

5. Prozac Politics:

How a Drug Helps Us to Understand Transparency in the Health Sector

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Introduction

Not less than 25 years ago, when people faced sadness and depression, they would remain isolated in their homes, unable to redirect themselves back into life and society. When their all-encompassing grief turned out to be too much to bear, they would seek either professional help or would be taken to a mental institution, where professionals would eventually teach them how to cope with their aggravated thoughts. This was then, before 1987. This was before a new psychiatric medication revolutionized the treatment of depression. And it was before we knew that, only 20 years later, this drug would give impetus to a major discussion about transparency in the health sector.

1987 was a year that saw one of the biggest turning points in the history of psychopharmacology – or so it seemed. It was the year in which scientists launched the introduction of the most famous new-generation antidepressant drug: *Prozac*, or fluoxetine in its generic form. Initially, the drug spawned a significant economic benefit for its manufacturer, *Eli Lilly and Company*. But, as more antidepressants entered the arena, the drug's success declined slowly but steadily. In 1997, Lilly could not help but initiate a fresh \$20 million campaign to catch up with the sale rates of Prozac. It would be the first in the history of psycho-pharmaceuticals that directly appealed to individuals and their heavy emotional burden.

The commercial, here to the right, used contrasting visual metaphors to reach out mainly to those individuals who had not yet sought medical assistance. By showing that



Prozac Campaign, Eli Lilly and Company, 1997

the world looked brighter with a daily dosage of Prozac, the strategy worked. “After the ads broke, Prozac had a new likeable personality, consumers asking for the drug by brand name nearly doubled, from 45% to 88%”,¹³ and the number of prescribed antidepressant drugs increased threefold (House of Commons Report, 2004). During the next decades, the number of people diagnosed with the mental disorder rose drastically. Today, major depression is estimated to affect 121 million people worldwide. Following heart disease, the World Health Organization ranks the mental disorder as the second leading cause of lifelong disability,¹⁴ with more than 40 million people on this planet are currently taking Prozac¹⁵ (Comer, 2007; World Health Organization 2011). The depression epidemic, as Trudy Dehue (2008) later came to call this phenomenon, was born, and it set the tone for the general paradigm in psychiatry in Western society.

While Prozac initially came to be termed the ‘wonder-drug’ for adults suffering from depression, the trend inevitably spread to the treatment of the pediatric population – that is, to children and adolescents aged 8 to 17 years. In 2003, however, America’s main drug regulator – the Food and Drug Authority (FDA) – was the first to approve Prozac for this age group. But reports of the scientific community followed soon, claiming that patients under the age of 18 should not be given antidepressants. There had been disturbing evidence that Prozac’s risks outweighed its benefits and that it led to severe adverse effects, most notably aggressive and suicidal behavior. Unfortunately, their voice was only partly heard: later that same year, the British Medicine and Healthcare Products Regulatory Agency (MHRA) issued a ban on new-generation antidepressants for the treatment of the pediatric population. But while it excluded Prozac from the ban, the European Medicine Agency (EMA) thought differently: it did not only decide to join the bandwagon of prohibiting the prescription of antidepressants for children two years later, but to extend the ban to Prozac as well. Eventually, the decisions by different European drug regulators – and their clashes with the American FDA – unleashed a heated debate about secretive proceedings in the health sector that affected the industry, its regulators, the scientific community, and the patient population.

Only three years later, in 2006, the EMA suddenly approved Prozac for the treatment of children and adolescents under the condition that further clinical research was done – notwithstanding previous skepticism. And the debate continues until today. As such, it

13 Retrieved May, 15 from http://valentiadv.com/our_work/client_experience/prozac/.

14 Retrieved May, 16 from http://www.who.int/mental_health/management/depression/definition/en/.

15 Retrieved May, 16 from <http://www.guardian.co.uk/society/2008/feb/26/mentalhealth.medical-research>.

illustrates the thin line between economic benefit, consumer protection, and scientific progress, together with its mediating factor: disclosure of information or transparency. Furthermore, the case-study mentioned above serves well to highlight the shallow proceedings in the pharmaceutical industry, which, to date, remain corrupt and secretive.

Methods and Structure

This paper will be structured in three parts. The *first chapter* of this essay aims at giving a proper definition of the type of transparency we are dealing with, as the concept differs somewhat from the notions of transparency in other areas. In line with Whitaker (2010) and Dehue (2008), I assume that our society employs a drug-based paradigm which renders both regulatory bodies and the pharmaceutical industry more vulnerable to secretive proceedings. The *second chapter* elaborates on the central case-study of this essay, focusing specifically on the lack of transparency with regard to the administration behind the approval of Prozac for the treatment of children and adolescents aged 8 to 17 years in Europe in 2006. It presents a qualitative analysis of various written statements – such as directives, assessment reports, and draft protocols for clinical trials – from main American and European drug regulators concerning Prozac’s approval, supported by newspaper articles and scholarly literature. With the admittedly scarce amount of literature that revealed itself after intensive periods of searching, it seemed most reasonable to divide this essay into two different periods. The first period departs from the beginnings of the debate in 2003 and spans until 2006; the second part spans from 2006 until today, focusing on clinical studies that Eli Lilly and Company had committed itself to. In the *third and last chapter*, we will see what the case tells us about transparency in the health sector. Furthermore, it integrates different theoretical accounts and gives some general recommendations as how to promote accountability, consumer protection and transparency without influencing or hampering scientific progress in the medical field. However, as drug companies surely differ with regard to internal transparency, it should be clear that the term ‘pharmaceutical industry’ in this essay refers to pharmaceutical companies that are involved in developing, selling, and marketing medication – specifically Prozac.

Transparency in a Nutshell: Definitions and Contested Concepts

Transparency: the buzzword of our times. Although the concept is most often linked with politics, its meaning extends into other areas of equal importance, especially into the health sector. Sooner or later, we all find ourselves in need of medical treatment; consequently, we dare to lay our well-being into the hands of professionals, physicians, and pharmacists. At the same time, we assume that they will inform us about eventual complications; in other words, we expect them to be *transparent*. Unfortunately, the promotion of transparency in the health sector has proven to be difficult. Herxheimer (1995) addressed this problem and identified three main obstacles in the pharmaceutical sector that hamper steps towards more transparent proceedings. Our definition of transparency will derive from a closer examination of those.

The first factor concerns the novelty of the field of psychopharmacology. Research on side-effects of drugs has “developed slowly, and is still lagging far behind the development of clinical trials of potentially therapeutic effects” (p. xix). As scientists often do not exactly know how drugs might affect the human body in the long run, adverse reactions are hardly foreseeable. This factor turns into a serious threat for transparency as soon as it gets linked with insecurity in the industry: according to Herxheimer, there is an “unwillingness of pharmaceutical companies and drug regulatory authorities to disclose information that they are uncertain about and that might threaten a product” (p. xix). Hence, we can formulate the first component of our definition: *transparency in the health sector refers to mandatory and thorough research on both short- and long-term side-effects of a drug prior to its approval. In addition to that, it denotes open disclosure of information about the results of the studies to the patient population, regardless of other, e.g. economic, benefits.*

Another obstacle that resides in the pharmaceutical industry is “the fact that some companies [...] try to suppress the publication of information that casts doubt on the safety or effectiveness on their products” (p. xix). Even carefully conducted research projects might remain unpublished or are, in case they are accessible to the public, often suffering from selective biases. Therefore, the threat of such needs to find a place in our definition as well. Transparency thus refers to *methodologically correct and unbiased clinical test trials about working mechanisms and side effects of a drug, and complete disclosure of obtained data to the patient. This includes studies prior to approval, as well as follow-up studies intended to monitor the security of the medication.*

From what we have said above, transparency ensures the protection of human beings from corruption, deception, and physical damage that might result from insufficient studies prior to the approval of a drug or unreported long-term risk. Unfortunately, however, “the industry affects every level of healthcare provision” (House of Commons Report, 2004, p. 3), although it is supposed to ensure that “research is designed to provide objective evidence of a drug’s efficacy and safety at the time of licensing” (p. 53). Economic profit plays major role in this context: while “medical need [should] be combined with the likelihood of a reasonable return on investment” (p. 3), the interests of the industry are – on the one hand – likely to influence those of drug regulators, and – on the other – unlikely to coincide with those of the patient. Therefore, *transparency implies impartiality and hence refers to the limited influence of key subgroups on other instances*. Drug companies, for example, should not pay physicians for recommending a drug for approval by the FDA. *Furthermore, in a transparent system, these subgroups place greater priority on consumer protection than on other incentives, such as economic profit*. In an ideal situation, transparency creates an autonomous patient; one that can make a reasonable decision about his own medical situation and treatment methods because he is provided with accurate information on the risk-benefit ratio of any drug.

Some scholars have argued that “markets and deliberative processes do not automatically produce all the information people need to make informed choices among goods and services” (Fung, 2007, p. 6). As scientific research breaks into the unknown, we become more and more reliant on medication; hence “transparency is critical to the sustainability of health systems in the future”.¹⁶ Only when individuals and patients can make well-grounded choices about healthcare – and an agreement to a treatment based on psychiatric medication, for example – “providers will improve the quality of care they deliver, government and other reimbursers can reward quality and efficiency, and consumers will assume a greater role in the management of their own health” (ibid.). Unfortunately, as we will see in the next chapter, the promotion of transparency in the health-related industries has been burdensome.

16 Retrieved June, 10 from http://www.asianhnm.com/healthcare_management/transparency_health-care.htm.

Prozac Politics:

How Prozac came to be Approved in Europe

Burdensome Beginnings: The First Period, 2003 - 2006

Decisions on drug approval are based mainly on the conduction of clinical test trials that report the medical efficiency of a drug (Turner et al., 2008). The general idea is to compare a new drug against pseudo-drugs, so-called placebos. The FDA approved Prozac for the treatment of children and adolescents in 2003 based on two such trials,¹⁷ which had revealed serious side-effects for the pediatric population. Surprisingly, the FDA did not attempt to deny those: “is very clear [...]”, so the regulator in a report of late 2004, “that the period after anti-depressant therapy is started is one in which suicidal behavior and thinking is frighteningly common”.¹⁸ Furthermore, it emphasizes that the “clinical significance of these findings is unknown at this time”.¹⁹ In general, we can infer that the FDA approved Prozac for children notwithstanding its severe side-effects or unknown long-term prospects. But let us go back to late 2003, when the British drug regulatory body – the MHRA – decided to publish a reaction to the previous statement that turned heads in the media. After reviewing clinical trials that had been conducted in the 1990s, the message of the British watchdog on drug safety was clear: doctors were going to be prohibited to administer new-generation antidepressants to children and young adolescents on the island. However, the ban did not include the famous wonder-drug of the 1980s, Prozac.

In a statement of September 23, 2004, Robert Temple – then-director of the Office of Medical Policy at the FDA – condemned Britain’s decision. In his report, he calls this conclusion “premature” and a “disservice to the public health given the serious and potentially life-threatening nature of severe depression”.²⁰ That is, the FDA justified the approval by stating that “there are no acceptable therapeutic alternatives for health care providers and their pediatric patients with depression” (ibid.) and concluded that it would be more reasonable to prescribe a drug with serious side-effects than none at all.

17 Retrieved June, 12 from <http://www.docguide.com/fda-approves-prozac-pediatric-use-treat-depression-obsessive-compulsive-disorder>.

18 Retrieved June, 12 from <http://www.fda.gov/NewsEvents/Testimony/ucm113265.htm>.

19 Retrieved June, 14 from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=14>.

20 Retrieved June, 16 from <http://www.fda.gov/NewsEvents/Testimony/ucm113265.htm>.

This line of reasoning came to represent the general position of the FDA in the Prozac-debate, according to which the risks of untreated depression were greater than possible physical long-term damage caused by antidepressants. Only a few months earlier, at the end of March, the FDA had issued a public document stating that the regulator “has not concluded that these drugs cause worsening depression or suicidality”. If we imagine a random patient reading these lines, he would most likely conclude that research had not shown these side-effects to occur frequently; he would believe that the warning is just a sensitive precaution on behalf of the FDA. However, in contrast with that, the statement simply – and probably intentionally – omits very important information: the FDA could not conclude that Prozac caused these side-effects for the simple reason that it *had not conducted any prior studies on it*. Therefore, we can conclude that the warning is highly misleading for any individual seeking information about the drug, and also for parental guardians who are making a decision on behalf of their children.

Children and adolescents on the European continent were next when the Swedish Medical Products Agency (MPA) entered the debate. In its comment on an assessment report dating April 2005, the regulator confirmed that there were some very serious concerns with regard to side-effects, but basically agreed that Prozac should be approved “provided commitments of further studies”. This time, the explanation for recommending the approval of Prozac hinted at the fact “that SSRIs, including fluoxetine, are used ‘off label’ in children and adolescents, and approving its use allows for providing treatment recommendations, better post marketing surveillance in these populations and possibilities to request further studies” (p.1).²¹ In short: children should, so the MPA, be given Prozac not because research on adverse effects could be done only *after* administering it to the pediatric population, and hence after seeing what long-term side-effects young patients naturally would experience.

In a striking article of the German newspaper *Die Zeit* in October 2006, it was argued that off-label prescriptions – “the use of drugs [...] in unapproved subpopulations, e.g for depression in children” (Stafford, 2008, p. 1427) – indeed reflect the “grey market of medicine”. *Die Zeit* concluded that no less than 50% of all drugs that were approved for adults had been tested for its effects on children²² and that off-label prescriptions were, until mid-2000, a common practice for several reasons. As research into the domain of adverse side-effects of psychiatric medication for children and adolescents lagged behind,

21 MPA, Mutual Variation Recognition Response Report, UK/H/636, April 29, 2005.

22 Retrieved June, 6 from <http://www.zeit.de/2006/36/MS-Kinderarznei>.

patient information leaflets did not contain warnings for the pediatric population. Physicians often had to estimate the appropriate dosage of the drug for their little patients, helping some of them, yet putting others at risk. Nowadays, estimates show that 10 to 30% of the children receive medications off-label from their physicians. The question whether this is an appropriate practice remains an ethical one, but it clearly refutes our definition of transparency and accountability and defies the idea of an autonomous patient. Not only are physicians and psychiatrists more likely to accept financial compensations from responsible drug companies; medications that benefit adults might severely damage youngsters, and might even lead to fatal reactions. In fact, research has shown that the risk of serious adverse-effects is 1,5 to 3 times higher in off-label prescriptions (ibid.). For the European Medicines and Health Agency (EMA), off-label prescriptions were not a valid argument. In contrast with the MPA, it found the concerns regarding increased suicidality in children highly disturbing; a disagreement that, as stated in a newspaper *The Independent*, put the EMA “on a collision course with Britain’s drugs regulator”.²³ This collision course needed to be resolved, and it was the Dutch Medicines Evaluation Board (CBG) that was responsible for evaluating the eventual approval of Prozac for the pediatric population in Europe in 2005.

The answer in the Rapporteur’s assessment report of October 2005²⁴ was straightforward: it claimed that administration of Prozac to the young population not only increased suicidal behavior, but that it also had adverse long-term effects on sexual, cognitive, and emotional development. The statement opens by saying that “it is not recommended to grant an indication to fluoxetine for the treatment of depression in children and adolescents because the benefit/risk balance in the claimed indication is deemed negative” (p. 34). Apart from the clinical concerns, the Board raised some questions about the research methodology that had been employed to prove any beneficial effect of Prozac, revealing another transparency gap that the company had been trying to conceal. Upon closer examination of test data, the CBG had found that “the patients population [...] included in the trials [was] a highly selected group [and] not likely to be representative of the total depressed patient population” (p. 9). That is, the results of the test trials that the FDA had used to justify the approval were . Furthermore, we have to keep in mind that “also non-significant increases [...] might represent a serious risk” (p. 11). As a perfect example of incorrect studies, it is needless to say that this directly goes against our definition of

23 Retrieved June, 22 from <http://health.groups.yahoo.com/group/pfpcnews/message/392>.

24 The Dutch Medicines Evaluation Board (CBG), Joint Assessment Report, 6 February 2006.

transparency. It is highly likely that the regulator chose to proceed behind closed doors in order to push through a dubious drug for the treatment of the pediatric population, which had – under strict medical and scientific standards – been impossible. In the light of all these concerns, the Dutch Evaluation Board urged the FDA to conduct more accurate research projects. And the latter declined.

The FDA rejected to conduct studies on adverse-effects on several grounds. First, it argued that it would be difficult – if not impossible – to study long-term implications of Prozac on sexual maturation in humans. They stated that such a study would be “unacceptable to patients, parents and investigators and [would] not likely to be approved by ethical review boards” (ibid., p. 12). Second, the FDA found that, “due to the negative publicity about SSRIs, the company now foresaw recruitment problems and claimed that it would be unrealistic to expect that the study could be finalized within the requested time frame” (p. 11). Instead, the FDA released data of some retrospective studies. Unfortunately, the Dutch Medicines Evaluation Board concluded that “the results of this study [were] not presented”, and that some “results from the company’s adverse event data-base [were in fact] presented but rendered as inconclusive” (p. 8). In general, we can infer that the FDA tried to somehow circumvent the possibility of any release of data that would prove the drug’s risk for the pediatric population. Therefore, the CBG concluded that “the responses do not provide any assurance that these issues will be explored in the future by the company” (p. 12). The Board’s criticism basically illustrates what had been described quite accurately in the House of Commons Health Committee Report of 2004. Here we read the following:

“We heard allegations that clinical trials were not adequately designed – that they could be designed to show the new drug in the best light – and sometimes fail to indicate the true effects of a medicine on health outcomes relevant to the patient. We were informed of several high-profile cases of suppression of trial results. The suppression of negative clinical trial findings leads to a body of evidence that does not reflect the true risk-benefit profile of the medicine” (p. 3).

In light of all these issues, we would naturally expect additional clinical trials to be conducted in order to shed light on the matter at hand. We would assume that those regulators arguing in favor of the approval of Prozac would conform to the reasonable opinion of the majority, the Rapporteur’s opinion to weigh heavier than superficial arguments, and that there would be a serious attempt to protect children who are too young to make autonomous decisions about alternative treatment methods. But none of this ever happened.

The first of June, 2006 turned out to be a historical moment in the history of psychopharmacology and for the general debate about transparency in the health sector. Notwithstanding previous concerns of several European member states, the EMA suddenly approved the use of Prozac for depressed children and adolescents aged 8 to 17 years. A Question and Answer Sheet accompanied the decision. Here, it states that the Committee for Medicinal Products for Human Use (CHMP) “gave a positive opinion to extend its use in the treatment of children suffering from depression, provided that the marketing authorization holder (MAH), Eli Lilly, carries out additional studies to ensure that the safety profile of Prozac remains acceptable”.²⁵ In short: Prozac was unexpectedly approved for the psychiatric treatment of the pediatric population given the condition that follow-up studies on risks and side-effects would be conducted in the future; studies that had, in the few months before, been rejected by Lilly due to reasons mentioned above.

The EMA soon came up with an explanation: the data that led to the decision to approve Prozac for the treatment of young people had been extracted from different sources, including databases and scientific journals. The conclusions are surprising: while “the studies in children and adolescents showed a positive effect”, they acknowledged that “doctors and parents should carefully monitor [them] for suicidal behavior” (ibid.). They concluded that the “benefits of Prozac are greater than its potential risks for the treatment of moderate to severe major depressive episode in children and adolescents”; a statement that clearly contradicted their original position. As the arguments for the approval of Prozac had basically not changed since 2003, the European drug regulator had undergone a transformation that remains rather elusive. The commitment to conduct post-licensing studies on behalf of the FDA brings us to the second half of this chapter, in which we will take a closer look at what happened after Prozac had been approved.

(In)Transparency continued: 2006 until Now

In the Dutch report of 2005,²⁶ the Rapporteur had been concerned about the effect of Prozac on sexual and cognitive maturation in youngsters. Lilly replied with a research proposal for a future study directed at investigating these effects in late 2006. However, the British MHRA urged for some answers concerning methodology and design of the

25 Retrieved June, 22 from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Prozac_6_12/WC500013226.pdf.

26 The Dutch Medicines Evaluation Board (CBG), Joint Assessment Report, Referral EMEA/H/A-6(12)/671, 6 February 2006.

follow-up.²⁷ In the Joint Assessment Report of the Dutch Medicines Evaluation Board of February 2006,²⁸ we get the uneasy feeling that the FDA did cooperate much in order to push through a concrete study. The conclusion of the report again states that “there are insufficient data for positive benefit/risk” (p. 8), and that Eli Lilly should be invited to address several unanswered issues. In September 2006, it published a report that refined the terms for the follow-up study concerning sexual maturation under treatment of Prozac in children.²⁹ In the next paragraph, we will look at the dialogue that took place between Lilly and the MHRA as a response to the research plan. Interestingly, the MHRA came to serve as Reference Member State (RMS) for the case, meaning that its decision on the approval of Prozac would be mutually recognized by other member states.³⁰

Shockingly, the assessment report³¹ reads as testimony revealing the unethical attitude of the company. Here, it states that the exact research method “have not been finalized” (ibid., p. 5). Furthermore, instead of conducting a five-year study, Lilly now stated that “the study [would] consist of 12 weeks [...] treatment” (p. 6). As if this was not enough, it also refused to conduct an analysis of blood samples that would otherwise be helpful in assessing the negative effect of Prozac on hormonal growth. As an explanation, the company argues that it “does not believe that [this] is an ethical and/or viable addition” to the proposed study. We can hardly believe that Eli Lilly regards regular blood tests to be less ethical than the prescription of drugs whose long-term risks have not yet been assessed. In turn, the MRAH replied by saying that “the [company’s] refusal to take the opportunity to assess effects of [Prozac] on emotional and behavioral development in children is not considered ethical”. In general, the conclusion of the communication between the company and the MHRA is highly disappointing: out of 12 outstanding issues, 10 could not be resolved.

The rejection of the FDA’s proceeding by the MHRA set in motion a whole series of documents that tried to solve the questions on which no agreement had been found. The MHRA published a second assessment report³² in March of the same year, which included an approval based on conditional changes that would have to be implemented by Lilly.

27 MHRA, Response Assessment Report, December 12, 2006.

28 The Dutch Medicines Evaluation Board (CBG), Joint Assessment Report, Referral EMEA/H/A-6(12)/671, 6 February 2006.

29 Eli Lilly, Draft Protocol, TADSjr, September 29, 2006.

30 Retrieved September, 6 from <http://www.pharmacovigilance.org.uk/tag/reference-member-state/>.

31 MHRA, Response Assessment Report, December 12, 2006.

32 MHRA, Response Assessment Report 2, 1 March 2007.

Amongst others, the company would now, so it reads, agree on the additional inclusion of hormone levels to assess the side-effects of Prozac on sexual maturation. All in all, the report resolved five issues but left another five for further discussion. Lilly responded once more in mid-April 2007, stating that the company is “eager to fulfill the follow-up measures committed to in the Letter of Undertaking, dated 31 May 2006, and believes that this communication brings us closer to resolving the outstanding issues” (p. 9).³³ As we will see later, it did not.

It was not until July 19, 2007, that the MHRA could issue a final assessment report³⁴ and hence approve the studies that had initially been planned by the company. We have to note that it took more than one year to agree on the methodological and organizational aspects – that is, only on the exact research plan and design – of a study that had been conditional for the approval of Prozac for the pediatric population in Europe. One year passed and no study had been conducted, no results had been published, and not a single statement about adverse effects and long-term risks for young people had seen the light. So much about transparency and accountability within the pharmaceutical industry and its companies, and so much about their influence on regulatory bodies.

The big blow came in September 2009 when, after all the correspondence of the years before, Lilly requested “*that the post-authorization commitment to clinically evaluate the effect of fluoxetine on sexual maturation to be considered fulfilled*” [my italics], and hence the MHRA surprisingly admitted that “the studies [would] not be conducted because of lack of funding”. The MHRA justified its decision by stating that “any clinical study to investigate the effects of [Prozac] on sexual maturation would be forbiddingly hard to conduct and difficult to interpret [... and it] therefore recommended accepting the company’s request that the [obligation] to clinically evaluate the effect of fluoxetine on sexual maturation be considered fulfilled” (p. 3). It is hard to grasp what is happening here: while the approval of Prozac itself had – in the light of missing supportive evidence in favor of the drug – been hard to justify, the post-commitment to further research on side-effects was now simply being disregarded. In fact, the post-licensing procedure was to be fulfilled *without any* further studies. This closely resembles what we can read in the House of Commons report, which emphasizes that the British regulator often “fail[s] to adequately scrutinize licensing data and its post-marketing surveillance is inadequate” (2004, p. 4).

33 Eli Lilly, Response to MHRA, April 12, 2007.

34 MHRA, Final Assessment Report, 19 July 2007.

So far, our analysis presents an interesting development. While the FDA approved Prozac in the U.S., the European Medicines Agency opposed the approval, but ended up lifting its ban on antidepressants for children and adolescents in 2006 – notwithstanding warnings of the scientific community. Eli Lilly had agreed to conduct further studies to shed light on side-effects. Yet, after months of negotiation on the design of the studies, the RMS concluded that this would be a difficult undertaking and hence granted Lilly's commitment to be fulfilled. We will know elaborate in more detail on the conclusions we can draw about this incident, and the implications for our discussion of transparency.

What can we learn from this Debate?

What the Case tells us about Transparency

For now we can infer that the incentive of economic benefit was surely one of the main reasons for the industry's proceedings in our case-study. First of all, by delaying – and ultimately, canceling – the studies that were initially needed for the approval of Prozac for children, Lilly was able to raise a significant amount of money: the *Wall Street Journal* estimated that the company's income lay around 800 million dollars, not including the benefit that derived from prescribing the drug to adults.³⁵ But let us dig a bit deeper and see how exactly Eli Lilly pushed buttons to enhance their economic benefit and influenced other drug regulators to join the bandwagon of approving Prozac.

There are various explanations as to why Eli Lilly kept reluctant to conduct the studies that it had committed itself to. One of them concerns the relatively small size of the market for psychiatric medication for children. The company probably did not want a lot of money to flow into a project that concerned only a small percentage of the patient population, and that would – most likely – not yield any supportive results anyway. Furthermore, the actions by the industry were also likely to be motivated by its previous miscalculations with regard to approval of drugs that later turned out to have severe, harmful effects. Ever since the scandals around Contergan in the 1980s, the industry has increasingly been reluctant to conduct studies that might reveal serious side-effects of a drug. Since these proceedings hamper scientific progress in the medical field, two publications have recently gained a lot of attention. Turner et al. (2008) and Johnson & Kirsch (2008), wanted to shed some light on the secretive proceedings of the FDA by investigating unpublished results of the directories of the regulator.

35 Retrieved July, 15 from <http://blogs.wsj.com/health/2009/07/31/eli-lillys-payments-to-doctors-revealed/>.

Johnson & Kirsch (2008) conducted a meta-analysis on the treatment effect of four new-generation antidepressants – including Prozac – whose clinical data trials had been submitted to the FDA a few years ago. They revealed that Prozac was not at all efficient for the treatment of light or mild depression; more concretely, antidepressants only had a positive effect in individuals who suffer from severe depression: “drug–placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients” (p. 261). It seems that both Eli Lilly and the FDA have mysteriously failed to notice that the benefit of their bestseller-drug “falls below accepted criteria for clinical significance” (p. 261). It is obvious that, in case Lilly and the FDA had considered the whole range of data, they would not have been able to justify the approval of Prozac at all. And Johnson and his colleague reveal even more: not only is the treatment effect very small; in case there *is* a treatment effect, it is *unlikely to be caused by the medication itself*. Instead, it has to be attributed to the subject’s belief that a placebo he is taking is, in fact, a drug that helps to treat his or her depression.

Johnson’s findings illustrate a fundamental problem with regard to transparency in the pharmaceutical industry: the so-called reporting bias, which was also criticized by Turner (2008). The authors obtained reviews from the FDA for clinical trials of 12 antidepressant drugs. In total, the studies involved an incredible number of more than 12.000 patients that had been treated with antidepressants. In the following, they compared both the published outcomes with the FDA outcomes, and the effect size of all clinical trials as published in the literature and those derived from the entire FDA data set (p. 252). This time, the results revealed a striking bias towards *significant data* as well: more than 30% of the studies had not been published *at all*. This reflects what the House of Commons had already criticized in their report, according to which the regulators “are [...] subject to influence by the pharmaceutical industry [and thus] many articles do not present an objective assessment of the merits of a medicine; for instance [...] there is a bias towards submission of articles that show new drugs in a positive light” (2004, p. 54). Again, we see how Lilly influenced the regulators, especially the FDA, which then has enough power to affect the decisions made by regulatory bodies in Europe. And while the scientific community is raising its voice, their concerns do not at all touch upon the ethical standards of the industry.

Yet both studies have found a relatively broad response in media. In that sense, they showed that “many clinical trials are designed to fit desired outcomes or, worse, primarily for marketing purposes, rather than the advance of health care or scientific understanding” (2004, p. 50). Second, the case illustrates the wide-ranging area of influence of the pharmaceutical industry, which “can run 10 or more trials in carefully

selected samples using instruments designed to pick up any effect and, even if the results show that the drug failed to beat placebo in the majority of trials, the drug may still be licensed". Similarly, "trials producing negative results are commonly identified as failed trials rather than drug failures" (p. 51). Now, "if pharmaceutical companies only publish clinical research that is positive and hold back on publishing clinical research which is negative, then patients may well be given treatments which are likely to do more harm than good" (p. 57). Sadly enough, the industry does not even seem to shy away from 'innocent' patient populations, such as children or adolescents. And the issue gets worse: earlier this year, Danish medical researcher Peter Gøtzsche planned to conduct a study on unpublished test trials regarding the effect of fluoxetine on children, but encountered severe problems when he contacted the MHRA and EMA. Upon request of data, the British drug-regulator responded by stating that it destroys data from clinical test trials after 15 years "unless they are needed for 'legal, regulatory or business' reasons, or unless they are considered to be of 'lasting historic interest'".³⁶ Here, we should remind ourselves that the MHRA had even served as the Reference Member State for the approval of Prozac for the treatment of the pediatric population in Europe. Gøtzsche states disappointedly that the regulators' behavior "makes it impossible for independent researchers to correct the 'seriously flawed publication record'" (ibid.). Besides that, children, adolescents, and their parental guardians unwillingly get caught in a twisted machinery of secretiveness, corruption, and the unaccountable and unethical proceedings of the pharmaceutical industry and drug companies. And so the next question arises: how can we increase or promote transparency in such a sensitive area?

How to Increase Transparency in the Health Sector

From the case study above, we saw that the main drug-releasing bodies sadly seem to constitute a huge obstacle to an honest and open administration behind drug approval. One reason for this is that they "have been too close to the industry, a closeness underpinned by common policy objectives, agreed processes, frequent contact, consultation and interchange of staff" (House of Commons Report, 2004, p. 4). It is not surprising that it is exactly this closeness between the regulators and the drug industry and companies that needs to be overcome if we were to change the status quo.

Obviously, the ideal goal would be to disentangle regulatory bodies from the influence of the industry. Considering its wide-ranging impact, the starting point should lie with

36 Retrieved August, 5 from <http://www.medscape.com/viewarticle/746109>.

the Food and Drug Authority. Our case-study illustrated the main reason for this: being influenced by individual drug companies – such as Eli Lilly – the FDA currently holds a monopoly on drug access and regulation; a monopoly whose tentacles extend into the decision-making processes of European drug regulators as well. Backed by the industry, the FDA was able to expand both by means of their victorious advertisement campaigns in the late 1990s, but also – as Madden (2004) states – due to “well-publicized episodes of unsafe products to promote pro-expansive legislation” (p. 64). Currently, the FDA has to agree with drug companies on warning labels for medications that are rendered to have severe side-effects. A recent survey conducted by *Consumer Reports* shows that more than two thirds of all Americans are afraid “that drug companies actually pay the FDA to review and approve their drugs, [...] a situation that turns drug companies into the ‘customers’ of the FDA”.³⁷ Therefore, we have to eliminate the deep concern about the impartiality of those working for the FDA by ensuring that “doctors and scientists with a financial conflict of interest should not be allowed to serve on FDA advisory boards” (ibid.). In fact, physicians can significantly raise their income by accepting so-called ‘consulting-fees’ from drug companies and physicians with ties to individual drug-companies are even entitled to vote positively in the FDA for approval of their drugs. Unfortunately, “there is not even any FDA requirement to disclose such conflicts of interest” (ibid.). It would be a start to decrease and limit the amount of money a physician can receive by means of these recommendations, although, ideally, doctors would not be allowed to accept payments from drug companies at all.

From what we have learned so far, it does not surprise us that “more research [must] be undertaken into the adverse effects of drugs, both during drug development and medicines licensing” (2004, p. 5). This can only be done by implementing changes in the registry and result-database of the FDA. Speaking of now, the FDA has a considerable amount of control about what information sees the light. Additionally, we need to consider the “limitations of existing post-marketing surveillance systems” (p. 88), which have been – as we have shown – often insufficient or purposely kept secretive. As a matter of fact, “approximately 90% of clinical drug trials and 70% of trials reported in major medical journals are conducted or commissioned by the pharmaceutical industry”.³⁸ This, in turn, limits the role of the scientific community: “inevitably the industry not only has

37 Retrieved August, 15 from <http://www.americanchinesemedicineassociation.org/Americans%20Fed%20up%20with%20Drug%20Industry%20Influence%20and%20FDA%20Corruption.htm>.

38 Retrieved September, 16 from <http://www.globalissues.org/article/52/pharmaceutical-corporations-and-medical-research>.

a major effect on what gets researched, but also how it is researched and how results are interpreted and reported” (House of Commons Report, 2004, p. 44). One important factor that might help to increase transparency is the licensing process. Their advise is to “establish a clinical register, but it is important that it should be independent” (p. 5). Furthermore, as we have seen, the latter is especially important as post-licensing regulations can grant drug-regulators time – a buffer so to say – in which simply no research is being conducted.

If we were able to abolish some of the corruption in the FDA and thereby increase transparency, other regulators could function independently as well – improved transparency in the FDA might lead to a ‘spill-over’ effect, eventually spreading to the scientific community, which would then have a bigger voice in decision-making processes and could serve as an advisory body for various drug-regulators. Additionally, we need to strengthen the ties between research and the government: the latter should not only promote research into adverse effects of drugs, but also “into the costs of drug-induced illness”. The government should have the authority to issue safety warnings on drugs that are rendered harmful. Fung and his colleagues (2007) add that “the government can help reduce those risks or improve services by stepping in to require the disclosure of missing information” (p. 6).

In the light of the incredible numbers of people falling prey to marketing strategies of drug companies, it also seems necessary to reconsider the role of drug advertisement, which can mislead patients and healthy individuals. In line with this, Fung states that

the aggressive promotion of medicines shortly after launch[...] and the promotional hospitality masquerading as education, in the absence of effective countervailing forces, all contribute to the inappropriate prescription of medicines (p. 7).

Medication does not, and should never be thought to, fall into the same category with other goods we purchase in our daily life, and hence it should not be treated as such. The government needs to perform regular checks and balances to planned marketing campaigns. Although this problem concerns the situation in America much more urgently, pre-cautious measures should be taken on European soil as well. Hence, Fung argues that transparency necessarily has to include “mandated public disclosure by corporations or other private or public organizations of standardized, comparable, and disaggregated information regarding specific products” (p. 8). In line with this, some have forcefully stated that “we need an industry which is led by the values of its scientists, not those of its marketing force” (p. 6). Yet we cannot simply assume that transparency is merely about the

amount of information made available to the public. Instead of overwhelming the patient with data, the promotion of transparency calls for careful moves; otherwise, “infusing a flood of information on the public can cause disruption and misunderstanding”,³⁹ thereby rendering patients immune to the idea of investigating on their own medical conditions.

All in all, the undertaking to achieve a higher degree of transparency will “require cross-sector collaboration that is unprecedented in even the most advanced health systems” (p. 90). Before we can implement concrete changes, so it seems, main stakeholders in the pharmaceutical industry and scientific community need to change their mindset. As Transparency International states, “health is a major global industry, a key responsibility and budget expense for governments and businesses; but more than that, it is a global human right”.⁴⁰ And it is beyond question it deserves to be treated like that.

Discussion and Conclusion

This essay focused on a case-study that illustrates the lack of transparency that, unfortunately, has become an indistinguishable feature of the health sector. Furthermore, it shows the impact of the drug industry on the FDA in the United States, and – in turn – its influence on European drug regulators, such as the MHRA and EMA. Specifically, we concentrated on the story behind the approval of Prozac for children in Europe in 2006. Sadly, we were unable to identify any sincere reasons that would have justified the approval of Prozac for the pediatric population on either American or European soil. Notwithstanding the doubts raised by the scientific community and the original skepticism of the EMA, the latter came to approve the drug in Europe even though there was a substantial lack of evidence for its benefits. Furthermore, the commitment to follow-up studies on behalf of the company never took place; instead, the requirement came to be seen as fulfilled a few years later, even though not a single study on behalf of Prozac’s Market Authorization Holder, Eli Lilly, had been conducted. Such unaccountable behavior renders the health sector vulnerable to secretive proceedings.

We saw the need for promoting transformations in the health sector; transformations that might initiate a cascade ultimately leading to increased transparency and accountability in a corrupt pharmaceutical industry. The last chapter of this essay concluded with

39 Retrieved June, 10 from http://www.asianhnm.com/healthcare_management/transparency_healthcare.htm.

40 Retrieved July, 23 from http://www.transparency.org/global_priorities/other_thematic_issues/health.

some general recommendations on how to do so. These included, amongst others, the disentanglement of drug companies from regulatory bodies, physicians and the scientific community, accompanied by more autonomy for the latter. Moreover, an independent database on clinical trials and side-effects is desirable, as well as a bigger role for the government. Implementing concrete changes in the relevant instances will only be the first step, however. In the long run, we are facing the challenge of moving away from the idea that every disorder necessarily has to be treated with medication. Long lingering beneath the surface of the companies, economic benefit can no longer precede ethical considerations. Children and adolescents deserve careful assessments, tight monitoring, and a sincere will to contribute to their normal development – all of which do, to a significant extent, concern the pharmaceutical industry. Undoubtedly, there is still a long way to go if we sincerely want to limit the pharmaceutical industry in their range of influence. Eventually, it seems, drug companies should finally dare to hold themselves accountable.

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