Original Article

Shadow science: Zyprexa, Eli Lilly and the globalization of pharmaceutical damage control

Kalman Applbaum
Department of Anthropology, University of Wisconsin, PO 413, Milwaukee, WI 53201, USA.

Abstract In 2002, following reports of adverse side effects experienced by Japanese patients taking the antipsychotic medication, Zyprexa, Japan's Ministry of Health, Labor and Welfare required Eli Lilly & Co. to place a new warning label on its drug and to send out a 'doctors letter'. The company feared that this would threaten its sales of Zyprexa not just in Japan, but globally. US court documents from suits against Lilly in 2006 show how Lilly focused their scientific and sales attention not on the reported side effects of their drug, but on how prescribing physicians *perceived* the side effect profile of the drug. The company actively pursued a strategy of creating a shadow science to drown out noncompany-sponsored (and competitors') research reports on the side effects of the drug. I draw on ethnographic research in Japan to describe how Lilly dealt with the threat to the brand equity of Zyprexa there, and how they sought to keep their global marketing program for the drug on course. I conclude with a discussion of the encounter between the global marketing aspiration of the firm and the contingencies associated with the Japanese environment in particular.
BioSocieties (2010) **5,** 236–255. doi:10.1057/biosoc.2010.5

Keywords: pharmaceuticals; marketing; Japan; antipsychotics; globalization; regulation

Introduction

Pharmaceutical companies are near the forefront of corporate globalization. This is so because their output is held to be the fruit of medical and pharmaceutical science, which operate on universal principles and whose importance is acknowledged everywhere. The global distribution of medicines carries the legitimating force both of science and ethics, insofar as the speedy delivery of drugs to the sick is an unquestioned good. Good medicines should 'sell themselves' insofar as their utility need not be argued.

What happens when the innovativeness or efficacy of a new drug is not self-evident? Or when the marketplace is crowded with competing drugs all backed by claims of superiority? What happens when the contexts for meaning and use, sensitivity to side effects and cost-effectiveness of treatment vary greatly according to the market in question? The existence of one or more of these considerations is the norm rather than the exception in the global pharmaceutical experience, to which the solution is more intense marketing. And the more

the above conditions pertain, either because the drug's profile is indefinite or the marketplace inhospitable, the larger the role of marketing becomes.

In this article, I depict an aspect of the global broadening and deepening dynamic associated with the marketing of Eli Lilly & Co's antipsychotic drug, Zyprexa, which was first approved for use in the treatment of schizophrenia in the United States in 1996. Since that time, the drug has been sold for use in a range of psychiatric disorders worldwide; through FY2008 it has brought US$44 billion in revenues to Lilly, with $4.7 billion in 2008 alone.[1] This staggering success has not been unmarred by allegations of equally staggering malfeasance in the marketing of the drug. A principal source of the drug's success has been its use for treating conditions beyond schizophrenia (Rosenheck and Sernyak, 2009). Over-zealous promotion for uses not approved by the Food and Drug Administration (FDA), or off-label promotion, led to an unprecedented fine of $1.42 billion in 2008. This included 'a criminal fine of $515 million, the largest ever in a health care case, and the largest criminal fine for an individual corporation ever imposed in a US criminal prosecution' (Mann, 2009). Between 2005 and 2007 the company paid out pre-tax product liability settlements of $1.6 billion, bringing the total liability costs to over $3 billion.

In the midst of the off-label scandal, lawsuits relating exclusively to the cover-up of data concerning the side effects of the drug (that is, for injuries suffered by those taking the drug for approved purposes) have also been lodged. The side effects in question are weight gain and the raising of blood glucose levels, both of which are risks for diabetes mellitus (DM) and cardiovascular disease (CDV).[2] The company documents concerning off-label promotions ordered by the court subsequently leaked, and turned out to reveal Lilly's intentional concealment of side effects data at least from 1999.

In the courts, the side effect issue has been secondary to the off-label scandal.[3] At Lilly, however, between the time the company discovered Zyprexa's liability and today, the side effect concern was (and remains, no doubt, because the drug is still on patent) of much greater importance. A review of the court documents regarding Zyprexa's marketing ('the Zyprexa documents' henceforth; see Applbaum, 2009; Spielmans, 2009[4]) reveals that a significant portion of them concern the company's attempts to minimize the damage and potential damage to the brand resulting from the drug's side effects.

Drawing on these documents, it is possible to demonstrate the variability or adaptability of Lilly's pursuit of scientific truth claims as regards Zyprexa's side effects in the United States. I will show how Lilly focused their scientific and sales attention not on the clinical characteristics of their drug as determined by their own research or that of external

1 Eli Lilly & Co. Annual Reports, available at: http://investor.lilly.com/annuals.cfm.

2 Some studies also associate the drug with hyperlipidemia, also associated with CDV (Wirshing *et al*, 2002).

3 This is likely the case for several reasons: (a) it is believed that the causal relationship of taking the drug to these diseases can be shown only statistically; (b) because all antipsychotic drugs have severe side effects (the same or different to Zyprexa, differing only by degree); and (c) because the company's argument, backed by studies it has commissioned, is that people with mental illness have a tendency to have high blood sugar and other metabolic disorder markers before they begin taking the drug. These claims have been staunchly disputed (Le Noury *et al*, 2008) but they have not, as yet, been unseated.

4 The documents are available for downloading here: http://www.furiousseasons.com/zyprexadocs.html. I have not labelled specific files in this paper, as I have drawn from a collated version and the Furious Seasons document breakdown is not systematic by theme or date. Key word searches on Google for exhibits cited in my paper will bring up the originals.

researchers, but on how prescribing physicians *perceived* those characteristics. In other words, the company treated the medical concerns associated with their drug as a relative and fungible truth – in short, as a brand truth that they had the right and resources to control. The Zyprexa documents show how Lilly sought to deceive physicians in the United States about the severity of the side effects, using the physicians' own incomplete knowledge against them. There is evidence also of a gap in certain places between executives' knowledge and what was issued to salesmen for answering doctors' concerns over the safety of the drug.

Although this activity was ongoing, a second threatening dimension to the side effect issue opened up for Lilly. This was in 2002, when the Japanese Ministry of Health, Labor and Welfare (MHLW) insisted that Zyprexa, marketed as Olanzapine in Japan (its generic name in the United States[5]), should be labeled with a new contraindication instructing physicians not to use the drug for patients with diabetes or those with a history of diabetes. The label also had to include a warning that patients on Olanzapine may experience a marked increased in blood glucose. Finally, Lilly had to send out a 'doctors letter' informing Japanese psychiatrists of the change. In reaction, Japanese psychiatric hospitals began dropping the drug from their formularies.

Beyond the threat to the success of the drug in Japan, which was considerable given the potential size of the market, Lilly executives were also faced with the prospect that the news of the MHLW's warning would harm the drug's reputation outside Japan. As company documents warned at the time: 'We must be fully aware that brush fires can turn into forest fires'.

Olanzapine was at that point only at the start of its battle to gain widespread adoption among Japanese psychiatrists and, more importantly for Lilly, to be recognized as a true innovation worthy of a high reimbursement under national insurance (Applbaum, 2006). I was in Japan in Winter 2001/2002 completing research on the introduction of SSRI or Prozac-class drugs to the Japanese market. Lilly was one of the companies I called on.

This was before the Olanzapine diabetes incident, which occurred in March 2002. In August 2002, I returned to Japan to attend the World Psychiatric Association (WPA) meetings. I met up there with some of my Lilly contacts, who shared with me their frustration over the MHLW's decision, which they believed to be out of proportion to the scale of the Olanzapine side effect incidents that had been reported. Their deepest frustration stemmed from the fact that the MHLW was separating the two – Japan and the rest of the world. Because the drug was only starting to be used in Japan, the data on side effect incidence worldwide were material, they thought. There were obstacles in Japan to gaining recognition for that fact. And yet, even while the MHLW was refusing to accept foreign data in its consideration, its actions might affect sales in other markets. Indeed, though it was hardly a tidal wave of reaction, within a short space of time the Korean FDA required a label change, mentioning the MHLW's actions. The Zyprexa documents convey an atmosphere of extreme concern. An incidental Reuters announcement in the United Kingdom on the subject of an earlier European label change excited a flurry of activity to prevent the misconception that this was somehow related to the Japan incident.

5 As Olanzapine is the brand name in Japan, I capitalize it throughout.

Lilly therefore experienced globalization as a double-edged sword. On the positive side, they could avail themselves of several mechanisms and opportunities for promotion that are unique to the current age. These included leveraging clinical trial bridging agreements under the International Conference on Harmonization (ICH3) to expedite the approval process of the drug in Japan; the routine dissemination of scientific studies (many or most of them company sponsored) from abroad to Japanese physicians in an effort to win their support and advance loyalty for the drug; the posting of promotional materials aimed directly at Japanese consumers on the internet because direct-to-consumer advertising there is prohibited; and the recruitment of patient family advocates for a trip to the impressive National Alliance of Mentally Ill convention in Chicago to teach Japanese how patient advocacy is organized in America. On the negative side, the intransigence of a local situation, linked to the particular laws and attitudes of the Japanese health-care administration environment in combination with the new facility of drug information exchange under international regulatory agreements such as ICH3, exposed Lilly to the threat that news of the warning label in Japan would spread to other markets and present a global drag to profits.

The company responded to the Japan crisis in a manner consistent with its approach in the United States, as I will describe, and the crisis passed without major incident. We might therefore trace the events in terms of their conformity to the global paradigm or structure of corporate expansion. This exercise is necessary to understand the ubiquitous corporate background against which variations in the adoption of drugs such as Zyprexa must be understood even in remote clinical environments. In all, 19 of the 20 top earners in the pharmaceutical industry are American or western European firms. The industry is moreover globalizing and concentrating through mergers, leading to a replication and amplification of the managerial practices common to these firms. At the nucleus of these practices and the aspiration to global dominance is marketing, the conceptual tool with which expansion is conceived and enacted (Applbaum, 2010). In Japan in 2002, all of the major purveyors of central nervous system drugs were foreign.

On the other hand, even a partial recounting of the Japanese case history will reveal precarious junctures in which Zyprexa's triumph in Japan after its halting start was anything but assured. Various pathways might have led to company failure. Had the events unfolded unsuccessfully for Zyprexa in Japan, the drug's biography in other parts of the world, particularly in places that look deferentially toward the Japanese approval process, might also have been different.

Bryan Turner has pointed out: 'Globalisation involves a qualitative and quantitative transformation of risk; the intensification of risk requires global regulation' (2001, p. 9). This is certainly true, and the following case study will reinforce this appeal. However, it is not only consumers and regulators who experience risk with globalization, but manufacturers as well. How manufacturers respond to perceived risk forms what Ian Hacking (1999) calls an 'interactive looping' among the various stakeholders; a full assessment of risks associated with the globalization of given drugs is therefore not possible without a corresponding account not just of the manufacturer's manifest marketing campaigns, but of the strategic logic whereby they reduce their exposure to competitive, regulatory, perceptual (in the minds of prescribers and end users) and ideological/cultural risks.

Compared with other areas of medicine, there is much uncertainty surrounding the biological effects of psychopharmaceuticals (Hacking, 1998; Lakoff, 2005). Individual and collective placebo effects in some instances rival those of the drugs (Kirsch and Saperstein, 1998). Psychiatric nosology and treatment efficacy are in general epistemologically unstable, both at the scientific end and in cultural context (Kirmayer, 2001, 2006). Psychopharmacology's particularly feeble anchorage to processes of scientific verification has rendered it uniquely susceptible to pharmaceutical marketing manipulation (Lane, 2007; Healy, 2009) as well as to other historical contingencies. As long as the universality of psychiatric science remains indeterminate, the aspiration to 'globalize' it, either by corporate or professional (that is psychiatric) agencies, will remain conditional.[6] In our case study, the same ambiguity that would allow Lilly to position and expand their drug differently to suit commercial expedience might also expose them to alternate 'readings' of the drug by physicians and health authorities in Japan.

We can thus identify three separate 'regimes of value' (Appadurai, 1986) that encounter one another in defining the course of the adoption and continued sale of the drug. First there is the tenuously universalizing biological psychiatry, positioned toward standardized diagnostic classification and conveyed by professional mechanisms including scientific associations and their communicational venues (conferences, journals and of course the Diagnostic and Statistical Manual of Mental Disorders (DSM), only lately adopted in Japan). Second, there is the Japanese mental health-care environment. Among providers, patients and regulators in Japan there are mixed stakes and attitudes relating to cost, safety, institutional constraints, and mental illness altogether, which might affect the future of the drug in unpredictable ways. There is also ever-present a low-frequency trade tension between the United States and Japan. The too-insistent push of an American pharmaceutical company could escalate into a miniature trade dispute, the debating terms of which may have little to do with the pursuit of the verification of scientific claims (Applbaum, 1998). Finally, there is the drug company, bent on standardization of a marketing variety, and managing contingency as it arises, as we will see in regard to the specific tensions associated with the global marketing of Zyprexa.

Zyprexa (Olanzapine) and Its Side Effects

Zyprexa belongs to a class of drugs known as atypical or second-generation anti-psychotics (or neuroleptics). First-generation antipsychotics, which included drugs such as haloperidol and perphenazine, were first introduced in the early 1950s, and represented a powerful new treatment tool for schizophrenia and related psychotic disorders. None of these drugs were able to cure the diseases they were intended to treat, but they became the most essential therapy for mitigating the symptoms. Although the claim that antipsychotics are single-handedly responsible for emptying American psychiatric hospitals in the 1960s and 1970s is exaggerated, they certainly played a role in this transition.

For all the utility of the typical antipsychotics, at least two problems remained with them: there were many patients not helped (or not helped much) by the drugs, and their side effect

6 For a comparable formulation of this situation and an enlightening case study of it, see Lakoff (2005).

profile was severe, which contributed to making treatment adherence a tenuous proposition (Awad, 2004). In addition to causing drowsiness and other unwanted effects, the drugs carried the threat of extrapyramidal side effects, including the dreaded tardive dyskenesia (TD). TD manifests as involuntary muscle movements, particularly in the face. When it occurs, it contributes to the stigma of the disease, and it is sometimes irreversible, even after withdrawal from the drug.

The search for new pharmacological therapies that would overcome these drawbacks resulted in the development of the atypicals. The claim embedded in the term 'atypical' was that their mechanism of action differed from that of the earlier 'typical' drugs; however, the neologism is apparently a marketing rather than a scientific invention (Tyrer and Kendall 2009; see also Healy 2002). The history of the atypicals is complex, particularly since the first one introduced, clozapine (Clozaril), was withdrawn from the market for 14 years between 1975 and 1989 owing to a potentially deadly side effect, agranulocytosis. Clozapine also, however, earned a reputation for being effective in the most treatment-resistant cases, which may have contributed to a similar hope for the newer atypicals, of which Zyprexa was one. Indeed, Lilly's initial strategic bid was, as stated in the documents: 'Market opportunity is for a "safer clozapine"'.

The combination of exaggerated company claims backed by marketing budgets, and the hope and expectation of breakthrough progress, led the psychiatric community to buy into the idea that the atypicals were superior in terms of both efficacy and side effects (Charlton, 2005). The 18-month CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study conducted on more than 1400 patients with schizophrenia contradicted the claim of greater efficacy (except for clozapine) (Lieberman *et al*, 2005), and the bad news about the atypicals' side effects has only expanded with use. Nevertheless, this news has not affected the rate of prescription of the atypicals, despite their being as much as 10–20 times more expensive (Rosenheck, 2005).

More recent studies have concentrated on the side effects of the atypicals, which as I said earlier surround the question of weight gain and diabetes. Zyprexa and clozapine are the most likely among the atypicals to result in these effects (Koller and Doraiswamy, 2002). Lilly itself had discovered early on that 16 per cent of patients gained an average of 66 lb during their first year on the drug, and hyperglycemia as a separate risk was also identified. In 2004, the American Diabetes Association fingered Zyprexa as the worst culprit among the atypicals for its role in causing diabetes. Alex Berenson of the *New York Times* reported in 2006:

> As early as 1999, the documents show that Lilly worried that side effects from Zyprexa, whose chemical name is olanzapine, would hurt sales. 'Olanzapine-associated weight gain and possible hyperglycemia is a major threat to the long-term success of this critically important molecule,' Dr Alan Breier wrote in a November 1999 e-mail message to two dozen Lilly employees that announced the formation of an 'executive steering committee for olanzapine-associated weight changes and hyperglycemia.'

The risk quotient of the drug came to seem even more serious as Lilly extended their brand by promoting its use for much less severe conditions than schizophrenia, and off-label to vulnerable populations such as children and the elderly.

That Lilly intentionally concealed information from physicians is not in question. How they did so is revealing of two facts. First, the company was actively pursuing a strategy of

creating a shadow science to drown out noncompany-sponsored research reports on the side effects of the drug. The Zyprexa documents suggest that each time a negative study came out or was about to come out, Lilly commissioned a study intended to counter it. These results were then published and, as part of a general marketing plan, publicized and disseminated in great numbers to overcome the impact of the negative study.[7] Thus, on 16 October 2002, Lilly manager Peter Beardsall sent an email to seven of his colleagues:

> I personally think that the time has come for a 'stake in the ground' Meta-analysis of the huge pool of data surrounding the issue of diabetes and antipsychotics. The recent list of all studies relating to diabetes that are now out there is huge, and characterised by a significant weighting overall of those that do not support our position. I would like to suggest that we now urgently embark on getting a credible 'landmark' paper written and published … somewhere impactful – e.g. Lancet … Written by someone who we know to be supportive of our position, but who is also clearly independent of us and above all CREDIBLE. The core conclusions of the piece most relevant to our position should be
>
> – any association is of minimal clinical significance due to the widely documented low levels of incidence
> – diabetes is seen more often with those with schizophrenia …
> – the risk of any increase in association is equivalent across anti-psychotics

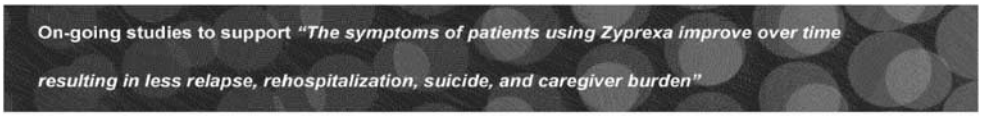
Someone went so far as to recommend an author, but the consensus was that it would be impossible to twist the data to fit Beardsall's proposal.

Sometimes the company was not strictly speaking in reaction to a disinterested study, but to a competitor's study, perhaps itself devised, in the manner Lilly could be wisely suspicious of given its own procedures, to win competitive positioning. Lilly employee Hiram Wildgust reacted to a poster presented at the 2002 European Neuropsychopharmacology Conference in Barcelona in an internal 2002 email whose subject is 'Barcelona air traffic control':

> One poster which caused me great concern was by Bruce Lambert 'titled' assessing the risk of antipsychotic induced diabetes among schizophrenics: A matched case control study (Bristol Myers sponsored).[8] … Conclusions was [sic] that exposure to clozapine, olanzapine, and quietiapine but not risperidone was associated with a significant risk of developing type 2 diabetes when compared to typical antipsychotics. I flag this up as almost certainly this poster will be published and raise the noise around diabetes and olanzapine.

Neil Archer replied: 'The Lambert poster is a concern. If we work on the assumption that this poster WILL be published as a manuscript soon, our attention needs to turn to how we can minimize its impact on both the global and the local level'. He goes on to address questions such as 'Where will this paper be published?', 'Can we stop/delay it?', 'Who sits on the editorial board of the targeted journal?, Can we influence them in any way, with respect to the limitations of this methodology?', 'Should we conduct a communications initiative aimed at all influential referees addressing the above point?'

7 It might be possible to show from the Zyprexa documents that company-sponsored research could build on prior company-sponsored research, creating a legitimating echo effect for their claims.
8 Lambert *et al* (2002).



Study Name	Study Management	Study Owner	Timeline for data analyses	Timeline for first presentation	Working title for first presentation	Working title for journal article	Timeline for paper publication
GEO	German Affiliate	Clouth	6-mth data - Q1, 2003	ECNP (Q3) 2003			
HGGD	US Outcomes Research	Tunis/Ascher-Svanum	Q1, 2003	IPS (Q3) 2003			
NONA	US Outcomes Research	Ascher-Svanum	Q1, 2003	IPS (Q3) 2003			

Figure 1: Company-sponsored research to support Zyprexa.

An initial estimate is that about three quarters of the 5506 pages of Zyprexa documents are devoted to what Sergio Sismondo (2007) calls the 'ghost management' of science, and much of that to the side effects issue. Research is manipulated into sales fodder. Each claim in the doctor's office should be supported by research, and research is 'ordered', as though from a shop, accordingly (see Figure 1, from Zyprexa documents).

The second strategic fact somewhat more relevant to the discussion of how clinical science (or the ambiguities in it) is converted into brand value can be observed by how the presentation of the data is carefully tailored to fit the audience. There is a constant measurement of physician attitudes toward the drugs. Physicians are 'neuro-segmented' into attitude types (rule-bound, high flyer, skeptical experimenters and so on) in relation to prescription habits (Applbaum, 2009). Setting (*hospital* v. *clinics*, for example), geography and other factors are figured in (Oldani, 2004, 2009). With respect to the side effects of Zyprexa, what the physician believes about the matter may be an opportunity to exploit what he or she does not know. Thus, if the physician thinks that the risk for diabetes is only through weight gain, as compared to both weight gain and/or the raising of blood glucose levels, then the sales rep is to proceed according to a sales algorithm for the specified concern. The 'weight change sell sheet' reads 'If MD's concern is weight gain only … Own the issue … Weight gain with Zyprexa is due to *increased appetite*. Not a metabolic response (that is, pill $\neq$ weight gain)'.

That the company felt they had the right of ownership to determine the reality before them is evident from sales strategy slides that read:

- Define what we want our customers to think and feel about the issue.
- State and determine the approach to do this. Create the 'story' that we will tell/live/etc.
  - Must be credible/on brand/right for patients.
- Define how we will ensure total *integrated* saturation of market with 'story'
  - All channels in the market/appropriate marketing mix.

Global Marketing of the Brand: Stages of Adaptation

> 'Develop a global marketing strategy around a consistent brand name and image that is shared by all of our affiliates and recognized by all of our customers' (Zyprexa documents).

The initial challenges of global expansion are establishing a beachhead for need and registering the product. Since Zyprexa's treatment market at first was for schizophrenia, not much needed to be done by way of stimulating the sense of need; schizophrenia was already a well-established disease category in most or all of the world. Later expansions of Zyprexa for use in bipolar disorder, dementia, insomnia and other conditions would be predicated on the ability to brand the conditions to fit the drug (Moynihan and Cassels, 2005). But in its initial global forays, what was required for Zyprexa to succeed was a strategy of registration or approval and the acquisition of favorable reimbursement schedules in each market. This entailed establishing relationships with regulatory authorities to expedite approvals. The plan was to begin with 'priority markets' and then proceed quickly to 'emerging markets'. This move was simplified by the fact that many emerging market countries trust the approval procedures taking place among their more developed neighbors (Timmermans, 2004).

A layer of adaptive actions was called for, including conducting specific trials and making appropriate product label adjustments to account for country differences in how schizophrenia was diagnosed, and designing health economics and quality of life studies designed to demonstrate the cost-effectiveness of Zyprexa in each specific market, where these considerations would vary. Where the data would not directly fall in line, the company would, in the language of the strategic vision, 'Develop a plan to "redefine" optimal standards of care'.

Thereafter, the marketing gets increasingly specific in its attempt to determine existing practices affecting the potential sales of the drug, followed by the campaign to bring all markets into alignment in keeping with the habits of prescription in the most successful markets. Thus, for instance, moving the site of prescription from the specialist's office to that of the primary care physician (PCP) is crucial to expanding sales because from a marketing standpoint PCPs represent both a larger distribution base (there are many more of them than there are psychiatrists) and an easier one to influence because they are less informed about mental illness and antipsychotic medications (Applbaum, 2009).

The next phase was the extension of the brand (so spoken of in the documents) to 'new indications and off-label indications' in as many different markets as possible: 'refractory bipolar disorder; psychotic depression; personality disorder with psychotic features; non-drug induced organic mental disorders; mania, bipolar disorder; drug-induced mental disorders; attention deficit disorder; dementia with psychosis; children/adolescent use'. There was a specific global 'Bipolar Data Timeline' (see Applbaum (2009) for a detailed discussion of the conceptual process of indication expansion), and a final summation of the global brand strategy, reproduced in Figure 2.

It would be erroneous to conclude that managing the side effect profile of the drug was separated conceptually or temporally from managing the brand equity in a general sense. All drugs have side effects, and Lilly was aware of those associated with Zyprexa. Controlling the brand image therefore included from the outset a built-in damage control mechanism. What took place in 2002 in Japan, however, was beyond what the company anticipated as far as country safety measures were concerned. It is instructive to consider the events from the company's point of view, beginning with brief background information about the Japanese environment for mental health care at the time.

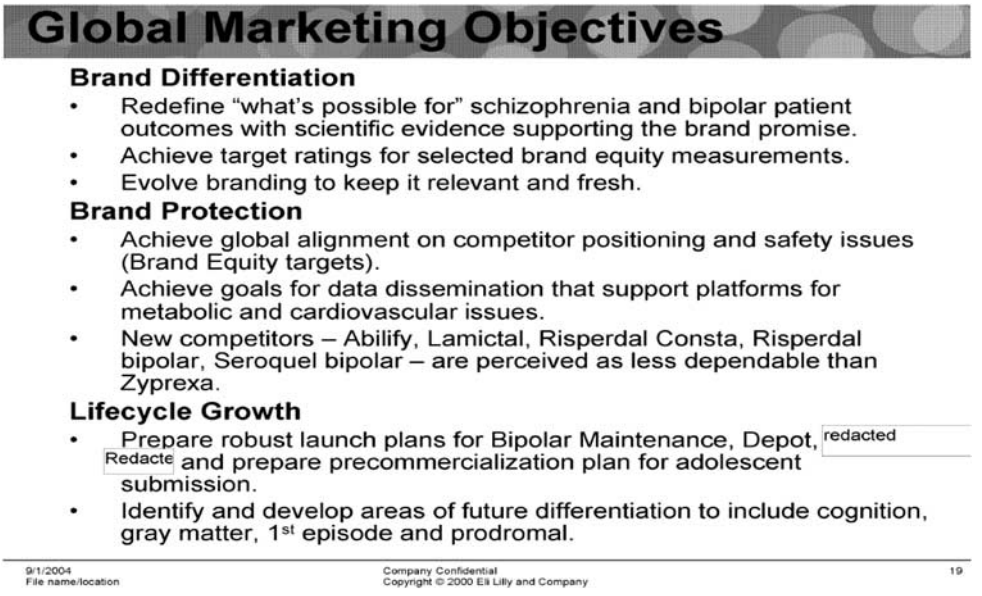


Figure 2: Summation of Lilly's global brand strategy for Zyprexa.

Brush Fires and Forest Fires: Managing the Side Effects Debacle in Japan

The Japanese mental health-care environment in 2002 was in flux. The most salient feature of the landscape was the number of psychiatric hospital beds: 350 000 (in 1999), or 28 for every 10 000 people, with an average length of stay of 406 days. By contrast, the United States had 4/10 000 (total 90 000 beds), and the United Kingdom 10/10 000 (Hiroto and Sederer, 1999). What is pertinent in the current context was the newly articulated plan to reduce the inpatient population by 20 per cent, or 70 000 patient beds, by 2015. Accomplishing this meant overcoming a host of medical challenges and structural and cultural obstacles.

The resistance to reintegrating schizophrenic individuals, who comprised 65 per cent of the inpatient population, was particularly strong. The MHLW and physicians were on the whole in favor of the plan, but municipalities were opposed, and patients and their families of mixed opinion. Schizophrenia bears much stigma, as does mental illness in general in Japan, and there is a general perception that the disease is incurable and associated with social disorder and violence. The shocking incident of a schizophrenic man entering an elementary school in Osaka in June 2001 and murdering eight children brought renewed public debate to the subject, but not one that favored deinstitutionalization as a solution. In addition, there is a dearth of psychologists, social workers and other counselors to provide ancillary services necessary to proposed community care.

The campaign to switch Japanese prescribers' loyalty to second-generation antipsychotics had thus far met with limited success, although Janssen's risperidone had been approved in 1996, and Olanzapine in 2001. Because it was not the first in class to gain approval, moreover, the MHLW had assigned a low reimbursement price for Lilly's drug (Applbaum, 2006). A senior Eli Lilly Japan manager (an American) complained to me in the context of a

discussion about how Lilly was trying to pressure the Ministry of Health Labor and Welfare to support their drug, 'The Japanese won't adopt Olanzapine because if they do they will have to shut the doors to their mental hospitals and they don't want to do that. It's not in their interest'.

A low side effect profile for medicines treating schizophrenia would be essential for success, for two reasons. First, monitoring them could be minimized, which is one of the benefits of deinstitutionalization in the first place. Second, the MHLW, in keeping with how many doctors and patients are said to view pharmaceuticals, is purported to be risk averse. There may have been particular sensitivity to safety because Olanzapine was in a relatively new class of drug.

Given this confluence of circumstances, the report of just nine cases of hyperglycemia, which included, however, two deaths, seemed to carry the potential of generating a situation in which a small-scale event might, in Marshall Sahlins' expression, become a flashpoint for 'historical melodrama' (Sahlins, 2004, p. 169). The possibility for a flash flood of negative attention focused on the warning label may not have been completely foreseen by anyone. Eli Lilly Japan was nevertheless alert to negative reports. The first (apparently, since this particular communication is not dated) mention in the Zyprexa documents of the MHLW taking notice of adverse effects of Olanzapine came in an internal email addressed 'Dear all':

> I would like to inform you that the forth [*sic*] case with diabetic coma was reported (below). Fortunately the patient did not passed out … [*sic*] We have to prevent further reports, because the MHLW do not care about incidence, but accumulated number of reports. It is reasonable the more ZYP sells, the more case of AEs [adverse events] reported, it means the incidence does not increase. But, the MHLW does not think about it!!

When further incidents accumulated and the MHLW reacted with a request for a label change and doctors letter, Lilly responded (as related in an internal email by the same person above, dated 26 March 2002):

> From the beginning of the meeting, the officers strongly suggested we take safety actions, such as 'doctors letter' or the revision of 'contraindications' section in the JP package insert. We, of course, did say we thought no safety actions were necessary now because of the following reasons:
>
> - The JP package insert already mentions 'to pay attention to the treatment for the patients with diabetes risk factors', and 'diabetic coma and ketoacidosis'.
> - Patients with schizophrenia have diabetes mellitus higher than the general population.
> - The incidence of diabetes between olanzapine v.s. haloperidol, or olanzapine v.s. risperidone were not different in studies.
> - Incidences of diabetes are not different among antipsychotic agents.
> - According to a study, olanzapine does not effect insulin secretion.
>
> The officers, however, said that they already know or understood what we have said. But the approximately 10 cases, especially including two death cases, for Olanzapine have been reported in only half a year. Therefore, they called us to request some safety actions, including distribution of a 'doctors letter' ASAP.

In the back-and-forths between Kobe and Indianapolis ('Indy'), there were signs of tension between how Japanese and American staff believed the crisis should be handled. The Japanese were more cautious about challenging the MHLW on its requests, even while, as seen above, they said they agreed that the requests are irrationally grounded. Presumably, their reasoning conformed to that which is familiar to many American firms conducting business in Japan. Namely, the Japanese partner is looking for signs of trustworthiness rather than proof that this or that proposition is reasonable (Hodgson *et al*, 2007). A 12 April 2002 email sent by Andrew Macarenhas exclusively to Anglo recipients revealed his frustration about being unable to budge the MHLW's request and his intention to proceed against the advice of Japanese staff at Eli Lilly Japan:

> ladies and gentlemen: after the meeting with the outside panel of safety experts, this is the text of the PI that the MHLW has given us to incorporate. as you can see this is equal or worse than the 'worst case scenario' and almost identical to the language that the MHLW had started off on the 1st day of negotiations. what remains to be done at the japan end is as follows: 1. we have to confirm the text and ensure that the japanese is correct. *while all the local advice is against it*, we are contacting them to suggest a small change in the warning section re blood glucose monitoring … the chances are close to zero but may be worth the risk [emphasis added].

In late August, the WPA meetings were held in Yokohama. A large contingent of Lilly personnel from US headquarters flew in, perhaps as a reassurance to the MHLW that company grandees were attentively on hand during this important time, and perhaps also as a reflection of the fact that headquarters was not entirely satisfied with how Eli Lilly Japan had been handling the crisis on their own. Following are some of my notes from the satellite session:

> The topic was the safety and efficacy of their drug for schizophrenia. The symposium was organized to clear the air following the death of two patients (and the near demise of several more) apparently from complications associated with side effects of the drug. Following the Japanese health ministry's behest to list death as a possible side effect of the medication, Japanese hospitals were yanking the drug off their formularies. The executive director of the subsidiary's research laboratories explained to me in all frankness that this conservative reaction was understandable. The drug can be dangerous for patients with diabetes, and patients treated for schizophrenia are not routinely screened for diabetes, as they are in most European countries and in the United States.
>
> The symposium was held at the dinner hour in one of the large halls; box dinners were handed out at the entry. I estimated attendance to be approximately 800, mostly Japanese. The session was held in Japanese, but there was also simultaneous interpretation into other languages. In attendance at this one were many of the company's senior-most brass. About 25 ancillary staff manned the film cameras, stage audio and hospitality.
>
> The speakers were mainly young, in keeping with the changing of the guard in Japan to a new generation of DSM-oriented psychiatrists. Using very well worked out clinical statistical data and PowerPoint presentations formatted by the same hand, they

showed that the only patients who had suffered the bad reactions had an abnormally large body mass index of over 30 – they were obese. In addition to high blood sugar, the patients were hypertensive. In one case, 10 empty cans of juice were found at the patient's bedside, indicating 'soft drink ketosis'. There was a photo shown of many empty soft drink bottles to emphasize the point.

The lesson Japanese doctors should learn is caution in application of the drug to obese patients and to those who may have what is known in Japan as 'pet[roleum] bottle syndrome', that is, an addiction to sugary soft drinks. Three more presentations make similar points, adding data on efficacy of the drug.

In our folders is a survey we are reminded to complete and turn in on our way out. The first question asks: 'Did the Symposium provide you with beneficial information about the relationship between Olanzapine, high blood pressure and diabetes?'

This session was a direct appeal from Lilly medical and marketing management to the Japanese psychiatric community. In effect, the company was bypassing the MHLW and taking their case directly to Japanese prescribers. That the WPA conference happened to be held in Yokohama just a few months after the label change and the doctors letter was fortuitous for the company, as it permitted them to address the issue as a 'brush fire', before the link between Olanzapine and diabetes became too entrenched. The direct communication between 'corporate' and its principal clients – prescribers – is unusual, as the everyday channel is the sales rep, and the usual intermediary for scientific instruction is the thought leader, or KOL (key opinion leader – an industry term).[9] At least two of the Zyprexa documents exhibits suggest that the events of Spring 2002 unsettled some or many Japanese sales reps, whose trust the company sought to win back. One slide was entitled 'Why we are struggling … Resolving these issues will result in rebuilding trust with the sales force'. It contains real or projected quotes from sales people:

- ELJ [Eli Lilly Japan] did not tell us about Hyperglycemia prior to Dear Dr Letter … (Some Drs still think ELJ hide something)
- ELJ do not let us know why Hyperglycemia happens …
- Drs are asking concrete guideline for key wordings in Dear Dr Letter
  - 'What is *Explain sufficiently to the patient and family members*?'
  - 'Which patients ELJ recommend to use Zyprexa?'
- Global data always shows no particular difference between atypicals regarding hyperglycemia. It reminds Drs of 'Why only Zyprexa only in Japan?' Drs tend to conclude:
  - Lilly's data is not neutral. Still hide something.
  - Japanese patients must be different. Lilly should tell us mechanism to occur Hyperglycemia.
- Thought leaders are angry with Lilly due to combination of above.

9 I do not have data on the number of sales reps to physicians in Japan (in the United Kingdom it is one rep for every three MDs; in the United States one for every six); however, Japanese doctors refer to the reps as *otoko geisha*, or male geisha.

The credibility gap might thus have extended beyond the MHLW to sales reps, thought leaders and physicians. If so, the debate surrounding Olanzapine might have in fact shifted from being about the drug's merits or dangers to being about Eli Lilly's trustworthiness in its marketing of the drug. There is some evidence for this in an email exchanged (on 23 October 2002) in regard to a separate investigation the MHLW was conducting about adverse liver reactions to Olanzapine. Noriko Akagi from Lilly Japan wrote to 11 recipients in Japan and the US announcing that the MHLW was dropping its case: 'As we exchange emails on this matter … there seems to be a gap derived from cultural differences between the US and Japan. From the viewpoint of MHLW … Lilly seem to choose the way of too much strong denial of causality between the drug and AE [adverse effects], and attributing AEs to other factors. Under the situation, MHLW may conclude that Lilly always hesitate to take safety actions'. Corporate trustworthiness, if this was at issue in the Olanzapine/hyperglycemia affair as well, would have been measured by interpersonal rather than scientific criteria. Lilly's claim that the MHLW was behaving irrationally in their evaluation of the safety profile of Olanzapine would have made sense to them on that level.[10]

The Zyprexa documents reveal that there were at least perceived short-term repercussions of the Japanese incident for sales outside Japan, less for contraindications, warnings, or other label inclusions imposed by regulatory agencies than for doctor perceptions that Zyprexa was more dangerous than other atypicals. Growth in US Zyprexa sales slowed to 4 per cent in 2003 (from $2.53 billion in 2002 to $2.64 billion in 2003), down from a 16 per cent sales growth rate in 2002. In 2004, sales in the United States dropped 8 per cent to $2.42 billion. (International sales continued to rise, reaching $4.42 in 2004.) Lilly executives believed that this decline was because of their failure to deal effectively with doctor's perceptions in the United States regarding the side effects of Zyprexa. Although even the declining sales figures may seem like commercial triumph to anyone likely to be reading this article, the documents reveal a sense of corporate fear that their credibility – which is to say the brand equity of both Zyprexa and the company – was under threat.

The Japan brouhaha simmered down, and sales of Zyprexa resumed its upward path in the United States as well as in Japan.[11] Then in February 2006, Alaska and West Virginia began what turned out to be a torrent of successful lawsuits against Lilly for promoting off-label uses of the drug, exaggerating its efficacy and concealing data on side effects. A rhetorical centerpiece in each of these suits and those ongoing is the label change in Japan in 2002. Typical reports on blogs, in newspapers and at lawyers' websites repeat, 'In 2002,

10 The confusion of rationality and morality appears to me a regular feature of US–Japan trade. In regard to the national trade disputes of the 1990s, 'The polarity between fair trade and unfair trade – the explicitly moral terminology originating from the US side – was met by an equally polarized rejoinder from the Japanese. When the Americans claimed to be rational, the Japanese were "hyperrational", and where the Americans were logical, the Japanese claimed to be "supra-logical". This Japanese repartee to an accusation of unfairness with a baffling indictment that Americans are too logical does not imply that the two nations misinterpreted one another. Rather, the transposition of discourse from the moral to the rational domain was entirely natural to the terms of the debate. The US side of the negotiation habitually interspersed notions of the virtues of economic efficiency and rationality with Virtue in general. The Japanese were simply responding in kind' (Applbaum, 1998, p. 8).

11 However, as of March 2009, Olanzapine has been approved in Japan only for schizophrenia, and for many years was not considered useful there as a first-line treatment.

Japanese regulators imposed requirements that Eli Lilly warn doctors about Zyprexa's diabetes risks. Even after this occurred, however, the company's US policy was still to pretend the issue did not exist'.[12]

Conclusion: Marketing-controlled Pharmaceutical Value and the Possibility for Alternative Histories

It is marketing's task to seek to control the meaning and value of the company's products and the behavior and perceptions of their exchangers in respect to those products. The determination to do so stems from the perceived necessity to resist the points at which the object can slip back into undifferentiated places where its uniqueness, its branded essence, is lost or captured or co-opted to other meanings and uses – the point at which the product is 'commoditized', in marketers' own terms (Applbaum, 2004). The product must remain unique and operational in a sphere in which it competes with similar objects through techniques of differentiation. Its name, image, reputation and competitive position are managed through the brand, and the measurement of what is preserved and maximized through marketing control is called brand equity, or brand value. Brand value is the essence that marketers seek actually to control and protect in their work.

In pursuing the all-out creation, expression and demonstration of brand value, marketers are working with more than a token or a label wrapped around their product. Brand value is rather more like a magnetic field intended to bring all manners of attraction and fascination to the object it endows with meaning and potency. If it is in the nature of capitalism to 'completely redefine the categories of value, social relations, and the commodity in its striving toward totality' (Lee and LiPuma, 2002, p. 199), we need to grasp the comprehensiveness of the corporate effort to 'strive toward totality' in their effort to control brand value. Regardless of the meaningful variation in how globally marketed drugs commercially succeed, fail or are localized in different places, the facts associated with the spread of drugs such as Zyprexa render undeniable the need for studying the culturally constituted strategic logic at the 'core' enabling that spread. Within a year of Zyprexa's first approval, there were already 84 submissions, 52 approvals and 37 launches, with 14 more in the wings in such diverse markets as that of Kazakhstan, Latvia, Tobago, Botswana and Estonia. The approval of the drug in what might be called the 'key opinion countries' of the United States, the EU and Japan would precipitate a domino effect of approvals in those places where the means for elaborate testing may be lacking.

I wish to emphasize here the contrast, indeed the competition between the unique value and knowledge sphere surrounding the aspiration to brand dominance, and that of other stakeholders, including scientists, psychiatrists and regulators. It may be a fair characterization, through the lens of Actor Network Theory, for instance, to argue that the boundary between science and non-science or disinterested and interested science is often blurred, and critical analysts must seek the threshold where valid clinical research reports verge into

12 http://www.naturalnews.com/024089.html, accessed 19 May 2009. See also, for example, http://www.pharmalot.com/2008/03/zyprexa-label-in-japan-was-tougher-than-in-us/, accessed 19 May 2009 and http://www.zyprexasideeffectslawyer.com/html/reports.html, accessed 19 May 2009.

manipulated publicity (for example Matheson, 2008). The Zyprexa documents suggest that a blunter process is also often at work, in which a firm may disregard inconvenient data or contravene it as necessary to preserve their stake in the brand, or brand equity. Released court documents pertaining to illegal marketing activities of several other of the most reputable pharmaceutical companies reveal regimes of marketing influence astonishingly similar to those at Eli Lilly.

I suggest that what we are witnessing is not a subtle process of the commercialization of scientific exploration, but the reconfiguration of the infrastructure for knowledge management in the service of promoting brand values. The context for this conversion is the competitive orientation of firms, while strategic intent is guided in accordance with the marketing concept. The increase in size and power of the companies, in terms of their internal capabilities but also their political clout, has enabled them to bend the creation of value to their convenience, as historically they had perhaps successfully only mastered the art of exaggerating through salesmanship the value that had been produced in the laboratory.

We can discern the marketing thought model that gives rise to an opposition between corporate goals and those of the public interest. It is not the facts of the side effects of Zyprexa that matter to Eli Lilly, but the side effects as perceived by prescribers and other relevant decision makers in the distribution of the drugs. The marketing research of doctors' perceptions in the United States was extended more or less without modification to measure the cultural perceptions of regulators and doctors in Japan, adding only a superficial layer of national culture as context and variable. In Figure 3 (from the Zyprexa documents), we are shown how the company assembles perceptual data by country and setting. The marketing effort will be adjusted in each market to meet the specific challenges of that market; it will not make the same pronouncement regarding side effects in each locale, as expected by

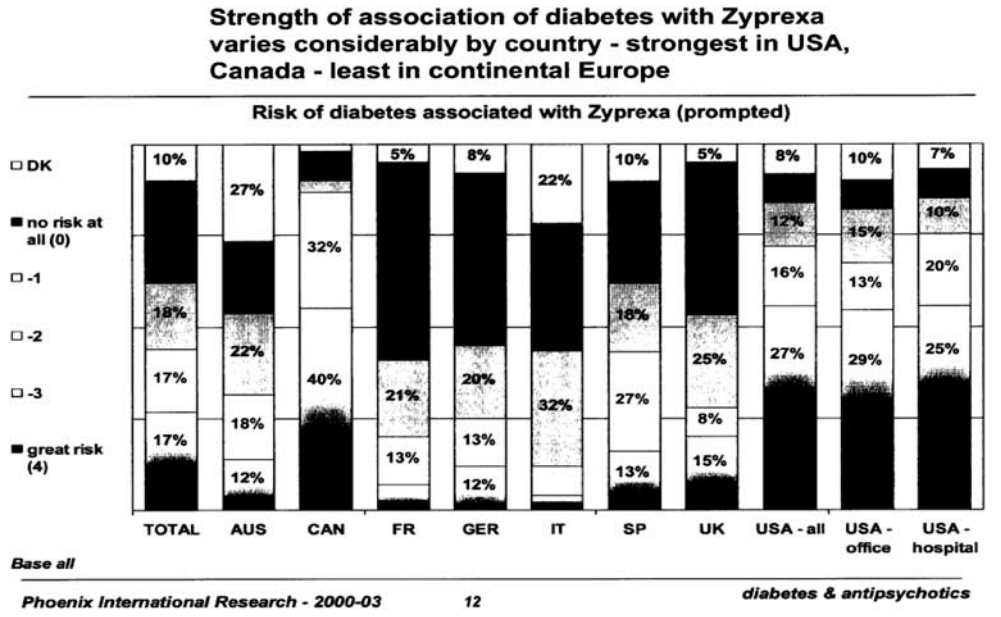


Figure 3: MD perceptions of Zyprexa side effects by country.

standards of regulatory authorities – unless the unifying force of globalization itself forces it to, as to some extent, occured following the Japan incident.

From the point of view of the theory of practice (Bourdieu, 1977) of marketers, universal principles such as those ideally espoused by scientists are the antithesis to brand ownership because brand/marketing value is predicated upon uniqueness of identity in the eye of the consumer. One's product must remain unique relative to competitors' products, and this is what enables it to remain proprietary. Product uniqueness is the essence of marketing value (Levitt, 1983); in some sense it is its *truth claim*: 'brand Z is better because …' The brand serves as both a legal protection, a proprietary copyright (analogous to the patent, which companies seek to protect against genericization) and as a signifier to that uniqueness.

And yet, if marketing value is a relative proposition, it is thereby also vulnerable to historical contingency and resistance. What might have happened if the WPA had not taken place in Yokohama in 2002, and the reputation of Olanzapine in Japan had continued to slide? What if Indy managers had acted in a more headstrong way toward the MHLW, driving the MHLW to distrust it and to impose still further restrictions on the drug for that reason? What if Japanese drug reps and KOLs were more inquisitive or ethical than their American counterparts, and they continued to ask, 'Why only Zyprexa only in Japan?' What consequences might yet emerge from the growing suspicion – were it to reach the MHLW and similar agencies around the world – that pediatric bipolar disorder (for instance), which has brought much profit to the purveyors of atypical antipsychotics, is specifically an American disease?[13]

In the case presented here, we can observe Lilly navigating contradictions and attempting to seal the fissures from which their control of the brand threatened to be drained. The company was interested in shaping beliefs and perceptions about Zyprexa that would augment its brand equity. The regulatory authorities in Japan, themselves responding as much to political as to scientific concerns (beginning with the elusive question of how to define safety), may have been reacting in kind, driving Lilly further into public relations tactics. The outcome of their efforts may or may not significantly affect Japanese psychiatric practice, patient health or regulatory precedents.

The stakes in medicines are high, commercially, scientifically and ethically, and the potential perils to a company of revealed discrepancy in safety reporting is correspondingly severe. Grounded comparative research focused on the articulation of pharmaceutical company motives and theories of practice with those of local medical providers can reveal the extent to which the analysis of risks and outcomes in relation to drugs are being driven by commercial as against scientific categories of analysis in diverse locales, as well as shed light on the unresolved issues surrounding cross-cultural differences in medicine. Questions as broad as how international trade and regulatory mechanisms affect the authority of local agencies, and as narrow as how sales forces are trained, have their place in understanding how global pharmaceutical companies create legitimacy for their drugs and the marketing programs that support them in different country environments. As I suggested at the outset,

13 Contingencies associated with cultures of international trade can also have decisive effects. Andrew Lakoff reports that many Argentinian psychiatrists regard psychopharmaceuticals as an imperialist invasion (Lakoff, 2005). The grounds for cultural resistance to US influence as expressed through commerce are also in evidence in Japan (Applbaum, 1998), a sentiment liable to be deployed expediently by domestic pharmaceutical competitors.

corporate strategic logic (vis-à-vis risk, for instance) is but one element in a larger dialectic involving medical authority (Abraham and Lewis, 2002), pharmaceutical citizenship (Ecks, 2008), emergent bioethics (Petryna *et al*, 2006), regulatory histories and cultures (Abraham and Reed, 2001; Abraham and Davis, 2009), and other contingencies relating to current psychiatry and to specific classes of therapeutic drugs.

Mental illness is a rapidly expanding cause of disability and social suffering. Globalization is often cited as a cause of the increased incidence of mental illness. A partnership of biological psychiatry and psychopharmaceuticals, at once disembedded from local social worlds and global in scope, has been promoted as a universal solution to this problem. An increasingly globalized psychiatry profession, pharmaceutical marketing, international trade mechanisms and the failure of public health authorities to sustain inpatient treatment all encourage adoption of a predominantly pharmacological paradigm. The materials presented here have afforded a peek into corporate ways of knowing and establishing value for a drug. Further investigation of pharmaceutical industry values, practices and theories of practice in specific instances of local articulation will enhance our grasp of the dynamics of emergent biosocieties.

Acknowledgements

I thank Robert Rosenheck for his corrections and comments on the first draft of this article. Thanks are also due to Ingrid Jordt, Lawrence Cohen, Paul Brodwin, Martha Poon and *BioSocieties*' conscientious reviewers for their input.

About the Author

Kalman Applbaum teaches Medical Anthropology and Global Studies at the University of Wisconsin, Milwaukee. His current research focuses on the comparative adoption and use of new psychiatric drugs, with a specific focus on long-acting injectable antipsychotics. He is the co-editor (forthcoming, with Michael Oldani) of a special issue of *Anthropology & Medicine* entitled 'New Anthropologies of Medical Compliance'.

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