

August 26th 2004

Dr Robert Temple
Director of the Office of Drug Evaluation 1 (HFD 101)
Rockwall 2
5515 Security Lane
Rockville MD 20852

Cc Dr Anuja Patel

Dear Drs Temple & Patel

Owing to other commitments, I had not intended to attend the forthcoming PDAC hearings on the use of antidepressants in children. However, my attention has just been drawn (today August 26th) to a posting by Pfizer on the FDA site, concerning my work in this area, and concerning a previous communication from me to you.

This letter from Pfizer demands some response. Given that I only have 24 hours in which to make a submission to the PDAC hearings, this response will necessarily be focused rather than comprehensive. But I would also hope to re-organize my schedule to permit attendance at the PDAC meeting, where I will be available to answer any further questions you, or other interested parties, may have in connection with these matters.

Both you and anyone else reading this response should also know that in completing this I remain heavily constrained by confidentiality orders, and that Pfizer in particular have attempted to enforce such orders vigorously by means of Court action.

I trust this response as it stands will also be posted on your site. I would be happy to supplement it on request with further material if indicated, after tomorrow's closing date for submissions.

General Points from Pfizer's Letter:

Pfizer's letter starts with a commitment to open debate. The letter then seeks to attack my credibility as a scientist, and does so in a particularly ad hominem way. This attack comes despite the fact that I have been previously invited by Pfizer to chair symposia for them, to author articles for journal supplements for them, to give international guest lectures for them, and to adjudicate on studies submitted for Pfizer research awards for them. Pfizer clearly at one point thought me a credible scientist in the area of psychopharmacology.

More recently, however, when scientists from Pfizer have sought to have me come and speak at forums, they have been told by their superiors that this is not appropriate.

It has in fact been very difficult to get issues of suicidality and psychotropic drugs debated in academic forums. In one of the few such forums, at an Irish College of Psychiatrists meeting last year, my understanding is that many clinicians and academics in the audience were briefed by figures linked to Pfizer and Glaxo SmithKline on questions to ask Healy, many of which are reproduced in this letter from Pfizer.

At other scientific meetings to which I have been invited to contribute on these issues distinguished academics with links to some of the major companies producing SSRIs, who have never heard me present the data, it would appear have sought to have me removed from the scientific program or otherwise managed, and yet when later given the chance to challenge the points I make have failed to ask any questions in public. The main surprise with this current Pfizer letter is that the kinds of things being said in corridors are being aired more publicly.

This effort to close down debate I believe has little to do with the scientific qualities of my work in this area, which has been extensively peer-reviewed and published in 5 different journals. I have taken the unusual step of presenting many of these reviews, especially the negative ones, on the Internet. I believe the issue has much more to do with my temerity in being prepared to testify as an expert for

plaintiffs. Since my involvement as an expert witness, documents from at least one PR company working to one of the relevant SSRI companies have listed me as a problem to be managed.

Pfizer's letter appears to follow a management strategy they have regularly adopted over the past 4 years, since my involvement in the Miller case. None of these points are new.

Before proceeding, it is worth putting the issue of expert witnessing in context. In over 90% of cases specifically to do with SSRIs on which I have been approached, I have given the view that the injuries in question have not been caused by the SSRI supposed by plaintiffs or their legal representatives. I have charged nothing for the great majority of these reports, or nothing for any reports I have offered to coroners Courts for the purposes of inquests.

Moreover as regards actions by plaintiffs in general, far from being plaintiff friendly, I have been used as an expert by the National Health Service in the United Kingdom, and in that capacity have offered reports favoring the defense rather than plaintiffs in again over 90% of cases.

It should also be noted that I have no interests in any competing treatments. I use antidepressants, including SSRIs, to treat both adults and children, and as a former secretary of the British Association for Psychopharmacology convened a consensus conference and authored the ensuing guidelines on the issue of treating children with psychotropic drugs. These guidelines endorsed the cautious use of such drugs, a position I maintain to this day.

Specific Points from Pfizer's letter:

1/ Pfizer claim their depression program has shown no evidence of suicidality. Pfizer's depression program has in fact demonstrated a roughly 50% failure to demonstrate efficacy in clinical trials, a great number of which remain unpublished. So poor were the results from the early trials that they raised concerns that this drug might not get through the regulatory authorities, as the attached memoranda from Dr P Leber to yourself (Dr R Temple) indicate (See appendix 1).

Zoloft, however, on the back of published studies only, rather than the totality of the studies undertaken, has been sold by Pfizer as an SSRI with unparalleled evidence of efficacy. This comes close to the kind of position that recently led the attorney general from New York State, Mr Spitzer, to take action against other pharmaceutical companies for misrepresenting the data on their products.

As regards the evidence for suicidality from these same studies, Pfizer's own program shows over 20 cases of investigators concluding that Zoloft has caused suicidality/suicidal acts, and in more than 20 further cases, Pfizer monitors overrode the judgments of the clinical investigators and attributed causality to Zoloft in cases of suicidality/suicidal acts. Given this, it will be a mystery to many how Pfizer can claim there is no evidence that their drug causes suicide. The trick lies in a specialized (and probably incorrect) use of statistical arguments to hide the problem – this issue is outlined below in the final section of this response and in an attached appendix of material submitted to the UK's Health Select Committee's hearings on the pharmaceutical industry, at which I have been invited to present further on these issues.

Handling the available data from the studies undertaken and submitted to FDA statistically demonstrates that the point estimates for the odds ratio of suicidal acts on Zoloft compared to placebo, demonstrates repeatedly that this figure is always greater than 1.0. Pfizer have sought to manage this problem by a variety of methods, which are detailed further below.

The question of what a point estimate greater than 1.0 means in the context of SSRIs and suicide raises issues of interpretation that epidemiologists and others interested in safety issues have to deal with. Many reputable figures in these areas, including some working in FDA would argue that the correct interpretation of a point estimate greater than 1.0 is that our best information points to a real hazard posed by treatment, and that given that this hazard is a potentially lethal one, it deserves appropriate warnings and monitoring.

2/ As regards studies in 800 healthy volunteers, 75% of Pfizer's data remains unpublished. Were all the data published in its entirety, the primary reason for the issue of suicidality being less visible in these studies than it might otherwise be probably lies in the fact that the lead investigators in these studies for the most part were either non-clinicians or clinicians with a primary training in for instance

otorhinolaryngology. These clinicians had no directions to look out for suicidality and no expertise in pursuing indications of suicidality further had they noticed them.

Despite this there are clear indications of probable suicidality from studies on Zoloft in healthy volunteers who for instance have become agitated and apprehensive on Zoloft. The Saletu article cited by Pfizer makes this clear.

The Hindmarch study cited by Pfizer also makes this clear. This matter could be settled easily by Pfizer making the full data from this study available, along with the reports from Pfizer clinicians responsible for the study.

Making these reports available would also undercut claims made by Pfizer in point 4 of their letter, where they claimed that Ian Hindmarch settled issues to do with this study in Court. In Court, Ian Hindmarch did not settle any issues to do with this study. He primarily claimed that what had happened was that one of his volunteers had effectively induced a collective hysteria in other volunteers and this explained the profile of adverse effects that the British MHRA has described as serious and concerning. This was not explored further by the Court in Miller. The reports of Pfizer monitors would shed light on just this issue and I would invite Pfizer to make this report public, or at least available to members of the PDAC.

3/ Pfizer then argue that my approach to the scientific issues was rejected by the Court in Miller versus Pfizer. The first point to make clear is that the Court in Miller v Pfizer characterized Pfizer's position as extreme, incredible and self-serving.

The second point is that my approach to issues in this area has been reviewed by American Courts in 5 other Daubert or Frye hearings, that have taken place both before and after Miller, and in all of those cases the Court found my opinions legitimate.

The Daubert hearing in Miller v Pfizer was a unique event triggered by a proposal from Andy Vickery, counsel for the plaintiffs to have an independent expert to assist the Court in determining the validity of my expert testimony. This proposal was unusual and stemmed from the real and ongoing difficulties Courts and others have in sifting the relevant evidence that can be brought to bear on cases.

Several experts were approached who declined. Finally, John Davis was put forward by the plaintiffs. Dr Davis had sat on the Zoloft Psychopharmacologic Drugs Advisory Committee meeting in 1991 that somewhat controversially approved Zoloft. This on the face of it was not someone who might have been expected to be sympathetic to the plaintiff's claim. Pfizer then altered the initial proposal and put forward Dr John Concato from Yale as a further expert. The plaintiffs had no background on Dr Concato.

The resulting hearing and its outcome are currently the subject of an appeal to the US Supreme Court, so in what follows my remarks should not be taken to in any way reflect on the relevant legal issues or as an effort to pre-empt or pre-judge any hearings that may result. These remarks are the remarks of a clinician not a lawyer, observing aspects of the process and they do not as far as I am aware touch on the legal basis for this appeal.

In brief, the instructions to the experts were to look at aspects of my methodological approach towards the issues rather than the content of my opinions, as in classic Daubert and Frye assessments of medical evidence. The attempt to distinguish comments on content from comments on methodological approach typically causes considerable confusion on both medical and legal sides of Frye and Daubert hearings.

In this case, the transcript from the open hearings suggests that the procedure generated an unprecedented amount of confusion, perhaps because of its unusual and unprecedented procedural format. This confusion came to a focus in a series of exchanges regarding the replicability of some of my figures that are cited verbatim below.

The independent experts indicated that they had not been able to reproduce some of these figures. In the course of attempting to establish why this might have been a series of exchanges took place in which Dr Davis put forward the view that the precise methodological approach taken to generating the

figures had not been made available in my initial expert causation report and therefore unlike for instance attempting to replicate the results of a scientific study, the experts were unable to replicate what had happened.

Judge Vrtil was clearly unhappy that anything presented to the Court might apparently fall short of the standards of a scientific paper and this appears to have heavily colored the Court's interpretation of the proceedings and their findings. See transcript.

Reading this transcript makes it clear that there was considerable scope for multiple confusions. There was scope for the independent experts for example to believe that requests of them to assess my methodological approach could not happen for example in the absence of a sheet of detailed calculations which would have laid out how a particular figure (the relative risk of 2.19 for suicidal acts on Zoloft over placebo) had been generated.

On issues like this, it would presumably have been possible for the experts to approach me through the Court in the 18 months during which they pondered the issues, indicating difficulties in seeing how particular figures had been generated and requesting a breakdown on the steps taken to arrive at a particular figure. No such approaches to me were made. No allowance was made by the Court for me to explain in Court just where these figures came from.

Such steps could have been included in the original report but had not been included for the simple reason that detail of this sort is not ordinarily and perhaps has rarely, if ever, been presented as part of a plaintiff's expert report. It is, however, the kind of detail I have presented ever since.

This point goes to the confusion at the heart of this issue, which hinges on the word methodology. In the ordinary course of events in Frye and Daubert hearings, the word methodology refers to the general approach taken by experts. For example, do experts take into account randomized controlled trial evidence and epidemiological evidence or are they basing their views on some unproven theory or on statements based on the authority of others rather than on scientific procedures.

In common scientific parlance, however, methodology can also refer to mundane aspects of an approach taken such as precise calculations. One could therefore have an appropriate scientific methodology and yet have no calculations present in a paper, or have an expert report full of calculations but yet not have an appropriate methodological approach to the issues at stake.

To put it in other terms, the term methodology in general refers in chemistry experiments for instance to whether the experimenters are adopting a set of procedures such as distillation, condensation, fractionation etc, but it can also include a specification of the precise amount of chemical a and chemical b that will need to be added to the mix. Daubert and Frye hearings refer in general to determining whether valid chemical procedures such as condensation, distillation etc are being used rather than to a specification of the precise chemical ingredients. This is for the rather obvious reason that an expert could precisely specify the chemical ingredients but could then simply toss those chemicals to the wind and such an approach would be no more scientific than attempting to divine the future from the entrails of a goat.

The Miller Daubert hearing effectively ended by focusing on the question of whether the precise chemical ingredients had been outlined in the expert report.

A further point worth noting here was that the notion of an independent expert was proposed a long time after the expert report on causation had been first generated. The precise form that the expert report on causation took did not take into account the possibility of a review by independent experts in the context of a Daubert procedure and in particular did not take into account the need to construct an expert report that would be fireproof against the many confusions that Daubert procedures can generate.

The situation arguably would have been a lot more fair if having agreed to the Daubert approach the Court had indicated to me and the experts that a report on expert causation would be assessed in this way, that the focus of the independent expert scrutiny would be under specific headings – viz a, b and c and that a report should be submitted to the Court on a specified date that would achieve maximum clarity on these points, thus facilitating the work of the independent experts.

Such an approach would have meant at the very least that in the actual hearing that took place both Counsel for the plaintiffs and Counsel for the defense as well as the judge and the experts both for the plaintiffs and the defense and the independent experts would have been in a position to examine and cross-examine in a meaningful way. This clearly did not happen, as I believe any scrutiny of the transcript will reveal.

Finally, at the same time as this hearing took place I had a series of articles under peer review. Two of these were accepted, one wasn't. The reviews of all three are available and one of the published articles comes with a detailed published commentary by a distinguished scientist taking the opposite point of view. None of them, even the most hostile, claim that I used invalid methodological procedures in the sense that such methodologies are usually scrutinized in Frye and Daubert hearings. These hostile reviews have been made publicly available on the internet at healyprozac.com.

Transcript from Miller v Pfizer November 20th Afternoon:

13 DR. DAVIS: And it may be an evolving field and
14 that, so there is a matter of judgment. I'm reminded of a
15 short story, one of the Sherlock Holmes stories where I think
16 the title was "On the Matter of the Dog That Did Not Bark."
17 And the night of the murder, the dog didn't bark. It was a
18 very irritable dog that had barked at strangers very
19 vigorously. The clue was that the murderer was a friend or
20 the master.
21 And what I anticipated when I came today that Dr.
22 Healy might present his calculations or there might be a lot
23 of discussions of the techniques of the calculations. And
24 the normal scientific process, you present your method in
25 some detail, you present your data, you do your statistics,

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1 and you describe exactly how you do it. And then in the
2 discussion you might speculate. And as I-- and we commented
3 in our report that we couldn't replicate the relative risk of
4 two point whatever it was. And I would have anticipated that
5 Dr. Healy would have calculated it or there would have been
6 more said about it.

7 And the numbers here on this last page of -- is the
8 unadjusted incidence is .28 for Zoloft, and .31 for placebo
9 so that Zoloft would have a trivial protective factor. The
10 unadjusted incidence for people going in blinded trials for
11 Zoloft is .26 and for placebo is .29. So it's about the
12 same.

13 But there's been -- Dr. Healy in his testimony has
14 given a lot of relative risk, and I've never been sure how
15 they were calculated. One of them was 2,000 to 1. One of
16 them is you assume that the average patients getting SSRIs
17 are less sick than the profoundly depressed patients, so
18 forth and so on, the relative risk is 10. In other cases he
19 said the relative risk was 4. In all these cases, I am--
20 there's no methodology, there's no way of calculating it.
21 And there's just -- and I don't know where these numbers come
22 from, what their methodology is. And it's also sprung on me
23 at the last moment. And I have a feeling that numbers have
24 come up in the court before and there's no methodology. And
25 I don't feel that that conforms with scientific methodology.

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1 Now, it's quite possible that this was sprung on
2 Dr. Healy at the last moment because I think I heard him say
3 that it's something he only recently got into, and it may not

4 be fair to ask him before.

5 THE COURT: Maybe I can shed some light on this,
6 especially in regard to your comment that you may be expected
7 to hear some more full explanation of where the 2.19 figure
8 was derived. This is part of where the intersection of law
9 and science is maybe not clear to somebody coming in from the
10 outside.

11 But under our federal rules which govern pretrial
12 proceedings, each side obviously has a chance to call their
13 own experts who will testify, and there's a time set as part
14 of the discovery process where each expert is required to
15 produce a written report that states all of the opinions that
16 that expert will offer at the trial, and also the basis for
17 the opinions. That has to be done by a certain time prior to
18 trial. Both sides then have a chance to take the depositions
19 of the experts or, as Dr. Healy says, I love this, the
20 depositions. And both sides have a chance to file objections
21 to that testimony so that we then determine whether it's
22 sufficient under Daubert, sufficiently scientifically
23 reliable that that information should be allowed to be
24 presented before a jury.

25 And what I've told the parties is that to the

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1 extent that Dr. Healy had information and could have made
2 calculations by that deadline, he was required to do that if
3 that was part of what he relied upon in developing his
4 theories and opinions in the case, and he can't go back now
5 and reread that information. So that if he had this figure
6 of 2.19 and he didn't do the figures and explain it to the
7 other side earlier on in the case, it's not fair for him to
8 sit back and come back at this time and spring it on them at
9 this particular hearing.

10 So that's why, that's what my ruling was earlier,
11 and that's why you haven't heard the Power Point presentation
12 that was alluded to earlier. Now, I'm with you in that some
13 of these figures that I've heard today I've never heard
14 before and I don't know where they're coming from. So --

15 DR. DAVIS: And I feel that -- of course, I'm
16 biased. I'm a statistically oriented psychiatrist, but I
17 feel that it's important to say your method, to say how you
18 got your numbers, and the statistical parts are really not as
19 complicated if you lay it on the line beforehand because it's
20 really four numbers. It's the number who suicided on drug,
21 and the number who got the drug, and the number who suicided
22 on placebo, and the number who didn't, and put it in a
23 percentage. After that, you can go to statistical
24 significance and beyond. And I want to comment on that. And
25 there is a common sense test looking at the raw numbers and
1 knowing where they came from. Then you have something to
2 work from.

Where Pfizer refer to the independent experts' differing assessments of the medical evidence, a scrutiny of the report of Drs Concato and Davis will reveal that in their minds articles like the Beasley et al 1991 paper in the British Medical Journal remained the gold standard in the field. I think with the benefit of some further years and a great deal more information on the Beasley meta-analysis and related meta-analyses such as that by Dr Stuart Montgomery – see below - that such a position would be impossible to sustain and is probably not sustained for instance even by Dr Davis who, since the Miller hearings, has indicated to me a willingness to be approached as a possible expert witness on behalf of the plaintiffs.

4/ This point is dealt with under point 2.

5/ I am happy to stand by my interpretation of the Saletu et al article. Anyone wishing to pursue this further should note that two different versions of this article were published.

6/ As regards my healthy volunteer study, I have got used to Pfizer since April 2000 mischaracterizing aspects of this study. The claims made have in many instances been quite extraordinary. They have suggested that one of the volunteers had an alcohol problem (untrue). That all or most of the volunteers were my employees (untrue – only 1 of 20 could be regarded as an employee). They have implied that suicidality appeared in one volunteer with a prior history of depression that had been missed. One volunteer had a prior history of depression that had been missed but this was not a volunteer who became suicidal – this volunteer in fact responded well to Zoloft. Pfizer have no evidence that any of these volunteers were unblinded. This study in fact was less likely to suffer from unblinding than Pfizer's own healthy volunteer studies in which the contrast between placebo and Zoloft was likely to be much more clear-cut.

Perhaps the most telling point here though is that Pfizer have been invited to depose the two volunteers who became suicidal on Zoloft, but have declined to do so.

7 & 8/ As regards Pfizer's assertion that the FDA chose not to criticize their report on suicidal behavior and thinking in the 1990 submission made to the agency, this may or may not be true. I am not in possession of all the documents. The statistical review of the data carried out by the FDA does note an inclusion of placebo run-in suicidal acts under the placebo heading, which FDA regulations and pretty well all books on clinical trial methodology would regard as inappropriate.

Why FDA might chose not to further criticize this report is perhaps a key point at the heart of these hearings. At the same time, Martin Brecher who was handling the Paxil submission for the FDA had contacted SmithKline and asked them to resubmit their data. As reported by SmithKline personnel, he indicated that the agencies view of the issue of suicidality on SSRIs was that this was a public relations issue, and that it would help if SmithKline resubmitted their data (See appendix 2).

SmithKline did so. In the process an 8-fold excess of suicidal acts on Paxil over placebo was transformed into a parity of suicidal acts between Paxil and placebo. SmithKline achieved this by resorting to some of the inappropriate methods used by Pfizer, namely recoding under the heading of placebo suicidal acts that had occurred during the run-in phase of the trial, without in any other way adjusting the denominators for placebo etc.

Three years later Dr Stuart Montgomery supposedly meta-analyzed SmithKline's database in an article that cites exactly the same revised SmithKline figures (Montgomery SA, Dunner DL, Dunbar G. Reduction of suicidal thoughts with paroxetine in comparison to reference antidepressants and placebo. *European Neuropsychopharmacology*. 1995; 5: 5-13).

This article appears in a journal of which Dr Montgomery was the editor. It's second author Dr Dunner has since said he did not see the raw data. The third author, Dr Dunbar was an employee of SmithKline. The resulting article has been at the heart Glaxo SmithKline's defense in legal actions involving Paxil.

In this case Dr Montgomery claimed that Paxil was 5 times less likely to be linked to suicide than placebo. This dramatic manipulation was achieved by introducing another inappropriate step that Pfizer have also availed themselves of, and continue to avail themselves of, namely adjusting the figures to take into account exposure to the drug. This maneuver introduces a "space shuttle" fallacy into the debate; according to this fallacy, space shuttle travel is proven to be safer than walking around a resort town on the Virginia Coast by virtue of there being fewer deaths per million miles traveled. But as anyone at the PDAC hearings could explain to Pfizer, Glaxo SmithKline or Lilly, the hazard in shuttle travel lies in entries to and exits from orbit/treatment, and factoring in the millions of miles safely traveled is inappropriate.

Dr Montgomery was also the leading psychiatry expert to the UK's Committee on the Safety of Medicines, which was responsible for licensing Paxil and Zoloft in the UK. Dr Montgomery was in fact consulted extensively by Pfizer in connection with their submission regarding Zoloft, but did not declare this interest at CSM meetings.

Dr Montgomery was also a panelist at the 1991 PDAC hearings on Prozac, where he spoke against the position that Prozac could cause suicidality, although as a consultant to Lilly at this time he would appear to have authored a report indicating that it was no surprise that the issue of suicidality on Prozac had surfaced.

This was doubly interesting to me, when I made efforts to get a hearing at the February 2004 hearings only to learn that the committee does not have experts from outside the United States.

9/ The time constraints outlined above preclude a full consideration of the Alderman paper. But I will be happy to deal with this on the day, if the media or others raise the issues.

I think the key issue here is the fact that ghostwriting has eviscerated the scientific literature in this area. It's difficult to know whether any articles on therapeutics are any more dependable than Olympic gold medals these days. This is a state of affairs for which Pfizer would appear to have some responsibility. This is a matter on which I have peer-reviewed published work specifically relating to Zoloft (Healy D, Cattell D (2003). The Interface between authorship, industry and science in the domain of therapeutics. *British Journal of Psychiatry* 182, 22-27).

10/ As to why the FDA failed to think that a seven-fold increase in suicidal acts on Zoloft in their pediatric OCD studies was not a matter warranting warnings, I would imagine members of the media would be more interested to chase the relevant FDA officials rather than me on this issue.

11/ As regards the model of deaths on SSRIs, it appears that no matter how conservatively the figures are handled that there are good indications that the number of deaths and injuries on SSRIs have been greater than for instance on thalidomide, fen-phen, or in any other drug disaster. The model I have been using will be subject to peer-review later this year. It has been reviewed by MHRA in the UK, who have not to date pointed to any failure of logic in the model as it applies to antidepressants.

12/ Later in their more detailed argument, Pfizer claim that there are inconsistencies in the statements I have made before and after my involvement as an expert witness. I dispute that there are any inconsistencies. The points raised by Pfizer are ones that are handled in my book *Let Them Eat Prozac*. Pfizer cite the Canadian edition of this – there is now also a New York University Press edition.

Overarching Issues

The current crisis with SSRI agents has profound philosophical and methodological underpinnings that deserve better than ad hominem attacks. (This current section is excerpted from a submission to the British Health Select Committee hearings on the pharmaceutical industry attached as appendix 3).

Current procedures to manage the entry of drugs onto the market favor the detection of drug effects and set a higher threshold for safety effects. For instance, in order for a drug to be licensed it has to show superiority to placebo in two controlled trials. Companies however can run ten or more trials in carefully selected samples using instruments carefully designed to pick up any effect in order to demonstrate this, and even if the results show the drug failing to beat placebo in the clear majority of trials, this is not held against them. These other trials are commonly termed failed trials rather than drug failures.

This was a live issue in the licensing of Zoloft – see memoranda in appendix 1 and quotes from P Leber in *Let Them Eat Prozac*.

In contrast, the demonstration of a safety issue is not handled in this way. In the case of safety, regulators only act if the overwhelming preponderance of the data show a hazard.

These differences in approach have at their heart unresolved philosophical issues about the nature of statistics. Safety data is typically presented in terms of Confidence Intervals, so that for instance in recent antidepressant studies the rate of suicides on drugs compared to placebo is typically of the order of 2 times greater but what is termed the confidence interval surrounding this figure of 2.0 might be for example 0.9 to 4.4.

There are two ways to interpret such a finding. First according to a school of thought stemming from R.A. Fisher is the view that nothing has in fact been shown unless the confidence interval does not include 1.0, thus for instance a confidence interval of 1.1 to 4.4. Pfizer are relying heavily on just this point to claim that it has not been proven that Zoloft causes suicidal acts.

Second, the Neymann-Pearson school of thought argues that the best estimate of the effect is 2.0, in this case. That 2.0 is the figure regarding which we can be most confident.

In practice regulators adopt Fisher's approach. This cannot be viewed as a rigorous approach to safety.

On the other hand, epidemiologists (including in all probability most epidemiologists within the FDA), or a drug regulatory process concerned with safety, would argue that in this example the figure of 4.4 is the one that we should be concerned with. In other words the data on the hazard in question points to the fact that this hazard may in fact happen up to 4.4 times more often on the drug than on placebo or non-treatment. If the hazard is serious, it follows that there is a considerable onus on regulators to warn patients and doctors about this possibility, but FDA has not been inclined to do so.

If a sauce for the goose is sauce for the gander approach were taken to the issue of whether the drugs in fact do work, and a company's trials were all analyzed together, in the case of Pfizer's Zoloft there is every chance that it would result in a figure of less than 1.0. In other words the evidence that Zoloft works is in many respects less strong than the evidence it causes suicidal behaviors. When it comes to efficacy however, the regulators are prepared to accept a signal that Zoloft might work in order to let it on the market, but not prepared to accept a signal that Zoloft might pose hazards as a basis for warnings.

What the public need to know at this point is there is no way to deciding that one or other of these approaches is correct – if the field of statistics leans one way in general it leans more toward the second than the first option.

The science in other words shows nothing without a choice by regulators or companies to adopt one or other approach. And at present companies and regulators adopt an approach that facilitates drug entry to the marketplace and minimizes the likelihood that the company will have to warn about hazards.

This is a matter regarding which the public has a right to be as fully informed as possible. If I can help in this process, I will try to do so.

Yours sincerely

David Healy MDFRCPsych

Appendix 1:
Memo August 26th 1991 P Leber to R Temple
Memo Dec 24th 1991 P Leber to R Temple.

Appendix 2:
FDA Conversation Record, October 3rd 1990, Conversation with M Brecher.

Appendix 3:

APPENDIX 1

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: August 26, 1991
FROM: PAUL LEBER, M.D.
DIRECTOR,
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
SUBJECT: Zoloft NDA Approvable Action Recommendation
TO: File NDA 19-839
Director, ODE 1

Dr. Laughren's Supervisory Overview of 8/9/91 provides a comprehensive review and discussion of the evidence presented in Pfizer's NDA for Zoloft (sertraline HCl). He concludes, based upon his review of that evidence and the reviews in the administrative file, that the NDA is approvable. I endorse his conclusion and recommend that the attached approvable action letter that he prepared be issued.

In recommending this action, I have considered the fact that the evidence marshalled to support sertraline's efficacy as an antidepressant is not as consistent or robust as one might prefer it to be. Two, 4 week long, parallel, multiple fixed dose, placebo controlled inpatient studies, one in the US (Protocol) and one in the UK (Protocol) found no difference between placebo and sertraline treated subjects. It has been suggested by some, by Dr. Laughren in particular, that this may be attributable to their inadequate power, but this argument cannot explain the failure of Protocol to document sertraline's efficacy as it had the capacity to distinguish amitriptyline from placebo. These facts, however, although they are consistent with the view that sertraline (at least under the condition of use employed in these studies) is less potent than and/or effective in a smaller proportion of the population of depressed patients than the classic tricyclic antidepressants, are insufficient to undermine

! A three way parallel randomized, blinded, comparison of amitriptyline, sertraline and placebo, the same design as that employed in the positive study, Protocol

my conclusion that Pfizer's NDA provides substantial evidence of Sertraline's antidepressant efficacy. Importantly, the agency's Psychopharmacologic Drugs Advisory Committee at its November 19, 1990 meeting considered these same issues and concluded (6 for, 1 against, 2 abstaining) that the efficacy of sertraline had been demonstrated.

Incidentally, the lack of unanimity among members of the PDAC documents, once again, that where judgments about drug efficacy are concerned, experts are not invariably willing to treat statistically significant differences on 'valid' outcome measures as substantial evidence of a drug's effectiveness. For some experts, the absolute size of the measured effect must regularly be considered. In light of the decision in Heckler vs. Warner-Lambert, their position now can enjoy official regulatory support. In any event, the 'small' size of sertraline's effect notwithstanding, the majority of experts advising us found the evidence sufficient to meet the regulatory standard of efficacy.

The safety of sertraline in use seems more than adequately documented. The size of the premarketing clinical cohort, 2700 or so, although not as large as fluoxetine's, seems as large a sample of subjects as we might reasonably ask be studied in any NDA. The experience gained has not identified any particular risk of concern. Nonetheless, it bears emphasis that the experience must be considered inadequate to capture catastrophic events occurring at rates below one in one thousand exposures in patients and under conditions identical to those studied in the NDA development program. The capacity to detect events occurring at much higher rates in populations or under conditions of use not represented in this development cohort is, of course, considerably reduced.

In this regard, however, we can gain some further reassurance about sertraline's safety in use from the fact that sertraline's introduction in the UK (November 1990) has not been followed, at least to date, by any surge of adverse event reporting. Further, the firm's response to the

2 Substantial evidence of sertraline's efficacy derives primarily from Protocol (3 fixed dose vs placebo comparison) and 104 (three way comparison). Protocol a long term (44 week) randomized comparison of sertraline versus placebo in the maintenance of recently remitted depressives provides additional support.

approvable action, will include an update on the post-marketing reports being received in the UK.

The directions for sertraline's regimen of administration are not as precise as we would prefer and primarily reflect the conditions of administration employed in the controlled trials. Unfortunately, the firm has not developed systematic information on dose response (or concentration response) relationships, although they have made a commitment to do so after approval.

Current dosing instructions do consider the 26 hour half-life of elimination of sertraline, recommending that the dose be increased at intervals no less than that required to achieve steady state (i.e., one week). The desmethyl metabolite of sertraline is active. It has a terminal half-life of elimination that may be as long as 100 hours and as a result steady state for this metabolite may take up to 3 weeks to achieve. This point is not emphasized in labeling, presumably because the desmethyl metabolite is only about 0.1 as potent as sertraline in regard to 5-HT uptake blockade.

The draft labeling provided with the letter is by now virtually 'traditional.' The labeling does assume, however, that certain reactions presumed to be associated with serotonin uptake blockade, although not so far reported with sertraline, warrant emphasis. For example, the hyperthermic reaction attributed to the interaction between fluoxetine and MAOI's is presented in warnings.

Conclusions and Recommendations:

The NDA for Zoloft is approvable. Issue the attached approvable action letter.



Paul Leber, M.D.
August 26, 1991

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 24, 1991

FROM: PAUL LEBER, M.D.
 DIRECTOR,
 DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

SUBJECT: Recommendation to Approve NDA 19-839 (Zoloft; sertraline)

TO: Robert Temple, M.D.
 Director, ODE
 File NDA 19-839

This memorandum conveys my formal recommendation that Pfizer's NDA 19-839 for ZOLOFT (sertraline) be approved.

The administrative file documents that NDA review team under the direction of Dr. Thomas Laughren has completed its review of Pfizer's NDA for sertraline, including, in particular, the firm's response to the agency's 10/30/91 approvable action letter. The division's review has failed to find that any of the grounds enumerated in Section 505(d) of the Federal Food, Drug, and Cosmetic Act for the disapproval of an NDA apply, and consequently, we recommend that the NDA be approved as provided by Section 505(c)(1)(A) of the Act.

It is noteworthy that several foreign national drug regulatory authorities (see Dr. Laughren's 12/10/91 memorandum), presumably provided with the same body of information that is contained in the NDA submitted to us, have not yet been willing to allow sertraline's marketing in their respective countries. It is our understanding that these regulatory authorities are not concerned about the risks of sertraline for use, but by what may be considered the 'lack of robustness' of the clinical evidence supporting its efficacy in the treatment of depression.

This turn of events may seem somewhat surprising in view of the fact that the agency is traditionally more conservative than its European counterparts. Obviously, changes are underway throughout the western Europe, perhaps in response to the EEC's harmonization initiatives. In any case, with the

Important exception of the UK's CSM/MCA, standards for antidepressant drug product approval seem to be becoming more demanding in regard to 1) the duration of controlled trials serving as sources of evidence of efficacy, 2) the need to document efficacy in hospitalized depressed patients (because these are presumed, arguably, to be more severely depressed), 3) the need to show efficacy in maintaining remission, 4) the need to show efficacy in preventing relapse of euthymic patients with a history of recurrent episodes of affective illness, and 5) a need to establish equivalency and/or superiority of a new antidepressant to already marketed drug products.

Many of these foreign regulatory initiatives have potential merit, but, given the perceived urgency we express as an institution for expediting the public's access to new, potentially promising drugs, I do not believe we can successfully introduce similar, more demanding, requirements domestically, at least until there is a significant 'sea change' in our society's collective attitude toward Federal regulation of new drug approvals. Incidentally, if you disagree with my assessment, I would like to know because the division would certainly be willing to propose additional requirements, provided, of course, that we could be assured of support for the initiative from both the Office and the Center.

In any case, based upon our current interpretation of the Act's requirements, Pfizer's NDA for sertraline must be approved. Sertraline is safe for use, effective in use, and adequately labeled, a view confirmed, albeit not unanimously, by the vote of our public Advisory Committee (i.e., PDAC).

Furthermore, although sertraline may not be the most robustly powerful antidepressant drug product ever introduced (a point made forcefully by some of our advisors), it has some potential advantages. As a 'pure' serotonergic reuptake inhibitor it shares, with Prozac (fluoxetine), the only currently marketed drug of this type, freedom from the troubling side effects associated with the use of the classic tricyclic antidepressants (e.g., imipramine, desipramine, amitriptyline, etc.) and the dietary restrictions necessarily associated with the use of monoamine oxidase inhibitors.

Sertraline and fluoxetine have not undergone head to head comparative clinical testing, but sertraline, and its major metabolite, nor-sertraline, have somewhat shorter elimination half-lives respectively than fluoxetine and nor-fluoxetine, a potential advantage.

In sum, the approval of Sertraline is readily justified under existing rules

Leber: ZOLOFT Approval Action [12/24/91]

page 3 of 3

and regulations. Approval may, however, for the reasons enumerated above, come under attack by constituencies that do not believe the agency is as demanding as it ought to be in regard to its standards for establishing the efficacy of antidepressant drug products.



Paul Leber, M.D.

cc: NDA, 19-839

HFD-100: Temple

HFD-120: Katz,
Laughren,
Lee,
Knudsen,
David

Motus/Pfizer Docs

046943

APPENDIX 2

EXHIBIT
18
10/19/00

SmithKline Beecham Pharmaceuticals
Regulatory Affairs
FDA CONVERSATION RECORD

Date: October 3, 1990 Time: 10:00 AM
Conversation With: Martin Brecher, M.D.
Title/Affiliation: Medical Officer
Division of Neuropharmacological Drug Products
Telephone Number: (301) 443-4020
Regarding: PAROXETINE: Suicide-Ideation and Violence-Ideation; Efficacy Review

SUMMARY OF CONVERSATION:

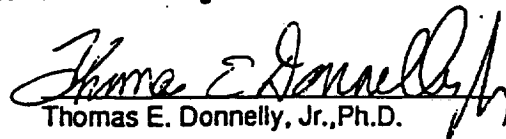
Dr. Brecher called and initially mentioned that the last submission was fine and he looked forward to receiving the weight gain response. He next said he was calling to inform us of a concern that has arisen about fluoxetine and he is formally requesting that we prepare a response to the same issues. He said that the public press has been widely discussing the relationship between fluoxetine and violence ideation and suicide ideation. Although the Division does not see it as a real issue, but rather as a public relations problem, Lilly has been asked to submit a detailed response to the public's concern. He therefore is requesting that we do the same since we have a drug with a similar mechanism of action. He said his request is not based on any concern that has developed from his review of paroxetine, but simply that it is an issue that must be addressed with this group of drugs.

He mentioned that one approach would be to address it from three types of data: 1) completed suicides, 2) acts broadly defined as attempted suicides (down to events as small as scratches on the wrists), 3) ideation. He said we should also address the kinds of things mentioned in the article by Dr. Teicher such as obsessional suicidal ideation and worsening of the suicidal ideation. Lilly has used the approach of looking at patients who had a value of 0 or 1 on the Hamilton Suicidal Ideation Item and have gone to 3 or 4. They presented the differences between patients on placebo, paroxetine and active controls.

Dr. Brecher said that he is working full time on the review of efficacy and expects to finish by the end of the year (December, 1990). He does not expect to have his time divided on any other drugs. Therefore he would like us to submit this report by the end of November. It does not need to be voluminous (e.g. 10 volumes of data listings) as he does not want to review something that large. It will require certain analyses, should be clearly laid out and should look at the issues in different ways. I mentioned that Dr. Tina Blumhardt was already working on this type of document and asked if she could call him for additional input concerning the document. He said that would be fine. Again, he emphasized that the Division does not think it is an issue, but it needs to be addressed.

He added that he was not calling from his office, but he would call again later as he is accumulating some questions concerning efficacy.

Signed:


Thomas E. Donnelly, Jr., Ph.D.

cc. Dr. C. Blumhardt
Mr. W. Bushnell
Ms. E. Donnelly
Dr. G. Dunbar
Dr. C. Fake
Dr. M. Fox

Ms. D. Mackleston
Dr. J. Mannion
Dr. J. O'Connor
Dr. R. L. Powell
Dr. B. Wallin

DOCUMENT RESOURCES
AND RETRIEVAL CENTER

PLAINTIFF'S
EXHIBIT
NO. 00CV0025
18

NOV 05 1990

SB 0000136

APPENDIX 3

North Wales Dept of Psychological Medicine
Hergest Unit
Bangor
Wales LL57 2PW
July 20th 2004

Staff of the Health Committee
Health Committee
7 Millbank
London
SW1P 3JA

Dear Sirs

Please find below a submission to the Inquiry on The Influence of the Pharmaceutical Industry. I shall post this and the following three pages to the committee as evidence of the genuineness of this electronic submission.

Yours faithfully

David Healy MD FRCPsych

HOW PHARMACEUTICAL COMPANIES MANUFACTURE CONSENSUS AT CLINICAL AND REGULATORY LEVELS

David Healy
North Wales Department of Psychological Medicine
Cardiff University (U of Wales College of Medicine)
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1. INTRODUCTION

2. In response to the select committee's call for comments, I wish to offer an analysis that may help explain how companies can engineer a clinical consensus that will favour their product – even in the absence of a scientific basis for claims for superiority for the new and usually much more expensive product – and how this process can feed through and shape even disinterested assessments of the evidence undertaken by NICE. These processes appear to many to underpin a relatively recent “capture” of regulatory and other professional domains.
3. I will also comment on how the safety of pharmaceutical products might be better ensured under current arrangements and on how current arrangements may be changed to produce a safer framework for healthcare.
4. I bring to this commentary a background in consultancy work with pharmaceutical companies, access to company archives through medico-legal work, (as outlined in the accompanying conflict of interest statement – appendix 1), and 10 years of work on mapping the history of the development of psychotropic drugs and pharmaceutical companies in their present form as published by Harvard and New York University Presses.

5. COMMENTARY

6. Clinical Consensus: The main point of note is that the scientific literature is being managed to an ever increasing extent, the most visible sign of which is that an increasing proportion of the scientific literature on aspects of therapeutics with pharmacological agents (over 50%) is now ghost-written. This is associated with a demonstrable failure to report important safety data on drugs, or with the reporting of such data in terms that mislead. The risks from ghost-writing stem from the fact that the data that ghostwriters purport to represent remain inaccessible to outside scrutiny.
7. As a consequence of the ghost-writing of articles, efforts to establish clinical consensus in the form of guidelines and algorithms, which depend on a review of the entire literature on a drug are compromised and can be shown to produce outcomes indistinguishable from the outcomes that would be produced by having a group of employees of the pharmaceutical company write the guidelines. Even though there may in fact be no evidence of superior efficacy or safety for newer agents, they will end being written up as superior to older agents and to be used in preference to older agents.
8. The effects of ghost-writing and other literature management strategies feed through into a process of pharmaco-economic modelling undertaken for new drugs, which can demonstrate that not only is a drug that is not proven to be in any way superior its predecessors better than its predecessors but is better to the extent that it should be in replace older agents, even though the costs of the new treatment may be 50 times greater than the older agent.
9. The details of how these processes work are laid out in appendix 2. Of note here is that I have been a participant in these processes and party to the generation of views favouring newer

over older agents, unaware that pharmaceutical companies were keeping key safety data hidden from the scientific community and that they would refuse to produce such data on request.

10. Safety Data: Current procedures to manage the entry of drugs onto the market favour the detection of drug effects and set a higher threshold for safety effects. This shows up in two ways.
11. First, in order for a drug to be licensed it has to show superiority to placebo in two controlled trials. Companies however can run ten or more trials in carefully selected samples using instruments carefully designed to pick up any effect in order to demonstrate this, and even if the results show the drug failing to beat placebo in the clear majority of trials, this is not held against them. These other trials are commonly termed failed trials rather than drug failures.
12. In contrast, the demonstration of a safety issue is not handled in this way. In this case regulators will only act if the overwhelming preponderance of the data show a hazard.
13. This issue has at its heart unresolved philosophical issues about the nature of statistics. Safety data is typically presented in terms of Confidence Intervals, so that for instance in recent antidepressant studies the rate of suicides on drugs compared to placebo is typically of the order of 2 times greater but what is termed the confidence interval surrounding this figure of 2.0 might be for example 0.9 to 4.4.
14. There is a deep philosophical divide between two ways to interpret such a finding. First according to a school of thought stemming from R.A. Fisher is the view that nothing has in fact been shown unless the confidence interval does not include 1.0, thus for instance a confidence interval of 1.1 to 4.4.
15. Second, the Neymann-Pearson school of thought argues that the best estimate of the effect is 2.0, in this case. This is the figure regarding which we can be most confident.
16. In practice regulators, adopt the Fisher approach. This cannot be viewed as a rigorous approach to safety. Epidemiologists or a drug regulatory process on the other hand, concerned with safety, would argue that in this case the figure of 4.4 is potentially consistent with the data – that is the hazard in question may well happen up to 4.4 times more often on the drug than on placebo or non-treatment, and that therefore if the hazard is serious patients and doctors should be warned about this possibility.
17. Safety Procedures and Informed Consent: At present when patients enter clinical trials they are asked to sign informed consent forms, which contain ever longer lists of potential problems a treatment may cause.
18. These consent forms though never inform patients or others that neither patient, nor physician nor any other third party will ever have access to the raw data from this trial, particularly data on safety issues. They are not told that pharmaceutical companies may choose only to “market” the bits of the data that suit them.
19. Changing informed consent forms to make this explicit might have salutary effects. Alternatively transforming informed consent forms into contracts between patients and companies that provided rights of access to experts in the event of safety concerns might make a big difference.

20. Requiring companies to permit access to the raw data, given for free by patients as part of a “gift” arrangement with the rest of the community, would simply require companies to conform to the norms of science under whose banner they claim they sell their products.
21. Until some arrangement is put in place to ensure access, then every patient who enters a clinical trial in the United Kingdom (or anywhere else) is putting every Member of Parliament and all the constituents those Members represent in a state of legal jeopardy. This follows as the absence of publicly available data on hazards will be used by pharmaceutical companies to argue that the hazard does not exist, even when the datasets available to industry establish clearly that the hazard does exist.
22. Regulators, who typically read study summaries prepared for them by pharmaceutical company employees, rather than scrutinise and analyse the raw data themselves, can miss these issues.
23. This evidence is being submitted on an individual rather than a corporate basis. I would be willing to give oral evidence on these issues, and can bring some benefit to any hearings by virtue of being an active participant in the processes described above and below.
24. I am a Reader in Psychological Medicine in the University of Wales College of Medicine (as of August Cardiff University).
25. David Healy July 20th 2004

26. Appendix 1:Competing interests
27. In recent years, I have had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend foreign meetings from Astra, Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, Solvay, Zeneca
28. I have also been an expert witness for the plaintiff in seven legal actions involving SSRIs, as well as for the defendant in 4 cases of assault involving SSRIs, but otherwise has offered the view that antidepressants have not been implicated in approximately 100 other cases. I have been an expert witness for the defendants (the British National Health Service) in a large series of LSD and ECT cases.

29. Appendix 2:
30. MANUFACTURING CONSENSUS David Healy MD FRCPsych. In Press in Greenslit, N. (Ed.). *Pharmaceutical Cultures: Marketing Drugs and Changing Lives in the U.S.* Rutgers University Press.
31. Background
32. Consider this excerpt from the 1993 FDA medical review of Janssen Pharmaceutical's application to market the antipsychotic drug, risperidone (Risperdal): 'We would consider any advertisement, promotion or labeling for Risperdal false, misleading or lacking fair balance under Section 502 of the Act if there is a presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness' (Mosholder 1993).
33. The clinical trials undertaken by Janssen with Risperdal prior to marketing had compared it to an older antipsychotic, another Janssen drug, haloperidol. In a similar way, all recently released antipsychotics, including olanzapine (Zyprexa), quetiapine (Seroquel) and ziprasidone (Geodon), were compared to haloperidol in key pre-marketing trials. All companies used much the same dose of haloperidol – a dose that was no more efficacious than lower doses of haloperidol but which did cause more side effects. The company rationale for using haloperidol was that haloperidol was supposedly the market leading antipsychotic agent. Whatever the real rationale, it was generally accepted at the time these trials were conducted that newer agents stood their best possible chance of looking better in terms of key side effects – or at least no worse – if compared to the doses of haloperidol used in these trials.
34. The role of a drug regulator in addition to gate-keeping the entry of a new drug to the marketplace is to regulate any claims a manufacturer might make as regards a new product in its advertising or in any statements its personnel might make to doctors afterwards. This assessment by the FDA would appear to produce problems for any company that might wish to market Risperdal.
35. But regulators have no control over what academics say in lectures, report in medical journals or elsewhere. FDA in addition have no control over what assessments these academics might make in their roles as experts called on to contribute to an expert consensus on new versus older drugs. Shortly after Risperdal was launched, it was being widely touted by academics as superior to older antipsychotics on the market.
36. Aside from the perennial need to market the product, the 1990s brought a new hurdle for drug companies to vault. It was increasingly necessary to persuade clinicians and pharmacists that a new drug should be listed on hospital formularies. These formularies were created to ensure new agents would not be used without good evidence of cost-benefit returns. The formularies are notionally meant to be evidence based and cost-sensitive. A certain amount of trade off was likely – if a new drug cost more but could show a real benefit over older agents it would be included.
37. No convincing evidence has ever been forthcoming that any of the new 'atypical' antipsychotics are superior to the older 'typicals' in either safety or efficacy. A study completed in 2003 by the VA hospitals compared olanzapine (Zyprexa) and haloperidol both in terms of efficacy and tolerability and found no difference between them; olanzapine in this study, however, cost approximately 80 times as much as haloperidol (Rosenheck, Perlick, Bingham et al 2003). Despite this lack of greater efficacy, olanzapine has won a place on formularies since its launch in 1996 to the extent that it has become the most profitable antipsychotic in the world.

38. In the absence of clear evidence from clinical trials sufficient to warrant claiming a new drug was superior to an older drug, it would appear difficult to make the extra step to advocating that the newer agent is more effective to the point of warranting a potential 80-fold increase in expenditure. Nevertheless, shortly after their launch, Risperdal and other recently released antipsychotics were available on most hospital formularies in both the United States and Europe.
39. Pharmaceutical companies have clearly found methods of circumventing these difficult areas of marketing terrain. Circumvention is achieved by recruiting senior academics and institutions to their cause, by means of three stratagems: consensus conferences, pharmacoeconomic modeling, and ghostwriting.
40. Consensus Conferences
41. Consensus conferences aimed at producing guidelines for clinical practice came into existence in the late 1980s (Sheldon and Smith 1993). A range of bodies took up this apparently academic development. Within psychiatry, groups such as the British Association of Psychopharmacology and the European College of Neuropsychopharmacology for example produced guidelines on the treatment of a range of conditions from depression through to schizophrenia. This may have happened in part in an effort to establish a political profile. In a number of the organizations that produced guidelines, the influence of key individuals with links to pharmaceutical companies is apparent.
42. At the same time pharmaceutical companies began to sponsor meetings aimed at producing expert consensus on issues such as the appropriate use of medication in schizophrenia. These company sponsored meetings have often resulted in products that may appear almost indistinguishable from non-company sponsored guidelines or algorithms. While this might be thought as an exercise designed to confound the recommendations of independent committees, in fact committees that should be independent have come up with recommendations that barely differ from explicitly company-sponsored exercises.
43. Given the lack of evidence-base for the superiority of the new antipsychotics, just how have all these guidelines ended up endorsing newer, more costly agents over older, less expensive, but equally effective ones? One such guideline system, the Texas Medication Algorithm Project (TMAP), offers one set of answers (Petersen 2004)¹.
44. Risperdal was launched in 1994. TMAP was instituted in 1995, initially funded by Janssen Pharmaceuticals (Johnson & Johnson), the makers of Risperdal. Soon afterwards it had attracted funding from all major pharmaceutical companies. TMAP drew up a panel of consultants to produce an expert consensus on the use of antipsychotics, and later on the use of antidepressants and mood-stabilizers (Gilbert, Altshuler, Rego et al 1998). Most had prior links to Janssen and the other major pharmaceutical companies operating in the mental health field.
45. The first set of TMAP guidelines concluded that the atypical antipsychotic medications Risperdal, Zyprexa and Seroquel were the drugs of choice for the management of schizophrenia (Chiles, Miller, Crismon et al 1999). A second set concluded that newer patented antidepressants, such as the SSRIs, Prozac, Paxil and Zoloft, were the drugs of choice for the treatment of depression rather than older agents such as the tricyclic antidepressants. Subsequently mood-stabilizers such as Depakote and Lamictal have been endorsed over other treatments for bipolar disorder. In all these instances, the claims have

¹ Note: In connection with TMAP, this article has benefited hugely by work undertaken by Allen Jones, Special Investigator in the United States OIG Office of Special Investigations, detailed in Dwight McKee and Allen Jones v Henry Hart, Sydni Guido, Wesley Rish, Albert Masland, James Sheehan and Daniel P. Sattelle, CIVIL ACTION No: 4:CV-02-1910, in the United States District Court for the Middle District of Pennsylvania.

been that the new drugs were safer, more effective and better tolerated than the older agents. The expert panels then formulated a set of algorithms or care pathways for the treatment of schizophrenia, depression and bipolar disorder based on these guidelines.

46. In a number of US states, legislators have the powers to rule that algorithms and guidelines such as these must be applied in the care of any patients receiving treatment in public facilities. The logic here is that evidence based guidelines and algorithms, if they really do reflect reality, can be expected to be cost-effective over time. The legislators faced with the question of adopting the algorithm and guideline proposals in Texas meet infrequently, are poorly paid and are intensively lobbied. Not surprisingly perhaps, TMAP was administratively endorsed in Texas, and as a result state hospital doctors were required to follow its algorithms and use these newer drugs first.
47. Researchers linked to TMAP were also able to access the records of patients in state facilities, including prison hospitals and mental hospitals, and report on the cases that appeared to do favorably. These surveys produced data supporting the selection of Risperdal and Zyprexa, for instance, as first line treatments for schizophrenia, and later the selection of SSRIs or other newer antidepressants over older treatments for depression. On this basis, the TMAP guidelines and algorithms began to be referred to as evidence-based guidelines and evidence-based best practices.
48. A related panel formulated a set of medication algorithms for children, which recommended new antipsychotics and antidepressants, such as Paxil (paroxetine), for the management of children's problems (Hughes 1999). In this case, not only was there a lack of evidence for the superiority of the newer over the older agents; there was essentially no evidence base for the recommendations other than a set of then unpublished clinical trials.
49. The TMAP algorithm and guidelines were subsequently marketed to other states on the basis of the Texas precedent and instituted by administrative decision in a number of these other states also². In this way a very few people had effectively paved the way for the acceptance of these guidelines and algorithms in many states, and produced a situation in which a growing cohort of patients treated in the public sector end up being put on and maintained on these drugs. It will probably come as no surprise that within Janssen there was a special unit aimed at maximizing the effectiveness of the companies marketing in the public sector.
50. From TMAP to NICE
51. While the TMAP process appears close to egregious, something very similar happened within the socialized system of medicine in Britain. In the first place, opinion leaders in Britain were recruited to panels to produce evidence-based guidelines for antipsychotics. The experts invited to such meetings will have had no pressure put on them to come to a particular point of view. All of the publications of clinical trial data for antipsychotic drugs will have been made available to them on request, and they will have been encouraged to be evidence based.
52. Again as with TMAP, the results, despite the assessment of the FDA, which will have been unknown to any of the participating experts, must have been gratifying to the sponsoring company (Mortimer, Healy, Gray et al 1998)³. The process involved no overt selling of named medications, but rather a set of positions endorsing the use of antipsychotics in monotherapy regimens, and in doses consistent with British National Formulary recommendations, and in a manner that would avoid precipitating acute treatment related side

² As of 2004, these guidelines had been adopted at some point by Pennsylvania, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, South Carolina, Maryland, Missouri, and Washington D.C., or by jurisdictions within those states.

³ It is important to note that the author participated as a guideline panel member in this Risperdal exercise.

effects. These positions along with exhortations to adhere to an evidence based approach were considered by the company as an effective marketing tool.

53. Subsequently, a National Institute of Clinical Excellence (NICE) was set up in Britain with a brief to make recommendations as to the most clinically effective and cost-effective treatments for both physical and mental illnesses. The NICE guidelines for psychiatric treatment are an essentially similar creation to TMAP, and earlier UK based industry sponsored guidelines: a consensus of expert views rather than evidence based views. The process involves a small number of psychiatrists, psychologists and other stakeholders in mental health such as psychiatric pharmacists collating evidence, preparing draft reports and then sending these to selected experts for comments. Decisions are reached not by experiment or evidence but by agreement. The process will also have to take into account prior algorithms, guidelines and Delphi panel recommendations (see below). And finally, as has been pointed out publicly by the World Health Organisation, the process operates within the constraints of the unwillingness of pharmaceutical companies to share the raw data arising from clinical trials (WHO 2003).
54. The upshot of this in the case of the antipsychotics has been a set of guidelines indistinguishable from the ones drawn up by TMAP, or by other guideline groups linked closely to pharmaceutical companies (NICE 2003). NICE recommends the use of the new antipsychotics over old, even though it acknowledges it does so without having any evidence base for this. In fact, the NICE guidelines fly in the face of evidence that new antipsychotics compared in clinical trials with the older antipsychotics and placebo produce significantly higher death rates from a variety of causes and significantly higher suicide rates, as well as a range of physical problems, from cardiovascular to endocrine disorders, that were not linked as frequently to the older antipsychotics.
55. In a public health system such as the NHS, NICE guidelines are implemented in a very similar way to the TMAP guidelines. The medical directors of hospitals will ordinarily seek to ensure that their clinical staff adhere to NICE guidelines. As a direct result of NICE then a much larger number of patients will end up being given new rather than old antipsychotics than would otherwise have been the case, with a probable resulting detriment in the collective patient health, brought about at vast cost. It is all but impossible for individual clinicians to opt out of the system as the public health system endorses adherence to these guidelines and practicing outside the guidelines may not be regarded as evidence based.
56. The critical influence here lies with the clinical trials that supposedly form the basis for the guideline process. Newer agents almost invariably have more and larger trials than older agents, especially if this is for indications that have been 'created' since the older drugs went off patent. A great number of older agents may in fact have minimal trial data. Those constructing the guidelines rarely appear to take into consideration the fact that the larger the trials needed, the weaker the drug must be, and that in general trials are only needed when there are some doubts as to whether the drug actually works or not. But, even more critically, the underlying data that might reveal increased deaths from suicide and other causes that might occasion a different set of conclusions are never available to those constructing the guidelines.
57. While the data that might have led NICE to a different conclusion were not available in the reports of randomized trials of these agents, a good deal of relevant data was in fact publicly available in reviews published by the Food & Drugs Administration (FDA) for each of the new antipsychotics at the time of licensing. In the case of suicides, a great deal of the data was available in a paper on rates of suicides and suicidal acts in clinical trials with novel antipsychotics.
58. These published data show high rates of suicide on Risperdal and perhaps the highest rates of suicide in clinical trial history on Zyprexa (see table 1). But the most surprising thing is that

the paper offers no figures for suicidal acts on Zyprexa, while it does offer figures for suicidal acts in the clinical trials programs for the other new antipsychotics. Against a background of possibly the highest suicide rates in clinical trial history, this absence of data on suicidal acts for Zyprexa is striking. Eli-Lilly, the makers of Zyprexa, have since refused to answer questions as to what the rate of suicidal acts on their drug might be. Despite this, this drug has become the best selling antipsychotic on the marketplace.

59. NICE guidelines however as mentioned endorse the use of both Risperdal and Zyprexa over older agents, although given the absence of these key data and public knowledge about this key absence, it is difficult to see how any patient taking Zyprexa can be taking it on the basis of informed consent. While NICE guidelines do not have the force of law, it would be difficult for clinicians in the UK to flout this guidance. Thus, there are good grounds to think that the availability of NICE, TMAP and other guidelines has resulted in a vast increase in the expenditure of drugs in the mental health domain at a presumptive cost to the development of other services, and this increase has also taken place without any reasonable expectation of health gains at either the individual or systems level.
60. Pharmaco-economics
61. In the case of these newer agents, another method resorted to by companies has been a set of pharmaco-economic procedures. Pharmaco-economics as a discipline began in the 1970s, heavily subsidized by the pharmaceutical industry (Healy 1998). It basically involves estimating and comparing the costs of leaving a condition untreated against the costs of treatment. The original view of the first pharmaco-economists was that the complications of establishing treatment effects and outcomes for psychotropic drugs across a range of domains of value in mental health meant it would be impossible to apply the procedures of pharmaco-economics to psychiatric conditions and treatments.
62. Nonetheless the emergence of a set of SSRI antidepressants and atypical antipsychotics that could not be distinguished from older agents in terms of efficacy or tolerability, but which were associated with greatly increased costs, led to a flurry of pharmaco-economic exercises. This is exemplified nicely by the emergence of supplements to major journals detailing a range of pharmaco-economic approaches that probably did a good deal to smooth the marketing path of the SSRI antidepressants (Eccleston 1993).
63. One of these methods involved the establishment of Delphi panels of experts. Delphi panels invite experts to consider clinical trial data and estimate the likely translation from the actually published randomized trial evidence to possible outcomes in clinical practice if the drugs are adopted widely. These outcomes are then costed by economists working to the manufacturing company.
64. The participants in these exercises will again be unaware of assessments such as those made by the FDA, or the data on suicide or death rates from trial programs. The invariable outcome of these proceedings has been sets of models indicating that treatment with newer agents costing ten to eighty times more than older agents would in fact lead to savings in either for profit healthcare systems such as that of the United States, or socialized medical systems such as the UK mental health system (Guest et al 1996)⁴.
65. No one seems prepared to say what the original exponents of pharmaco-economics realized, namely that short-term trials cannot be used for this purpose. This issue is now further complicated by something that would once have been all but inconceivable, which has been hinted at above and is developed below, namely, the fact that in a growing number of cases critical aspects of the raw data are substantially at odds with the published data.

⁴It is important to note that the author also participated as a Delphi panel member in this Risperdal exercise.

66. Ghost-writing
67. In the 1980s, pharmaceutical companies began to outsource a range of functions, such as the running of clinical trials and medical writing, to other companies. Medical writing was outsourced to medical communication agencies. With this development, the practice of ghost-writing academic articles picked up pace. Ghost-writing involves medical writers writing articles, which subsequently appear under the apparent authorship of academics who might or might not have reviewed the piece before publication; the ghost traditionally is the medical writer who receives no credit for her input. For some time it was believed that this form of medical communication was largely confined to journal supplements or peripheral journals (Healy 2003, & 2004). The first hints that the picture might be somewhat different came in the mid-1990s. Flanagan and colleagues for example reported in 1998 that up to 11% of articles published in six mainstream peer reviewed journals involved the use of ghostwriters (Flanagan, Carey, Fontanarosa et al 1998).
68. Recently a document became publicly available covering the co-ordination during the course of 1998 of medical articles on Pfizer's antidepressant Zoloft (sertraline) by a medical communications agency, Current Medical Directions (CMD). This has permitted the comparison of published articles written for Pfizer with other articles on Zoloft in terms of the impact factor of the journals in which they appeared, prior publication history of the respective authors and subsequent citation rates of the respective series of articles.
69. The analysis showed the journals in which Pfizer's articles were published had an impact factor three times greater than the journals in which other articles on Zoloft were published. The authors on Pfizer's articles had nearly three times more previously published articles, as cited in Medline and Embase, than the authors of articles not linked to Pfizer. Of greatest importance was the subsequent citation rate. It might be thought that, despite publication in the most prestigious journals and under the apparent authorship of the most distinguished academics, clinicians and researchers would find this literature too obviously industry linked and would not be influenced by it. However, the subsequent citation rates for the Pfizer-linked articles were three times greater than that of the non-Pfizer articles (Healy and Cattell 2003).
70. The profile of this so-called scientific activity suggests that Pfizer ended up with a set of authors whose background increased the possibility of the company's publications appearing in the most prestigious journals. The combination of distinguished journal, distinguished author, an efficient distribution system and sponsored platforms appears to have led to an impact on the therapeutics domain greatly in excess of 50% of the impact of the rest of the literature on Zoloft. At present roughly three-quarters of all randomized trials appearing in JAMA, NEJM or the Lancet are industry funded.
71. The impact of this literature on third party payers is at present unquantifiable, but authorship by perceived opinion leaders with minimal company representation and non-declaration of other authorship inputs increase the likelihood that these articles will be influential with purchasers as well as prescribers.
72. Academics become opinion leaders in a therapeutic field because they have their names on a larger proportion of the literature appearing in the most prestigious journals than their colleagues, and because they get asked to international meetings to present this data – with which they may not, in fact, have first hand acquaintance. This, allied to the volume of industry-linked authorship, is arguably leading to a situation in which the dominant figures in therapeutics actually have little first hand research experience and may have no raw data that they can share with others and probably have simply never seen the raw data. This is a situation in which, in contrast to the traditional perception of who the ghost authors are in the medical literature, our leading academics have become ghosts or ciphers.

73. It is in fact a situation in which ghost-writers increasingly have to take on ghost-acting as part of their repertoire. This happens because the apparent authors of a study will often now have so little familiarity or association with the basic data, that they either cannot present it at major meetings or are not inclined to do so in for instance poster form. As a result it is becoming increasingly common to find medical writers presenting posters at academic meetings, where they will in all probability often be assumed to be doctoral students linked to the research being presented⁵.
74. The situation that has developed underlines the significance of the proprietary control of raw data. The raw data from one trial of Zoloft compared to mianserin or placebo in the CMD series, for instance, shows that one patient on Zoloft committed suicide and three others had their treatment discontinued because of increasing suicidal ideation. In contrast there was just one case of emergent suicidality on the comparator drug mianserin and no problems on placebo. But the final published article makes no reference to any patient becoming suicidal in any way (Malt, Robak, Madsbu et al 1999).
75. Second, within the CMD series of articles on Zoloft, there were six that dealt with the use of Zoloft for children. Of these six articles, only one mentions suicidality – one single suicidal act. There were in fact six suicidal acts on sertraline in the trials that these articles report: a rate approximately six times higher than the published rate in adults⁶. The rate of suicidality in depressed children taking sertraline was in fact nine per cent. However the article dealing with the hazards of treatment in children who are depressed only reported on the side effects that occurred at a ten per cent rate or more (Alderman, Wolkow, Chung et al 1998).
76. The Consensus on Treating Children with Psychotropic Drugs
77. The consequences of these developments came to a focus in 2003 on the issue of treating children with psychotropic drugs. The TMAP children's algorithm project outlined above endorsed the use of SSRI antidepressants for treating childhood nervous disorders, largely on the basis of a series of unpublished trials. Although unpublished, the experts formulating algorithms for TMAP and the experts running these trials and appearing as authors on the few published trials were in many instances the same people. These experts therefore had a better opportunity to know what the raw data looked like than anyone else. As a result, the issue of treating children with psychotropic drugs offers a good case example to bring out a number of features of the new world of manufactured consensus.
78. There has been a long-standing awareness that it is difficult to show in clinical trials that antidepressant drugs offer benefits for children. Despite this there were grounds for using psychotropic drugs for children, and guidelines on the treatment of children who were depressed endorsed such usage (Healy and Nutt, 1998). The advent of the SSRI antidepressants offered some hope that these agents might be shown to be effective for children where efforts with older agents had failed.
79. In the early 1990s, regulatory authorities approved the use of the SSRIs Paxil and Zoloft for the treatment of depression for adults. They had previously approved Prozac and subsequently approved Celexa and Efexor. From the 1990s, standard letters of approval to companies noted that as these drugs were likely to be used to treat children studies to establish the safety of the drugs in these populations would be helpful. This encouragement led to a series of studies of SSRIs in children during the early to mid 1990s. A further incentive was put in place in 1998 with an FDA Modernization Act (FDAMA) (Sharav 2003), which offered patent extension on the basis of testing for rather than proving safety; if the

⁵This claim is based on the personal experience and discussions with ghost-writers/actors.

⁶Pfizer. Sertraline hydrochloride for obsessive-compulsive disorder in pediatric patients. Expert report. New York: Pfizer Inc., 1997, Available on www.healyprozac.com.

drugs showed hazards, the company still got patent extension but had to incorporate this information in the label.

80. Prozac

81. In the case of fluoxetine an early series of clinical trials failed to establish efficacy for this drug in treating childhood nervous problems. This work led to a study that started in 1990, which involved extensive pre-screening of patients so that less than one-fifth of those screened entered the study, and those who did were put through a placebo washout phase in an effort to reduce the high rate of placebo responsiveness found in SSRI trials in children. Using these procedures, an article that appeared in 1997 claimed that Prozac could produce beneficial effects for children and adolescents (Emslie, Rush, Weinberg et al 1997). However, in fact on the primary end-point measure, Prozac was no better than placebo and on secondary measures benefits were apparent on physician-based ratings but not on patient or carer ratings. In addition, there was a 29% drop-out rate on Prozac and the rate of behavioral side effects was greater on Prozac than on placebo⁷.

82. This Prozac study had been run under the auspices of the NIMH. Subsequently another study funded by the makers of Prozac, Eli Lilly, led to a comparable result (Emslie, Heiligenstein, Wagner et al 2002). The second study, in contrast to both the previous Prozac study and studies of other SSRIs and in contrast to clinical practice, showed no greater rate of adverse events on Prozac than on placebo. This combination of studies led to a license for Prozac for the treatment of depression in children and adolescents in 2003.

83. A further study had been undertaken on Prozac for obsessive-compulsive disorder (OCD). This showed somewhat more clearly positive results for Prozac over placebo, but equally an excess of suicidality over placebo.

84. Paxil

85. The first study undertaken with Paxil, protocol 329, was conducted in the early to mid-1990s. The published report from 2001 pointed to mixed benefits of Paxil on the primary endpoints of the trial, with apparent responsiveness on some measures accompanied by non-responsiveness on others, concluded that Paxil is effective, safe and generally well-tolerated (Keller, Ryan, Strober et al 2001). But in this study there was an increased rate of suicidal acts on Paxil (5/93, a 5.4% rate) compared with either imipramine (1/95) or placebo (0/89). The difference between Paxil and placebo was close to significance at the 95% level ($p = 0.06$), and the difference between Paxil and comparators (1/183) was significant.

86. These figures were not apparent from the published the paper, where suicidal children were coded as having had emotional lability. Hostility was also a reported side effect in 6.5% of Paxil patients in this study versus 1.1% on placebo. While the published paper does outline that emotional lability might include suicidal acts, this is not a common meaning of the term for most clinicians, who will be unaware that dictionaries for coding side-effects, such as the ADECs system, offer the possibility to code suicide, suicidal acts and suicidal ideation under the heading of emotional lability. The same dictionary codes homicidal acts, homicidal ideation and other aggressive acts under the heading of hostility.

87. A second, protocol 377, and a third protocol 701, and a fourth trial protocol 716 failed to demonstrate efficacy for Paxil for depression, and also seem to have returned an increased frequency of suicidality on Paxil. The first two of these studies, which appear to have been completed by 2000, were presented in part in abstracts in 2001 and 2002 that concluded that Paxil was effective, safe, and generally well-tolerated (Wagner, Wetherhold, Carpenter et al 2002). The fourth apparently remained unscrutinized by FDA, when FDA undertook a review of SSRI agents in children in 2003.

⁷ Food and Drug Administration Review

88. At much the same time studies of Paxil in obsessive-compulsive disorder (OCD) were instituted, protocols 453 and 704. Reports of these studies in abstract form also claimed that Paxil was effective safe and generally well tolerated (Geller, Wagner, Emslie et al 2002). However, company data on file point to an increased rate of side-effects on Paxil compared to placebo, in the domains of hostility, agitation and hyperkinesis. In 453, 6.3% of children taking Paxil (n = 97) became hostile compared with 0% on placebo (n=100). In 704, 9.2% of children became hostile on Paxil (n = 98) with 1% becoming hostile on placebo (n = 105). There was also an increased frequency of suicidal acts on Paxil (1/195) compared to placebo (0/205)⁸.
89. Finally, a study of Paxil was conducted in social phobia, protocol 658. The unpublished results indicate that Paxil might in some cases produce a beneficial effect in children, but as with depression and OCD there was a higher rate of adverse events in the behavioral domain on Paxil compared to placebo. In this case there appear to have been 3 suicidal acts in 165 children on Paxil compared to 0 in 157 on placebo⁹.
90. Zoloft
91. In the case of Zoloft, in the mid-1990s, a double blind placebo controlled study was undertaken in OCD, which reported that Zoloft can have a greater beneficial effect on core features of OCD than placebo (March, Biederman, Wolkow et al 1998). This paper, which was one of the CMD series, noted one suicidal act on Zoloft. A background expert report on the study, however, points to two suicidal acts on Zoloft compared with one that might have been on placebo¹⁰. In the absence of the raw data, it is not clear whether this suicidal act on placebo actually occurred during the randomized phase of the trial, as in the case of Pfizer's clinical trial program in adults suicidal acts that occurred during the washout phase of trials were coded under the heading of placebo (Healy 2003).
92. At the same time, Pfizer initiated open trials of Zoloft in children who were depressed. In the first of these, also reported in the CMD series of papers, 44 children were given Zoloft of whom 4 became suicidal, a 9% suicidality rate. The article reporting these results portrayed Zoloft as likely to be effective, and generally well-tolerated; this article also restricted itself to reporting on the side-effects that occurred at a 10% rate or more (Alderman, Wolkow, Chung et al 1998). A further open study of Zoloft in depression, also in the CMD series, reported that there were 3 suicidal acts among 53 children who were depressed, a 5.6% rate (Ambrosini, Wagner, Biederman et al 1999).
93. The expert report on these early OCD and depression studies undertaken for Pfizer commented, "Clinical studies in pediatric patients with OCD (aged 6-17 years) have shown that sertraline is well tolerated. The adverse events which led to discontinuation were generally psychiatric in nature, and there were no discontinuations due to laboratory safety data following administration of sertraline"¹¹.
95. Subsequently, Pfizer conducted two randomized controlled trials on Zoloft in depression. These were both negative; combined, however, they were reported as showing Zoloft was effective and well-tolerated (Wagner, Ambrosini, Rynn et al 2003). In fact, 59% of children on Zoloft showed a change of 5 points on a Clinical Global Impression scale against 49% of

⁸Data on File. Important Safety Information regarding Paxil in Pediatric Patients, Glaxo SmithKline, Therapeutic Products Directorate: TDP-Web, July 18th 2003. Health Canada, www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/paxil_pa_e.html

⁹Data on File. Important Safety Information regarding Paxil in Pediatric Patients, Glaxo SmithKline, Therapeutic Products Directorate: TDP-Web, July 18th 2003. Health Canada, www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/paxil_pa_e.html

¹⁰Pfizer Expert Report 1997. Sertraline hydrochloride for obsessive compulsive disorder in paediatric patients. Approved Oct 20th 1997.

¹¹Pfizer Expert Report 1997. Sertraline hydrochloride for obsessive compulsive disorder in paediatric patients. Approved Oct 20th 1997.

children on placebo showing comparable changes, a finding that only reached statistical significance when both studies are combined. In the case of the side-effect profile, there was a doubling of the rate of behavioral problems, including suicidal acts, suicidal ideation and aggression in children on Zoloft (6/189) compared to children taking placebo (2/187), and a 9% drop-out rate on Zoloft versus 3% on placebo for adverse events, but in fact 46 of 189 children on Zoloft, 24%, dropped out for one reason or another (Garland 2004).

96. The actual drop-out rates on Zoloft contrast with a lower rate of reported behavioral problems in this study compared to earlier studies on both Zoloft and Paxil. In addition it can be noted that the design in this study did not encourage detection of adverse events. In SSRI studies where side effects are more actively sought, the rates are higher. For example, in a study of fluvoxamine in anxiety, increased motor activity was found in 27% of children compared to 12% of placebo patients ($p=0.06$) (Walkup, Labellarte, Riddle et al 2001). This study in contrast to the Zoloft studies above used side effect checklists.
97. Efexor
98. In the case of Efexor, two studies have been undertaken in depression and two in generalized anxiety disorder. One study published in 1997 suggests venlafaxine was safe, and well-tolerated, but that efficacy had not been established (Mandoki, Tapla, Tapla et al 1997). However it now seems that in the combined depression studies there was an increased rate of children becoming hostile (2% v < 1% on placebo) and suicidal on venlafaxine compared to placebo (2% v 0%) (Kuslak 2003). There seems no prospect that the full findings from these studies will be published.
99. The Unraveling of the Consensus
100. In addition to a small number of publications (6 full articles with 3 abstracts) from approximately 15 randomized trials in children, there were approximately 70 publications of open studies or case reports with Celexa, Prozac, Paxil, Zoloft, Luvox and Efexor. The open studies and published double blind trials universally portrayed these drugs as safe, well-tolerated and effective when given to children.
101. In 2002, the issue of Newsweek coinciding with World Mental Health Day carried a cover feature of a depressed teenage girl (Newsweek 2002). The inside story outlined that there were 3 million depressed teenagers in the United States, and that if left untreated this would lead to high toll in substance abuse, failed marriages and careers and deaths from suicide. The article noted that there were a number of new antidepressants, such as Paxil, Zoloft and Prozac, which could help. Such articles commonly have input from PR companies working to pharmaceutical companies. The expectation in this case would appear to have been that a number of SSRIs would shortly have a license to treat teenage depression.
102. It is important to understand what licensing means in this context. It does not mean that physicians would thereafter be enabled to treat children who were depressed in a way that they had been unable to do before. It means rather that Pfizer, Lilly and Glaxo SmithKline would be enabled to convert the vicissitudes of teenage angst into an illness, one supposedly stemming from a chemical imbalance, and one that it was appropriate, indeed almost morally necessary to detect and treat.
103. There are no grounds to believe that NICE would have come to any different conclusions to TMAP on the issue of how to treat depressed children, when they in due course had gotten round to considering this issue, as they would have been called on to do had the drugs been licensed in the United Kingdom. Fate and the media intervened to ensure this never happened.
104. As a result of a Glaxo SmithKline application to the regulators for a license for Paxil to treat childhood nervous disorders, the raw data from clinical trials were lodged with a number of national regulators. Within a fortnight of seeing the raw data in response to

queries as to the events behind the term emotional lability, in May 2003 the regulators in the United Kingdom issued a warning against the use of Paxil (Seroxat) for minors. A few weeks later, Glaxo SmithKline wrote to all doctors noting that Paxil use was linked to suicidality and that withdrawal from Paxil was also linked to an apparent doubling of the rate of suicidality. Three months later, Wyeth recommended against the use of Efexor in children, in similar terms. Later that year in December, the British regulators issued a position statement in which they stated that none of these drugs, bar Prozac, had demonstrated efficacy in depression.

105. These developments led to a projected FDA hearing for February 2nd 2004. Ten days before this hearing, a working group for the American College of Neuropsychopharmacology reported that after reviewing the evidence it was the task force's view that SSRI drugs were safe and effective and well-tolerated by children (Emslie, Mann, Beardslee et al 2004)¹². The authors of this report included Emslie, Wagner and Ryan who had all been authors on study 329, and between had been authors on most of the randomized trial literature on SSRIs given to children. These three authors and their co-authors however noted that they might not be correct in their conclusions that there were no problems with SSRIs in that they had not seen the raw data.
106. Despite this move which was widely seen as a pre-emptive strike, in February 2004, an FDA hearing on the use of psychotropic drugs for children recommended strengthening the warnings on these drugs, against a background of regulatory assessments that at least 13 of the 15 studies undertaken of antidepressants in children failed to show efficacy for the drug¹³, and panel views that there appeared to be an activation syndrome on these drugs.
107. It transpired that in 1998, a SmithKline Beecham assessment of the Paxil studies, which had been completed at that time, 329 and 377, indicated that the drug did not work for depressed children, but that the data would not be submitted to the regulators, as a statement to the effect that the drug had not been shown to work for children would have a negative commercial impact¹⁴. Selected positive data, however, would be progressed to publication.
108. What lessons can be drawn from this situation which probably offers the greatest divide in all of medicine between the raw data on an issue on the one side and the published medical accounts purporting to represent those data on the other?
109. First, this divide gives the lie to a body of close to 100 papers and abstracts universally reporting the benefits of these drugs. These open and randomized trials it would seem have the appearances but not the substance of science. The discrepancy between the

¹² This was initially only available through GYMR, a Washington based public relations company, who specialise in translating the language of science and medicine into the more understandable language of health. From GYMR.com, GYMR was "founded in 1998 by a team of experts in healthcare and social change.. [it] offers clients marketing and communications expertise that strategically support public policy goals... [clients] include many of the nation's most respected associations, government agencies, pharmaceutical companies, philanthropic organizations and health initiatives." "Whether it's provoking action on a national health issue or crafting an organizational image that appeals to internal and external audiences, GYMR excels at designing and implementing issue and image campaigns." "Our media events are successful because we have a nose for news. We know how to take the language of science and medicine and transform it into the more understandable language of health. We advise clients of the best dissemination strategy for their news and make sure that the message they deliver is compelling, documented and contributes to other national dialogues in a real and meaningful way."

¹³ www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.htm

¹⁴ Central Medical Affairs Team. Seroxat/Paxil. Adolescent Depression. Position Piece on the Phase 111 studies. October 1998. SmithKline Beecham Confidential Document, available from the author. This is also available on the Canadian Medical Association Journal Website.

papers and the underlying data may stem from the possibility that many if not close to all of the key studies have been ghost-written. It is difficult to avoid such a conclusion when even the notional authors of the key papers claim not to have seen the raw data.

110. It follows from this that it is almost impossible to accept that these are scientific papers. What the field would appear to need is a new term with which to designate such infomercials, and a set of criteria that might reliably identify this new genre of marketing product that aims at manufacturing a clinical consensus. This it should be noted is the aim of all good marketing – to own the market, not just to sell the product (Applbaum 2004).
111. A second point is that while pharmaceutical companies know exactly how many prescriptions have been issued and just what each physician writes, almost no-one knows how many children or adults are on any psychotropic drugs. When this fact is allied to the fact that serious adverse events are reported by physicians to regulators in no more than one in one hundred cases, a picture emerges in which Americans and others track the fate of parcels put in the post 100 times more accurately than they track the occurrence of adverse events on these drugs. The quality of the information reported by patients on adverse events indeed would appear to be much better than that reported by physicians (Herxheimer and Mintzes 2004). This is a situation that could not have been tailored better to maximize the consensus building capacities of pharmaceutical companies.
112. There would appear to be reasonable grounds to state that there must be some fundamental opposition between marketing and science in that the former explicitly operates to build consensus, while the latter supposedly moves forward by fracturing consensus. When we have arrive at a situation in which the mental sets of clinicians have been captured so that it is difficult for them to conceive of alternatives to those being sold to them, there are reasonable grounds to state that such a field is no longer scientific. When there is almost no possibility of discrepant data emerging to trigger a thought that might be unwelcome to the marketing department of a pharmaceutical company, these marketing capabilities would seem appropriately described as totalitarian.

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154. Table1: Incidence of Suicides and Suicide Attempts in Antipsychotic Clinical Trials drawn from Regulatory license applications

	Number of Patients	Number of Suicides	Number of Suicide Attempts	All Suicidal Acts as %
Risperidone	2,607	9	43	2.00%
Comparator	621	1	5	1.00%
Placebo	195	0	1	0.50%
Olanzapine	2,500	12	?	?
Comparator	810	1	?	?
Placebo	236	0	?	?
Quetiapine	2,523	1	4	0.20%
Comparator	420	0	2	0.48%
Placebo	206	0	0	0.00%
Sertindole	2,194	5	20	1.14%
Comparator	632	0	2	0.32%
Placebo	290	0	1	0.34%
Ziprasidone	2993	6	?	
Comparator	951	1	?	
Placebo	424	0	?	
Total				
New Antipsychotic	12,817	33	(72	1.0%)
Comparator	3,434	3	(10	0.6%)
Placebo	1,351	0	(2	0.3%)

The data here comes from FDA medical and statistical reviews of risperidone, olanzapine, quetiapine and ziprasidone and from Lundbeck pharmaceuticals in the case of sertindole. Analyzing the data on suicides using an exact version Mantel Haenszel procedure and a one-sided test for significance yields an odds ratio with a Confidence Interval of (1.0825, Infinity), $p = 0.03955$, for new antipsychotics compared to placebo.

**E-MAIL CORRESPONDENCE
WITH ANUJA PATEL**

Dear Dr. Healy,

Thank you for your email. Unfortunately, I am unable to mail your submissions to the committee in advance of the September 13-14 meeting as the deadline was August 23, 2004. However, you may submit your comments to the Docket listed in the Federal Register (FR) Notice. The Docket will remain open until July 2005. Below is the link to the FR notices which includes instructions for submissions:

<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>

I would be more than happy to register you to speak at the Open Public Hearing (OPH) being held on September 13 between 2 PM and 6 PM. The deadline to register to speak for the Open Public Hearing is Friday, August 27, 2004, at 4:30 EST. Please email me your name, organization or affiliation, brief statement on what you wish to present, your phone number, and mailing address. Once I have received this information, I will send out a confirmation email. Unfortunately, I am unable to give you more time to speak than the other registered speakers. Time allotted to each speaker will be divided equally and will be determined after all requests for registration have been received by 4:30 PM tomorrow. Each speaker will have the same amount of time for their presentation regardless of their affiliation.

Feel free to contact me with any questions or concerns.

Kind Regards,
Anuja Patel

Anuja Patel, MPH
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-----Original Message-----

From: David Healy [mailto:healy_hergest@compuserve.com]
Sent: Thursday, August 26, 2004 1:52 PM
To: Anuja Patel; Robert Temple; Bethan Williams
Subject: PDAC hearings Sept 13-14th

Dear Dr Patel

Please find attached a letter to you and Dr Temple which should be read as a request to present at the Sept PDAC hearings on the use of antidepressants in children. Once I have a clear indication from you as to how much time is likely to be allocated I will select a section of the enclosed report on which to present further.

This attachment however is also a response to Pfizer's letter posted on your website. I would hope this response will also be posted.

There are three sets of appendices with the document involving 4

documents. You should therefore get a total of 5 documents.

David Healy

----- Internet Header -----
Sender: PatelA@cder.fda.gov
Received: from wall3-pub.fda.gov (wall3-pub.fda.gov [150.148.0.65])
by siaag2ac.compuserve.com (8.12.11/8.12.7/SUN-2.17) with SMTP id i7QJedeD005917
for <healy_hergest@compuserve.com>; Thu, 26 Aug 2004 15:40:40 -0400 (EDT)
Received: from no.name.available by wall3-pub.fda.gov
via smtpd (for mail.mx5.compuserve.com [149.174.40.183]) with SMTP; Thu, 26 Aug 2004
15:40:39 -0400
Received: from 10.11.2.117 by cdsmms01.cder.fda.gov with ESMTP (
Tumbleweed MMS SMTP Relay (MMS v5.5.1)); Thu, 26 Aug 2004 15:40:30
-0400
Received: by cdsx02.cder.fda.gov with Internet Mail Service (5.5.2653.19
) id <RTJLL9TL>; Thu, 26 Aug 2004 15:40:30 -0400
Message-ID: <D59BE0F66BB607449D3D02761D52C1F305348697@CDSX07.cder.fda.gov>
From: "Patel, Anuja" <PatelA@cder.fda.gov>
To: "David Healy" <healy_hergest@compuserve.com>,
"Patel, Anuja" <PatelA@cder.fda.gov>,
"Temple, Robert" <TEMPLE@cder.fda.gov>,
"Bethan Williams" <bethan.williams@nww-tr.wales.nhs.uk>
Subject: RE: PDAC hearings Sept 13 -14th
Date: Thu, 26 Aug 2004 15:40:29 -0400
Importance: high
X-Priority: 1
MIME-Version: 1.0
X-Mailer: Internet Mail Service (5.5.2653.19)
X-WSS-ID: 6D30E324181212-01-01
Content-Type: text/plain
Content-Transfer-Encoding: 7bit
X-Virus-Scanned: clamd / ClamAV version 0.70, clamav-milter version 0.70j

Dear Dr Patel

This is the second of two responses to your email yesterday.

I appreciate the bureaucratic framework that constrains you, but there are issues of optics here regarding which the FDA perhaps needs to take due cognizance.

The attack on me by Pfizer on your website is extraordinary, perhaps unprecedented. I am informed that FDA officials were sufficiently alarmed at the material to consult the General Counsel to the Agency, who I believe to be Daniel Troy, someone with close links to Pfizer.

Against this background, a failure of the FDA to provide an opportunity for even a limited response will certainly be seen as a case of bureaucratic inflexibility, but risks being seen as bureaucratic complicity in an attempt to stifle debate on an issue of international concern.

I would request you to reconsider your position, if only for the optics of this matter. I would imagine you have some scope to interpret my response to Pfizer as a linked posting, not necessarily bound by preset deadlines, rather than as a fresh posting which falls foul of preset deadlines.

David Healy

Dr Patel

There will be two answers to your recent email. This is the first.

I will certainly try to post the letter and material I sent you on the docket as you suggest. But I also think you need to consider other ways to handle this issue for reasons my second email will outline.

I would be happy if you could register me to speak at the Open Public Session for September 13th. My details are as follows:

Dr David Healy MD FRCPsych
Cardiff University
Hergest Unit
Ysbyty Gwynedd
Wales LL57 2PW
United Kingdom

phone 1144-1248-384452

A brief abstract of my presentation is attached. Please let me know if more is needed.

David Healy

Presentation to the Pediatric Psychopharmacologic Drugs Advisory Committee, September 13th 2004.

David Healy MD FRCPsych
Cardiff University

The current PDAC faces a scenario that is about more than whether one group of drugs causes one problem to children. The Lancet has framed the issues in terms of a crisis for Evidence Based Medicine in general. The issues also appear to intersect with bipartisan Congressional interest in tort reform.

Against this background, I will briefly present data indicating that comparable drug induced problems to those of concern in minors can be found in the trials of these drugs in adults. There is some evidence that regulators regarded the issues as a public relations matter when concerns were first raised in the early 1990s. However, I will show that regulatory responses at this time can also be framed in terms of incoherences in our methodological and statistical handling of both drug related efficacy and safety issues. I will end by proposing that there is no authority or general consensus behind FDA's, or anyone else's use of methods of handling safety and efficacy issues – that usage as it has developed is arbitrary and that the value base that might underpin a future usage that achieves general support among both the public and experts needs to be made explicit.