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The Damaging Impact of PDUFA and Why It Should be Repealed

Tuesday, 20 March 2007

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The prescription drug user fee act (PDUFA, 1992), which is up for renewal this year, linked the Food and Drug Administration to the pharmaceutical industry in a way that radically transformed the FDA from an oversight agency into a financially-dependent service provider/client. PDUFA fees pay for expedited drug approvals. Unlike other government user fee programs, the FDA negotiates with user agents-the Pharmaceutical Research and Manufacturers of America (PhRMA)-about how the agency may allocate these fees. User fees set FDA priority on speeding up the drug approval process. The re-prioritization of rapid approvals occurred at the expense of drug safety standards, and the consequences are documented by mounting drug-induced injuries, hospital emergency admissions, and preventable deaths.

What's different about psychiatry?
Indeed, more than any other field of medicine psychiatry welcomed drug manufacturers as "partners" in research and clinical practice. Psychiatry's weak theoretical foundation, uncertain boundaries of normality and disorder, and its subjective diagnostic criteria are easily manipulated to expand markets for drugs.

Psychiatry is so riddled with financial conflicts of interest: the expert panelists who established psychiatry's diagnostic guidelines (DSM-IV) in mood disorders and schizophrenia-the most lucrative market for industry- ALL had financial ties to drug manufacturers. [11] Psychiatry embraced industry's marketing claim that mental disorders were caused by a "chemical imbalance" and drugs fix that unsubstantiated "imbalance." Furthermore, psychiatry's low bar for measuring favorable treatment outcomes meant that even ineffective drugs that caused iatrogenic (treatment induced) harm would be acceptable.

Financial ties have forged a symbiotic relationship between psychiatry and industry. [12] Psychiatry has helped promote biased and misleading clinical trial reports [13] and provided industry with a shield for its hazardous drugs by interpreting drug induced manic and psychotic symptoms as "evidence of the underlying illness." The professional literature in psychiatry is overwhelmingly biased in favor of the latest patented psychotropic drugs -even as these drugs-in particular, the second generation antidepressants and antipsychotics, have failed to demonstrate a clinical benefit for most patients for whom they are prescribed. To overcome the negative findings, consensus panels have lent the appearance of legitimacy to commercially initiated prescribing guidelines. [14]

The field has also exhibited treatment mood swings which have been likened to the "bubble psychology" of the stock market. Robert Rosenheck, MD, [15] a leader in the field (professor of psychiatry and epidemiology, Yale University) who has analyzed the antipsychotic drug data, suggests that psychiatry's prescribing practices reflect an "irrational exuberance" not justified by the negative outcome data. Joanna Moncrieff, MD, (senior lecturer in psychiatry, University of London) points out that psychiatry's theories and practice are shaped by industry's interests which have pushed psychiatry into a "biological straightjacket." [16]

Psychiatry has been in denial for almost two decades about the undue influence of drug companies on their prescribing practices; about the serious adverse effects these drugs produce; about the drugs' failure to demonstrate a clinical benefit to justify the risks. Despite the compelling evidence showing that the new antidepressants and antipsychotic drugs have caused irreversible harm for some patients, [15] psychiatry defends these drugs-as though the profession's legitimacy depends on them. Indeed, U.S. psychiatrists widely and irresponsibly prescribe these drugs for children for whom they were not approved.

Only after the public learned that these drugs' safety and effectiveness were not backed by scientific evidence and that companies concealed the evidence of harm [2] [3] [17] [18]-only then did diehard defenders of psychiatry's ties to industry admit-as Dr. Michael Thase [19] (University of Pennsylvania) did-that it is no longer possible, in 2007, to argue against full disclosure and transparency: "To take such an untenable position would reflect both ignorance of the data and insensitivity to the issues involving public trust." Nevertheless he continues to accuse independent analysts who have criticized industry for its shoddy research methods with providing "negatively biased evaluations of industry-sponsored studies."

The journal commentaries by industry scientists and academics -with one exception-seem to have achieved a uniformity of focus: they affirm the need to "manage" undisclosed individual conflicts of interest but avoid any mention of enforcement mechanisms or penalties.

To borrow a refrain from Peggy Lee: "is that all there is?"

David Healy, MD [20], in his commentary, "One flew over the conflict of interest nest," suggests that there is more to it than individuals' failure to disclose conflicts of interest. The essential underlying source of corruption, he argues, is industry's hijacking of the scientific process. The overarching principles of science require transparency of both methodology and data. The legitimacy of science depends on a communal sharing of data so that claimed findings can be independently tested and either replicated or refuted. But corporate studies-and those under corporate control-fail to meet the standards of science. He argues that the apparent studies and related reviews that are at the centre of this crisis are in fact not scientific -"they are a cuckoo's egg in the nest of science." He notes that a key feature of the clinical trial reports and review articles that Fava makes reference to is that they do not conform to the central tenet of science which is to engage with issues that are replicable and/or to make the data publicly available.

The current problem for medical science involving patented therapeutics, he notes, is that a significant proportion of trials now remain unpublished and those that are published are often ghostwritten and bear an ambiguous relationship with the underlying data. "Company postings of trials on the internet do little to mitigate this problem. Indeed, an empirical

assessment by scientists from Oxford and the Cochrane Institute in JAMA (2004) concurs: To ensure transparency, planned trials should be registered and protocols should be made publicly available prior to trial completion. [1]

Dr. Healy states that the difficulties "are best symbolized by the case of the pediatric trials of selective serotonin reuptake inhibitors, where we have the greatest known divide in medicine between the raw data on an issue on the one side and the published accounts purporting to represent those data on the other.This divide, it is important to note, only came to light as a result of the efforts of journalists and lawyers. It came to light not because they chased the question of conflicting interests but because it seemed obvious to lay people that the data did not add up. To our shame, no clinician or scientist had a hand in questioning the validity of the "science".

The height of hipocrisy
In light of the contentious legal battle now being waged by Eli Lilly against patient advocates, family members, physicians, and lawyers who seek access to vital drug safety information contained in Lilly's secret Zyprexa documents, [18] a commentary by Lilly scientists, Steven Paul and Mauricio Tohen [21] who claim to support Dr. Fava's assessment exhibits the height of hypocrisy:

"The credibility of psychiatric research has been seriously compromised of late, undermined by both real and perceived - and some would argue all-too-pervasive - financial conflicts of interest (COI).. In fact, we believe the problem of financial (and other) COI could well erode the credibility of the entire enterprise of academic medicine, if not properly and promptly addressed. .the solution is not to focus solely on the funding source or potential COI. More importantly, efforts should be directed at assuring that the research methodology employed is sufficiently robust to avoid such bias in the first place."

If the Zyprexa documents had confirmed the company's claim that Zyprexa offers patients superior safety and efficacy-there clearly would be no reason for Lilly to fight their release to the public. Lilly's motives for fighting to maintain the documents under court seal are obvious to anyone who has read The New York Times reports of their content. These documents contain evidence contradicting Lilly's marketing claims: the company concealed the drug's potentially lethal hazardous effects from the public while its sales reps promoted the use of Zyprexa for children.

In an internal FDA memo, dated August 18, 1996, Dr. Paul Leber, [22] director of Neuropsychopharmacology division of the FDA, criticized Lilly's methodology in the Zyprexa premarketing clinical trials, specifically for using: "inappropriate design;" "inappropriate sample of patients;" "ill-suited titration;" high incidence of dropouts. The evidence submitted to the FDA, he stated, provided only "proof in principle" of the drug's acute antipsychotic action. Despite the absence of "robust" evidence or appropriate methodology, despite serious concerns about its safety-" No one should be surprised if, upon marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use"-in the post-PDUFA reduced standards for approval, FDA approved the drug . Thus, statements by Lilly scientists about "robust" "research methodology" are disingenuous.

In a commentary in the BMJ, psychiatrist, Stefan Kruszeuski, MD (a board member of AHRP) challenged Lilly to make good on its claim that the Zyprexa documents at issue were unfairly selective:
http://www.bmj.com/cgi/eletters/334/7586/171-a

"To avoid being hypocritical, Lilly should take the opportunity to release every clinical scientific document about Zyprexa."We physicians cannot assume to have or to provide expertise in the effects, effectiveness and adverse events of prescription medications if our fund of information is compromised by selectively-released or cherry-picked data. Since Lilly agrees with this premise in their report to the U.S. Federal Court, let's ask them to put all of the clinical data where their mouth says it should be—in the hands of physician-scientists who require it to make life-changing decisions."

Will Lilly disclose all the Zyprexa clinical trial data? If not, why not?

The hijacking of clinical research occurred with the tacit cooperation of institutional gatekeepers and clinicians. By gaining control of the entire process industry has perverted the integrity of science: protocol designs; the selection of subjects; selection of data for analysis; selection of named "authors" on ghostwritten articles based on partial data; publication in ostensibly peer reviewed journals; and dissemination of these ghost written fake reports bearing prestigious journal insignia to physicians directly and through professional societies is controlled by the drug industry. The FDA-whose mandate is to ensure that physicians and the public are provided accurate information about marketed drugs, and whose legal authority enables the agency to enforce that statutory mandate-has clearly failed to meet its public responsibility. Thus, drug companies disseminate deceptive reports masquerading as "evidence-based science" when they have

been crafted to promote rather than to inform.

What lessons can be drawn from this situation?

The obvious lesson is that none of the institutional gatekeepers that were supposed to preserve the integrity of science are meeting their responsibility. None of the gatekeepers is willing to stand up to Big Pharma because of its considerable financial clout. Instead, they are participating in a deceptive charade. Dr. Sheldon Krimsky argues for the preservation of science which must be able to correct itself, unlike religion or political ideology, which are static, doctrinaire belief systems. **"By withholding information industry violates the communitarian norm of science. It limits the possibilities of self-correction." [23]**

Dr. Healy challenges industry and science gatekeepers along these same lines: "If companies want to market their product under the banner of science, they can be required to conform to the norms of science. This will require journal editors and academic meeting organizers to refuse publication to articles or presentations on data not freely accessible. Taking a stand like this will challenge the conflicts of journal editors and meeting organizers, but this rather than conflict of interest declarations from individual academic authors or speakers is much more likely to have teeth."

He pulls the blinders that shield industry's tactic-including commentators employed by Lilly who readily acknowledge the problem in terms of individual academics' failure to disclose their competing financial interests, but avoiding the necessity of holding accountable those who conceal data or disseminate false and deceptive reports. Although individual academics' non-disclosure may reveal a lack of personal integrity, it does not itself corrupt the integrity of the science:
"If I were employed in a company marketing department I would much prefer to have the field think that all that is wrong is that a few corrupt academics fail to declare competing interests than to have the field think that company practices that restrict access to data while still claiming the moral high ground of science are the real source of the problem."

FDA's gatekeeping authority
The FDA was established to hold industry in check, to protect the public from harmful foods, drugs and cosmetics. FDA's gatekeeping authority is enormous-if the agency used its authority. The FDA has in its possession the data that is concealed from prescribing physicians-and it has the authority to withdraw a company's marketing license. Therefore, the FDA bears the greatest responsibility for drug-induced preventable injury and deaths-and it bears a measure of responsibility for the credibility crisis in medicine. If the FDA were performing its regulatory function as the public watchdog companies would not engage in fraudulent marketing for fear of losing their license.

A recent example involving the withholding of psychiatric drug data confirms this assessment:

"Calling the Piper's Tune" by David B Menkes, MD, [24] describes the "perverse effects of disclosure." Dr. Menkes was asked to comment about an open label clinical trial conducted in an underdeveloped country. The study was sponsored by a major pharmaceutical company; the study report and the commentary were provisionally accepted for publication in Primary Care Community Psychiatry. **http://www.librapharm.com/headeradmin/upload/0185C_3.pdf**
But the report was withdrawn without explanation, and the commentary was stripped of the specifics-including deletion of the name of the sponsoring company.

Ironically, Dr. Menkes notes that financial disclosure requirements have sometimes had a "perverse effect." Most of the study authors in this study were acknowledged employees of the company. Others were said to "have no conflicts of interest to disclose," which he finds perplexing since any personal or professional consequences of their involvement were not specified while the statistical analysis by another named individual was acknowledged, but no information given regarding their employment.

The case underscores the fact that journal disclosure requirements-much like the published reports-can be manipulated to serve a marketing purpose. In fact they can be used to deceive rather than to disclose.

*A follow-up Infomail will address cases of scientific fraud and research misconduct in other medical fields.

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