.* at *5.

[37] *Id.* at *6.

[38] *Id.* at *7.

[39] *Id.* at *8.

[40] *Id.* at *8.

[41] *Id.* at *8.

[42] *Id.* at *9.

[43] *Id.* at *10.

[44] *Id.* at *11.

[45] *Id.* at *10.

[46] *Id.* at *11.

[47] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1066 n.10, 1085, 1091 (D. Kan. 2002).

[48] *Miller v. Pfizer Inc*, 356 F.3d 1326 (10th Cir. 2004).

[49] International Registry Dossier (Sertraline), Vol. 5.5 (Sept. 1988).

[50] *Id.*

[51] Investigational New Drug (IND) No. 18-004 (Sertraline HCl CP-51,974), Vol. 13 (submitted 1984).

[52] Study Report: Protocol 206, New Drug Application (NDA) No. 19-839 (Sertraline HCl), Vol. 21 (1988) [hereinafter "Study Report: Protocol 206"].

[53] *Id.* at 7.

[54] *Id.* at 24-25.

[55] *Id.* 11-12.

[56] *Id.* at 10.

[57] *Id.* at 12.

[58] *Id.*

[59] *Id.*

[60] *Id.* at 25 (Table 10).

[61] Transcript, Hearing, *Miller v. Pfizer Inc,* No. 99-CV-2326-KHV, 440:17-445:24 (D. Kan. Nov. 20, 2001) (testimony of Prof. Ian Hindmarch).

[62] Report of Independent Experts at *8.

[63] Transcript, Hearing, *Miller v. Pfizer Inc,* No. 99-CV-2326-KHV, 446:11-22; 448:13-24 (D. Kan. Nov. 20, 2001) (testimony of Prof. Ian Hindmarch).

[64] *Id.*448:3-24.

[65] Letter from Sarah Wark, Medicines Control Agency, to Medical Director, Pfizer Ltd, re: Sertraline Volunteer Studies (May 24, 2000).

[66] Pfizer Ltd., Response to Medicines Control Agency Query: Adverse Event Summaries from Setraline Trials Conducted in Normal Healthy Volunteers (June 12, 2000).

[67] *Id.* at 20.

[68] Letter from Dr. Keith Jones, Medicines Control Agency, to Dr. David Healy (July 26, 2000).

[69] Letter from Sarah Wark, Medicines Control Agency, to Rhona Scoffield, Pfizer, re: SSRIs and Suicidal Behaviour (Aug. 14, 2000).

[70] David Healy, *Emergence of Antidepressant Induced Suicidality*, 6 Primary Care Psychiatry 23, 27 (2000).

[71] *Id.* at 24.

[72] Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 316:11-317:17 (D. Kan. Nov. 20, 2001).

[73] *Id.* at 311:5-23; unpublished "Wellbeing Baseline" records produced by David Healy in *Miller v. Pfizer Inc* for subjects M. Harris, A. Griffiths, J. Yorke, and J. Morgan.

[74] David Healy, *Emergence of Antidepressant Induced Suicidality*, 6 Primary Care Psychiatry 23, 24 (2000).

[75] *Id.*

[76] Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 311:24-314:5 (D. Kan. Nov. 20, 2001).

[77] *Id.*

[78] David Healy, *Emergence of Antidepressant Induced Suicidality*, 6 Primary Care Psychiatry 23, 26 (2000).

[79] *Id.* at 25.

[80] Healy *Miller* Deposition 426:2-20.

[81] *Id.* at 435:9-436:10.

[82] *Id.* at 433:20-434:19.

[83] Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 334:3-10 (D. Kan. Nov. 19, 2001).

[84] *Id.* at 317:18-329:12.

[85] *Id.*

[86] Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 388:12-14 (J. Davis, M.D.) (D. Kan. Nov. 20, 2001).

[87] David Healy, *Emergence of Antidepressant Induced Suicidality*, 6 Primary Care Psychiatry 23, 24 (2000).

[88] *Id.*; *see* Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 337:18-338:16 (D. Kan. Nov. 19, 2001).

[89] Unpublished study records produced by David Healy in *Miller v. Pfizer* for subjects I. Logan and K. Oldale.

[90] Letter from Robert F. Myers, Pfizer, to Paul Leber, FDA, with enclosed Report on Suicide Attempts and HAMD Suicide Item (#3) in the Sertraline Depression Program (Sept. 14, 1990) [hereinafter, the "Pfizer 1990 Report"].

[91] David Healy, *Lines of Evidence on the Risks of Suicide with Selective Serotonin Reuptake Inhibitors*, 72 Psychotherapy & Psychosomatics 71 (2003).

[92] A. Khan *et al.*, *Symptom Reduction and Suicide Risk in Patients Treated with Placebo in Antidepressant Clinical Trials,* 57 Archives Gen. Psychiatry 311 (2000); A. Khan *et al.*, *Suicide*

Rates in Clinical Trials of SSRIs, Other Antidepressants, and Placebo: Analysis of FDA Reports, 160 Am. J. Psychiatry 790 (2003).

[93] T. Hammad *et al.*, *Incidence of Suicide in Randomized Controlled Trials of Patients with Major Depressive Disorder*, 12 Pharmacoepidemiology & Drug Safety S156 (2003).

[94] *See* Thomas P. Laughren, *et al.*, *Premarketing Safety Evaluation of Psychotropic Drugs*, Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines 185 (R.F. Prien & D.S. Robinson eds. 1994).

[95] Pfizer 1990 Report at 3-10; *see also* FDA, Summary Basis of Approval, NDA 19-839 (Sertraline HCl), § 5.2.2.4.1 (Dec. 30, 1991).

[96] Pfizer 1990 Report at 5 (Table 1).

[97] *Id.* at 3-5.

[98] *Id.* at 10-26 (Appendix 1).

[99] *Id.*

[100] *Id.* at 5 (Table 1).

[101] *Id.* at 10-26.

[102] *See* Thomas P. Laughren, *et al.*, *Premarketing Safety Evaluation of Psychotropic Drugs*, Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines 185, 197-98 (R.F. Prien & D.S. Robinson eds. 1994).

[103] FDA, Summary Basis of Approval, NDA 19-839 (Sertraline HCl), pp. 38-39, § 5.2.2.4.1 (Dec. 30, 1991).

[104] Pfizer Inc, Report on Suicide Attempts and Suicidal Ideation in the Sertraline Depression Development Program (May 21, 1992) [hereinafter, the "Pfizer 1992 Report"]; E.W. Henry *et al.*, *Evaluation of Suicidality in the Sertraline, Placebo, and Active Control Groups in the Sertraline Depression Program*, Collegium Internationale Neuro-Psychopharmacologicum (CINP) (June 28, 1992).

[105] Pfizer 1992 Report at 9.

[106] *Id.* at 12.

[107] *Id.* at 12, 36 (Table 1A).

[108] Transcript, Hearing, *Miller v. Pfizer Inc*, No. 99-2326-KHV, 198:1-19 (D. Kan. Nov. 19-20, 2001).

[109] Report of Independent Experts at *8-9.

[110] Appendix 1, WHO Adverse Event Dictionary at 18, submitted to the FDA as part of NDA 19-839, Vol. 71 (Apr. 13, 1988).

[111] *Id.* at 60.

[112] Letter from Alan Dunbar, Pfizer, to Russell Katz, FDA (Sept. 12, 2003); Letter from Alan Dunbar, Pfizer, to Russell Katz, FDA (Jan. 16, 2004).

[113] J. Alderman, *et al.*, *Sertraline Treatment of Children and Adolescents with Obsessive-Compulsive Disorder or Depression: Pharmacokinetics, Tolerability, and Efficacy*, 37 J. Am. Acad. Child & Adolescent Psychiatry 386 (1998).

[114] *Id.* at 390.

[115] *Id.* at 390-91.

[116] Letter from Martha Brumfield, Pfizer, to Paul Leber, FDA (May 28, 1996) (enclosing Report on Suicide Related Behavior in Children and Adolescents in the Sertraline OCD Clinical Development Program).

[117] *Id.*

[118] T. Laughren, U.S. FDA, Memorandum to File (Oct. 25, 1996).

[119] *Miller v. Pfizer Inc*, 196 F. Supp. 2d 1062, 1069 (D. Kan. 2002).

[120] P.J. Ambrosini *et al.*, *Multicenter Open-Label Sertraline Study in Adolescent Outpatients with Major Depression*, 38 J. Am. Acad. Child & Adolescent Psychiatry 566, 568 (1999).

[121] *Id.* at 570.

[122] *Id.*

[123] American College of Neuropsychopharmacology, Executive Summary: Preliminary Report of the Task Force on SSRIs and Suicidal Behavior in Youth (Jan. 21, 2004).

[124] The Healy letter states:

> For the 0% depressed cohort the figures come to 21,900 or 28 per week or 1,460 per year.

These gross estimates represent figures averaged over the 15-year period from Prozac's launch in 1988.

The increasing proportion of anxious patients, and US fashions for co-prescribing other drugs, in particular the benzodiazepines, may have minimized some of the risk. However it can be noted that the model discounts all those suicides caused by drug that have been balanced out by patients made less suicidal by treatment. Given these factors, we suggest using our baseline estimate – that is 21,900.

[125] The Healy letter states:

> Re-analyzing the Khan data as outlined above it is clear that there have been approximately 180 suicides per 100,000 exposures to antidepressants compared with a figure of 68 per 100,000 exposures to placebo - an excess of 100 per 100,000 exposures to active treatment.

[126] *See* n.125, *supra*.

[127] The Healy letter states:

> In order to estimate the number of suicides that have actually happened in the US however it must be recognized that the patients initially given SSRIs in the US/UK may have been depressed and at greater risk of suicide than those patients subsequently given SSRIs in both the US and the UK, of whom an increasing proportion will have been either less severely depressed or anxious patients or indeed patients given these drugs for weight loss, migraine or other purposes where the risk of suicide was effectively either that of the normal population or even lower. To account for this problem we have constructed a grid, which assumes a rate of 100 suicides per 100,000 patients if all patients entered into this study were relatively severely depressed, or a rate as low as 32/100,000 suicides if all patients were anxious.

[128] The Healy letter states:

> To account for this problem we have constructed a grid, which assumes a rate of 100 suicides per 100,000 patients if all patients entered into this study were relatively severely depressed, or a rate as low as 32/100,000 suicides if all patients were anxious. The matrix then includes estimates for the number of suicides if 80%, 60%, 40%, 20%, or 0% per cent of the patients are depressed, and the remainder are anxious.
>
> The resulting estimates for the number of excess American suicides on Paxil/Seroxat, Prozac and Zoloft can be found in Figure 6. For the 100% depression figure, this gives 70,290 suicides, or 90 per week, or 4,686 per year. ... For the 0% depressed cohort the figures come to 21,900 or 28 per week or 1,460 per year.

Dr. Healy does not report explicitly his assumed value for X but this value may be inferred from $100 \times (X/100{,}000) = 70{,}290$ or, alternatively, from $32 \times (X/100{,}000) = 21{,}900$. Allowing for

rounding of Dr. Healy's reported numbers of suicides, these two expressions for X imply ranges of values of 70.285-70.295 and 68.281-68.591 million, respectively. These two ranges are inconsistent in that they have no candidate value of X in common; Dr. Healy's description of his calculation does not explain the discrepancy. Both are inconsistent with Dr. Healy's claim in his letter to FDA that

> [i]n total, there have been over 75 million treatment starts on Prozac, Paxil/Seroxat and Zoloft since these drugs launched in the US. Taking into account the fact that some patients will have had two or three of these three drugs, or one of these drugs on more than one occasion, a reasonable estimate of the numbers of patients exposed to one of these three major SSRIs may be as high as 50 million Americans.

[129] The Healy letter states:

> For the 0% depressed cohort the figures come to 21,900 or 28 per week or 1,460 per year. These gross estimates represent figures averaged over the 15-year period from Prozac's launch in 1988.
>
> The increasing proportion of anxious patients, and US fashions for co-prescribing other drugs, in particular the benzodiazepines, may have minimized some of the risk. However it can be noted that the model discounts all those suicides caused by drug that have been balanced out by patients made less suicidal by treatment. Given these factors, we suggest using our baseline estimate - that is 21,900.

[130] D. Healy & C. Whitaker, *Antidepressants and Suicide: Risk-Benefit Conundrums*, 28 J. Psychiatry & Neuroscience 331, 332 (2003).

[131] Table 1 shows underlying detail of sertraline data also summarized in Table 1 of Dr. Healy's letter to the FDA, Table 1 of Healy and Whitaker (2003), and Table 1 of Khan, Warner and Brown (2000).

[132] This conclusion is based on exact binomial tests applied to the distribution of suicide attempts over partitions of trial time into "early" and "late" sub-periods.

[133] More precisely, patient numbers are very highly correlated with exposure in terms of patient time during weeks 0 and 1, somewhat less so during week 2 (due to dropouts), even less so during week 3, and so on.