Drug Safety and Corporate Governance

Kathy Moscou, Jillian Clare Kohler, and Joel Lexchin

Pharmacovigilance in low and lower middle-income countries has not been commensurate with increasing access to medicines, despite growing recognition that it is important to health outcomes. Pharmacovigilance is impeded where healthcare systems are overburdened and under-resourced. In countries such as India, the population is increasingly exposed to potential adverse drug reactions. Pharmaceutical industry corporate governance, that advances pharmacovigilance in under-resourced countries, would support postmarket drug safety. An analytic framework is used to guide this comparative analysis of pharmacovigilance governance within global pharmaceutical corporations (GPCs) and their Indian subsidiaries. Findings reveal that pharmacovigilance is not fully integrated into corporate governance of the GPCs studied. GPCs exhibiting the least integration have more outstanding drug safety issues. Policy incentives would advance integration of corporate governance and pharmacovigilance.

INTRODUCTION

There is growing recognition that pharmacovigilance matters for health outcomes. Pharmacovigilance is defined as activities to detect, assess, understand and prevent adverse drug effects and drug-related problems. Adverse drug reactions (ADRs) remain among the top 10 causes of death globally and an estimated 2 to 4 million serious, disabling or fatal injuries in the United States (US) are attributable to ADRs annually.\(^1,2\) Pharmacovigilance in low and lower middle-income (LMI) countries such as India, is more hindered than in developed countries, by poverty and an overburdened, under-resourced health care system.\(^3\) It has not kept pace with increasing access to medicines.\(^4,5\) In a study of two teaching hospitals in India, it was found that more than 32% of elderly patients experienced ADRs.\(^6\) The 2012 Access to Medicine Index (AMI) ranking of the twenty largest global pharmaceutical corporations (GPCs), by their actions to improve access to medicine in developing countries, found that gains have been made.\(^7,8\) The AMI report also found that, “Overall companies show an apparent lack of willingness to engage in building national pharmacovigilance systems in developing countries.”\(^9\) Despite greater access to medicines that treat AIDS, malaria, tuberculosis (TB) and chronic disease, knowledge about their use in patients with comorbid disease (e.g., TB and AIDS) and tropical diseases (e.g., TB and malaria), not endemic in the countries where drug clinical trials have been conducted, is limited.\(^10\) Millions worldwide, receiving antiretroviral, antimalarial, anti-tuberculosis and other medicines, are at increased risk for serious, disabling or fatal ADRs.\(^11,12\) Evidence for real-world effectiveness and safety of fixed dose combination (FDC) medicines is incomplete. Up to 44% of India’s top selling medicines are FDCs, and the rationale and safety of 294 FDCs has been questioned by India’s Ministry of Health.\(^13,14\)

The primary method for collecting information about ADRs globally is spontaneous reporting, a passive method for detecting drug safety issues. A study of
ADR reporting in low-income countries found that fewer than 2% of ADRs associated with antimalarial drugs were spontaneously submitted over a 40-year period.\textsuperscript{15} The ADR reporting rate in India is 1%, despite the recent establishment of 40 ADR monitoring centers and 140 medical college reporting centers.\textsuperscript{16}

Compliance with pharmacovigilance regulations has been low in some developing countries.\textsuperscript{17} Endemic corruption, as one example, in emerging economies may de-incentivize regulatory compliance.\textsuperscript{18} India’s largest producer of pharmaceuticals for domestic use and export was sanctioned by the US Food and Drug Administration (FDA) for submitting fraudulent data regarding drug stability for several products manufactured at one of its facilities.\textsuperscript{19} The consent decree signed between Ranbaxy and the US Department of Justice on behalf of the FDA in 2012 enforces external audits and other remedies for five years.\textsuperscript{20}

Corporate governance, the process of setting and monitoring business goals and strategies by the board of trustees, directors, and shareholders, that advances pharmacovigilance in under-resourced countries would support postmarket drug safety. Maennl (2008) posited that effective pharmacovigilance requires a corporate culture that aligns safety and risk management with corporate business strategy. Misaligned priorities between responsibility to shareholders and corporate social responsibility (CSR) may create tensions that impede pharmacovigilance.\textsuperscript{21}

Our paper examines the integration of pharmacovigilance into broader corporate governance policies of GPCs (multinational entities that operate across national boundaries). We further examine the commitment of GPCs to pharmacovigilance internationally and in India, a lower-middle income country with a domestic pharmaceutical industry.

**METHODS**

Our research investigates six of the top ten pharmaceutical corporations internationally (Abbott Laboratories, Eli Lilly and Company, GlaxoSmithKline, Merck & Co, Novartis Group, and Pfizer Inc.) and their Indian subsidiaries. The GPCs researched reported the highest revenues for pharmaceutical corporations in 2011-2012.\textsuperscript{22,23,24} Qualitative research methods that included a document and thematic analysis of corporate annual reports, CSR reports, corporate websites, and publicly available FDA, European Medicines Agency (EMA), and the Indian Ministry of Health and Family Welfare documents were used. The data was read and reread in an iterative process. Data was coded using an open coding process. A codebook was created with operational definitions for codes to check coder reliability and reproducibility of the categories (Appendix 1). Themes that explain how postmarket drug safety is integrated into GPC corporate governance were identified. An analytic framework was developed to guide the comparative analysis of pharmacovigilance governance of GPCs (Table 1). GPCs were compared in the following categories: (i) Pharmacovigilance is described as a corporate value, (ii) Pharmacovigilance flow chart or safety framework is published, (iii) Position on pharmacovigilance is publicly available, (iv) Drug safety practices are described as a CSR or in terms of Global Citizenship, (v) GPC participates in extramural pharmacovigilance activities (i.e., contributes to pharmacovigilance activities led by actors external to the company), (vi) GPC complies with regulatory reporting requirements, (vii) Postmarket drug safety is described as a threat, (viii) Action has been
Table 1: Corporate Governance and Pharmacovigilance Framework

<table>
<thead>
<tr>
<th>Corporation</th>
<th>Pharmacovigilance described as a corporate value</th>
<th>Pharmacovigilance flow chart published</th>
<th>Company position papers posted on website</th>
<th>Drug safety practice is a Global Citizen or a CSR</th>
<th>Participates in extramural pharmacovigilance activities</th>
<th>Complies with regulatory reporting requirements</th>
<th>Post market drug safety requirements described as a ‘threat’</th>
<th>Actions taken against company for safety issues with drug products</th>
<th>Pending or uninitiated postmarket requirements</th>
<th>Pharmacovigilance or drug safety not described in annual report</th>
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Pending or uninitiated postmarket requirements: X= Fewer than 15% of PMR studies are pending or uninitiated, XX= PMR studies pending or uninitiated are greater than 15% and less than 50%, XXX= More that 50% of PMR requirements are pending or uninitiated.

taken against the corporation for drug safety issues (s), (ix) Pending or uninitiated postmarket requirements (PMR), and (x) Pharmacovigilance or drug safety is not described in the corporate annual report. Using the analytic framework, consistency between corporate statements and actions was compared to aid in the analysis of corporate governance and commitment to pharmacovigilance. GPCs were categorized into four tiers, using the analytic framework and based on the publicly available sources outlined in the methodology (Table 2). Unless otherwise stated, references made are attributed to the parent company, not the Indian subsidiary.
Table 2: Criteria for Classification of Global Pharmaceutical Corporations

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<th>Tier 3</th>
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<td>≥ 3 corporate values that are characteristic of pharmacovigilance governance and drug safety practices described as CSR or Global Citizenship</td>
<td>≤ 3 corporate values that are characteristic of pharmacovigilance governance and drug safety practices described as CSR or Global Citizenship and Postmarket drug safety requirements described as a ‘threat’</td>
<td>≤ 3 corporate values that are characteristic of pharmacovigilance governance and 3 corporate values not characteristic of pharmacovigilance governance and &gt; 15% PMR requirements pending or uninitiated</td>
<td>≤ 2 corporate values that are characteristic of pharmacovigilance governance or ≥ 3 corporate values not characteristics of pharmacovigilance governance and &gt; 50% PMR requirements pending or uninitiated</td>
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a Corporate values characteristic of pharmacovigilance governance: Pharmacovigilance is described as a corporate value, Pharmacovigilance flow chart or safety framework is published, Pharmacovigilance position is publically available, Drug safety practices are described as a Corporate Social Responsibility or in terms of Global Citizenship, Company participates in extramural pharmacovigilance activities, Company complies with regulatory reporting requirements.

b Corporate values not characteristic of pharmacovigilance governance: Post-market drug safety is described as a threat, Action has been taken against the corporation due to safety issues with drug product(s), Pending or uninitiated postmarket requirements, Pharmacovigilance or drug safety is not described in the corporate annual report.

RESULTS

Our research found variation in integration of pharmacovigilance and corporate governance among the companies analyzed, which falls along a continuum (Figure 1). Differences were also found between each parent company and their Indian subsidiary, except where the subsidiary claimed to have adopted all of the parent company policies (e.g., Merck India).

Figure 1: Continuum for Integration of Pharmacovigilance into Corporate Governance

Less integration into corporate governance

Greater integration into corporate governance

PHARMACOVIGILANCE AS A CORPORATE VALUE

Eli Lilly

Eli Lilly ranked highest in integration of pharmacovigilance and corporate governance and is the only company in tier 1. Postmarket drug safety is described as a CSR and safety monitoring is shown as a core area in Lilly’s integrated global quality system diagram. Pharmacovigilance is described in three separate sections of its CSR report. The Lilly Bioethics Program governs research and development (R&D) and is headed by the vice president of Global Patient Safety and Bioethics. R&D is characterized in the CSR report as a 7-stage process that begins with drug discovery and concludes with postmarket testing. Lilly’s Global Patient Safety Organization (GPSO)
network of physicians, pharmacists, nurses and other healthcare providers monitors, collects, evaluates and reports information pertaining to product safety. The GPSO’s mandate is to, “report adverse events and continuously monitor the safety of Lilly’s products throughout their entire life cycle, including the identification of changes in the benefit/risk balance.” The Public Policy and Compliance Committee terms of reference that requires annual review of the effectiveness of Lilly’s compliance program in meeting FDA and other US federal health care program requirements, including pharmacovigilance, provides further evidence for integration of corporate governance and drug safety.

The Eli Lilly (India) website claims that corporate governance is guided by company values for integrity, respect for people, and excellence. It is the only Indian subsidiary that provides information about adverse drug reactions and a link for ADR reporting on its homepage. Corporate accountability, however, is built on “clear, consistent, and truthful communication about [our] performance”, and is framed in the context of investor confidence rather than patient safety and pharmacovigilance.

Abbott

Abbott and the independent biopharmaceutical spin off company AbbVie are ranked in tier 2. The companies describe drug safety as a CSR, participate in extramural pharmacovigilance activities and comply with regulatory reporting. Their websites claim that they prioritize patient safety, product safety and integrity. Patient safety is linked to CSR. Citing the importance of regulatory compliance in protecting public health, AbbVie reports that it upholds ‘the letter and spirit of healthcare laws... complies with all legal and regulatory requirements that govern the reporting of safety information to regulatory or public health agencies and communicate[s] with each government agency that oversees our products to address potential safety concerns’ in its business code of conduct.

In contrast to statements reported in its code of conduct, AbbVie states that regulatory compliance cannot be guaranteed in its Security and Exchange Commission (SEC) 10K report. AbbVie and Abbott describe counterfeit medicines and products diverted from the legal supply chain as drug safety threats rather than ADRs.

Abbott and AbbVie report the status of clinical trials (premarket and postmarket) and list postmarket commitments on their websites. Abbott publishes this information on its Global Citizen webpage, supporting its claim of commitment to transparency.

In contrast, Abbott India states that its philosophy of corporate governance is to protect the company, be accountable to shareholders and conduct business ethically and transparently. In its 2010 annual report, Abbott India describes counterfeit drugs as a risk to company profit rather than to patient safety. Abbott India continued to market Leptos (sibutramine) until it was banned by India’s Ministry of Health and Family Welfare, one year after it was withdrawn from European Union (EU) and US markets. Phenylpropanolamine (PPA) continues to be marketed by Abbott in India despite an FDA request that ‘all drug companies discontinue marketing products containing PPA’ in the US.
Merck

Merck is ranked in tier 3 of our continuum. The company addresses pharmacovigilance governance on its website, participates in extramural pharmacovigilance activities and complies with regulatory reporting. The executive vice president and president of Merck Research Laboratories (MRL) are responsible for Merck’s global pharmacovigilance strategy. MRL safety teams evaluate the safety of medicines and vaccines. Merck’s Global Compliance Organization periodically audits global pharmacovigilance practices for compliance with regulations and guidelines. Risk Management & Safety (RMS) teams ‘assess patient safety using product labeling, physician and patient educational programs, and other risk-minimization strategies’ and ‘implement strategies to determine the effectiveness of these interventions, as appropriate’.

Pursuant to Fagin v. Scolnick (2010), the class action suit involving Vioxx (rofecoxib), Merck has made corporate governance changes to create a product safety committee. However, details about the committee are not posted on the company website. Merck also added pharmacovigilance topics to its Code of Conduct as required, which in aggregate comprise approximately one of forty-three pages. Topics covered pertain to post-authorization safety studies (e.g., ethics questions regarding inappropriate promotion of observational studies in order to increase sales) and reporting ADRs even when mentioned in an informal setting. Selective reporting of study results is denounced however a limitation on dissemination and publication of the results persists. Merck’s Code of Conduct states, “As a researcher, before you consider releasing any scientific result or information that is based on work conducted at Merck/MSD, you are required to first seek the approval of your divisional vice president, or have the information reviewed by the Office of Scientific and Technical Information Clearance process for approval.” This has implications for identifying and publicly reporting early signals of safety issues and risk communication. Merck proclaims it is committed to timely registering, conducting and reporting of clinical trial results, however, it was issued a warning by the FDA in 2012 for failing to meet the agreed upon timetable for completion of required postmarket studies. Merck also claims to have integrated CSR into its governance and business strategy, and has established the Office of Corporate Responsibility, the Public Policy and Responsibility Council and the Corporate Responsibility Report Working Group (external stakeholders) to develop and monitor CSR targets and performance indicators. However, Merck defines corporate citizenship as being committed to complying with laws and regulations governing the way they market and sell medicines and other products, and does not specifically address pharmacovigilance.

The Merck India website claims that it is committed to patient safety, maintains an Adverse Event Reporting database and follows procedures for safety monitoring and compiling information about adverse events (ADEs) in compliance with global regulations. The link to information directs the viewer to the Merck parent company website. Ethics and transparency are a corporate value according to Merck India, yet Merck continued marketing Vioxx in India one year after the drug was withdrawn in US and EU markets and continues to include PPA in Indian cold products. Although PPA-containing products were banned in India in 2011, the ban was stayed by the High Court of Madras, India as a result of a successful challenge by CIPLA, an Indian company.
GlaxoSmithKline

GlaxoSmithKline (GSK) is also ranked in tier 3. Characteristics of integration of pharmacovigilance into corporate governance that were identified are a publicly accessible pharmacovigilance policy, participation in extramural pharmacovigilance activities and compliance with reporting requirements.

GSK’s policy on pharmacovigilance is outlined in a position paper on its website. It supports the European Federation of Pharmaceutical Industries and Associations (EFPIA) harmonization directive that ‘no additional national requirements will be allowed unless justifiable for pharmacovigilance reasons’. Pharmacovigilance is incorporated into GSK’s Global Safety Board mission to ‘ensure that human safety is addressed proactively throughout product development and to review the safety of GSK Products as may be warranted in light of clinical experience’. This value is contrasted with GSK India’s statement on Research & Development and Regulatory Matters which states that ‘Efforts towards ensuring a speedy review and approval by regulatory authorities... will help achieve early access to new and innovative therapeutic options to patients in the country’. GSK India’s annual report 2011-12 states that corporate governance is ‘guided by a strong emphasis on transparency, accountability and integrity... codified [in a] Corporate Governance Charter, which is in line with the best practice,... meets all the relevant legal and regulatory requirements’. Yet, GSK India does not explain the nature of the seven consumer cases pending against the company. The GSK India postmarket drug safety philosophy is not stated in its annual report, however, its commitment to protecting the rights and safety of patients in drug studies is stated. GSK’s standard for clinical trials in developing countries, posted on the parent company website, is that comparator drugs used in drug trials will never be less beneficial than the local standard of care. Though, the drugs may be less beneficial than the ‘best current treatment available anywhere in the world’. This is unlike trials that might be conducted in developed countries.

Novartis

Novartis is ranked in tier 4 of our continuum. The R&D process is described as concluding with market approval and information about postmarket drug safety is limited in its annual report. Novartis alludes to post-approval commitments by describing its requirement to conduct a Phase IV study of Gilenya (fingolimod), a drug used in the treatment of multiple sclerosis. In the Novartis 2010 and 2012 annual reports, sections titled “Increasingly challenging business environment” and “Increasing regulatory and safety hurdles”, the company decries that, “...post-approval regulatory burden on pharmaceutical companies has also been growing... and further heighten the risk of recalls, product withdrawals, or loss of market share.” In summarizing its corporate citizenship in 2010, Novartis reports, “engaging with society to improve healthcare... access-to-medicine [and] ...R&D institutes for diseases in developing countries, [and] ...USD $1.5 billion or 3% of net sales.” By linking sales goals to increasing access to medicine, it can be inferred that the company’s interest in R&D in developing countries is motivated by projected sales. As developing countries begin to strengthen their pharmacovigilance systems and impose greater regulatory
requirements for postmarket drug safety, it is unclear whether Novartis will find this to be a disincentive to continued R&D for diseases endemic to developing countries.

The Novartis India annual report describes corporate citizenship as meeting, “the expectations of stakeholders ...and rules concerning ethical business conduct.” In prioritizing responsibility to shareholders Novartis India shows that a culture for drug safety is not well integrated into corporate governance. Whereas the importance of patent protection is described in five pages of the Novartis India annual report, there is no description of pharmacovigilance policies or drug safety.

Pfizer

Pfizer illustrates the least integration of pharmacovigilance governance and is also placed in tier 4. Despite statements in its 2010 annual report that “Patient safety is our absolute first priority”, Pfizer’s 2010 and 2012 global financial reports tell a different story about corporate values and drug safety. Pfizer was the only company that did not include information about pharmacovigilance in its 2010 annual report. Drug safety was described in the context of potential risks to its projected financial outlook and litigation. The company has included two references in its 2012 annual report pertaining to PMRs for product life cycle monitoring and postmarket studies. Pfizer has been delinquent in meeting its postmarket commitments and has received warning letters from the FDA. Pfizer’s activities to support pharmacovigilance are not highlighted in its annual report. In contrast, company activities to increase access to Pfizer products in emerging markets through its 30 programs and partnerships are highlighted.

Pfizer India claims to have adopted the corporate values of its parent company: integrity, respect for people, customer focus, community, innovation, collaboration, performance, leadership, and quality. None of the core values are directly related to drug safety. The only reference to pharmacovigilance cited in the Pfizer India annual report is the Medical Affairs and Research Division which, “... provides medical support to regulatory registration as well as safety review and labeling activities.” Pfizer India states that, “...recent regulatory uncertainties like the proposed new drug policy coupled with the policy paralysis and economic downturn could cripple the growth curve.” The drug policy the company deems unfavorable is not specified.

PUBLIC ACCESSIBILITY TO PHARMACOVIGILANCE FLOW CHART AND POSITION PAPERS

Public accessibility to information about pharmacovigilance and drug safety is limited for GPC Indian subsidiaries. Abbott India describes drug safety relative to counterfeit drugs. Merck’s and Pfizer’s Indian subsidiaries reference their parent company policies. The Eli Lilly (India) website provides the most information pertaining to pharmacovigilance. Their Patient Safety webpage describes the physician and patient responsibility to report adverse drug reactions and Lilly’s role to continue monitoring the safety of medicines even after the drug reaches the market. The company states that “Safety Information is continually assessed and we share new findings and emerging concerns openly with regulators and physicians to appropriately manage risks associated with the use of our medicines”. A banner across the bottom of the Eli Lilly
(India) homepage informs visitors to the website about reporting adverse events and complaints about Lilly products. The Eli Lilly (India) Patient Safety web page provides a direct link to India’s Drug Controller General of India (DCGI) national pharmacovigilance program to report adverse drug reactions.

The parent company’s position on pharmacovigilance is more widely accessible on its Headquarters’ website. Abundant information explaining pharmacovigilance and Lilly’s role in postmarket safety is posted to its Patient Safety website. The documents are written in lay language and describe the role of the company, patient, healthcare provider, and the FDA for patient safety. The website describes postmarket studies and spontaneous reporting as sources of information for emerging safety issues. Lilly does not state how or why decisions are made to conduct postmarket studies and only states that data collected through studies and spontaneous reporting is reviewed periodically, without giving the frequency. If a safety issue arises, the company’s risk management program includes risk communication to physicians, health regulators, and patients (e.g., Dear Health Professional letter). Voluntary market withdrawal of the product, as a possible outcome of a newly discovered safety issue, is not mentioned on this webpage. Product withdrawal is cited as an outcome of unexpected safety concerns in Lilly’s annual report.

GSK’s position on pharmacovigilance is posted on its website in a policy statement that claims the corporation is committed to placing patient interests above corporate interests and to monitoring the safety profile of a drug throughout the product life cycle. GSK’s description of postmarket drug safety as a threat in its annual report, and support for EFPIA’s limits on regulation, is inconsistent with statements about patient interests.

Abbott’s strategy for addressing drug safety is briefly described on its webpage entitled Global Citizenship. Abbott claims that it investigates drug safety signals and acts in accordance with established corrective and preventative action plans. The plans are not published on its website, despite corporate governance statements about commitment to transparency.

Merck’s position statements on pharmacovigilance are found on the Patient Safety page of its website. The role of its RMS teams in monitoring safety issues throughout the product life cycle and in the development of Risk Management Plans is described.

**Extramural Pharmacovigilance Activities**

Novartis, Pfizer, Merck, Abbott and GSK are partners in the International Serious Adverse Event Consortium (iSAEC). The iSAEC is a consortium of corporate, scientific, and commercial partners that includes government regulatory authorities (e.g., FDA, EMA), US Veterans Administration, universities, private and public research networks (e.g., Wellcome Trust, Dundee University, and HMO Research Network). The consortium pools data on serious adverse events (SAE) and analyzes it to identify genetic markers of risks for rare SAEs (e.g., acute hypersensitivity syndrome). Eli Lilly is the only GPC studied that is not a member. GSK is the deputy coordinator of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium.
REGULATORY COMPLIANCE

Pharmaceutical manufacturers are required to collect information about ADRs and submit a Periodic Safety and Update Report annually (PSUR) to the FDA. According to draft guidelines, a serious adverse event that occurs during clinical trials must also be reported to India’s regulatory authority. Abbott claims to comply with reporting requirements but does not provide specific details on its website. Eli Lilly provides information about Risk Management Plan (RMP) requirements and claims to submit a RMP with each new drug application. RMPs are described as proactive and systematic activities designed to identify, characterize, minimize, and communicate product risks rather than a regulatory burden. Merck claims to follow local laws and practices for ADR reporting outside the US. This may place patients at risk for unnecessary exposure to known ADRs in countries e.g., India, where reporting requirements are more lax. One year after Vioxx was withdrawn from the US market, a warning still had not been issued in India. In contrast, AbbVie claims to follow the higher regulatory requirement and laws where country differences exist.

Merck states that PMRs for US marketed products are posted on its website quarterly, as required by US FDA regulations. PMRs may include clinical, non-clinical, and pharmacovigilance studies/trials. The web link to more information directs the reader to the FDA’s website for a description of PMR requirements rather than linking to Merck’s quarterly report. Merck was issued a warning letter on February 17, 2012 by the FDA regarding the company’s failure to complete postmarket studies for Januvia (sitagliptin) and Janumet (sitagliptin and metformin), required as a condition for market approval in 2010. Merck must now meet a revised timetable for the studies or face regulatory actions by the FDA, including but not limited to, civil or monetary penalties. The studies’ status for meeting the revised timetable is unavailable. Pfizer also received a warning letter from the FDA in 2010 regarding its failure to submit reports of adverse events within required timeframes.

POSTMARKET DRUG SAFETY REQUIREMENT AS A “THREAT”

Increasing regulatory scrutiny and PMRs are described as a business threat in Merck, Pfizer, GlaxoSmithKline, Novartis, Abbott and AbbVie annual reports. Regulatory discretion to require postmarket Phase IV trials or other studies, re-review of drug safety and effectiveness of marketed products in the US and EU, and changing public and government expectations for safety and efficacy, are cited as risks to the demand for Merck products. Clinical trials and postmarket surveillance of marketed drugs that lead to recalls, increased scrutiny, concerns by prescribers and patients, government action and litigation (civil and criminal) are predicted to continue, further exposing the pharmaceutical industry and Merck to risk, according to Merck annual report statements.

For example, GSK’s 2012 annual report states:

...emerging markets have been increasing their regulatory expectations based on their own national interpretations of US and EU standards. Stricter regulatory controls heighten the risk of changes in product profile or withdrawal by regulators on the basis of post-approval concerns over product safety, which
could reduce revenues and result in product recalls and product liability lawsuits.  

The statement is inconsistent with website claims valuing patient interests above corporate interests. Pharmacovigilance is not listed as a GSK strategic priority.

Novartis’ corporate literature describes postmarket drug safety as a threat. The company received FDA warning letters regarding several of its drugs between 2010-2013, for failure to cite risks for use in product advertising, including Gleevec (imatinab), Tasigna (nilotinib), and Exforge (amlodipine + valsartan). Zelnorm (tesagerod) was available in India in 2011, nearly four years after it was withdrawn from the market in the US and European countries. A parliamentary standing committee in India reported that Novartis submitted clinical trial results for approval of aliskeran, in which only 46 out of the required 100 patients were enrolled.

Increasing regulatory scrutiny is described as a risk to financial targets in both Pfizer parent company and Pfizer India’s 2012 annual reports. The Pfizer India annual report claims that regulatory uncertainties and a proposed new drug policy could cripple growth, although the report does not identify the specific policy.

Compliance with FDA, international and supranational regulatory requirements for postmarket studies and other post-approval regulatory requirements, according to statements in Abbott and AbbVie’s 2013 annual reports, “is costly and materially affects Abbott's business... health care regulations substantially increase the time, difficulty, and costs...obtaining and maintaining approval to market...products.” The 2012 AbbVie annual report asserts that postmarket studies may find new safety or efficacy issues that could halt sales or reduce market acceptance of its products. Neither Abbott nor AbbVie guarantees that regulatory compliance will be maintained once product approval has been obtained, including postmarket pharmacovigilance and adverse event reporting.

Noticeably absent from Lilly’s annual report is a characterization of pharmacovigilance and drug regulatory requirements as a threat to the company’s business. The company acknowledges that, “Unexpected safety or efficacy concerns can arise with respect to marketed products, leading to product recalls, withdrawals, or declining revenue, as well as costly product liability claims.” This single negative reference to postmarket drug safety in the annual report is characterized as the nature of the pharmaceutical industry.

**ACTIONS TAKEN AGAINST THE CORPORATION FOR SAFETY ISSUES**

The New Jersey Superior Court settlement related to Vioxx in *Fagin v Scolnick (2010)*, which required Merck to create a product safety committee, also required it to register all clinical trials, submit results to the clinical trial registry (clinicaltrials.gov), and accurately report all study results in compliance with the FDA Amendment Act 2007. Despite the settlement, Merck was issued an FDA warning in 2012 for failing to meet the agreed upon timetable for completion of postmarket safety studies for Januvia and Janumet.

Pfizer reported that it received an FDA warning in its 2010 annual report, “with respect to the reporting of certain post-marketing adverse events relating to certain drugs.” The warning letter sent to Pfizer, posted on the FDA website, admonished...
Pfizer for failing to submit reports of serious unexpected adverse drug reactions (SUSARs) for five drugs; two were the Pfizer blockbusters Lipitor (atorvastatin) and Viagra (sildenafil). In the case of Viagra, the FDA claimed that the company misclassified the ADR as non-serious to avoid increased requirements for reporting SUSARs. The FDA admonished Pfizer for a decline in timely reporting of adverse drug events between 2008 and 2009.

POSTMARKET REQUIREMENTS

All of the companies were required by the FDA to conduct postmarket studies for select drugs (Figure 2). As of June 2013, Abbott had submitted the final report to the FDA for its one required PMR. Eli Lilly was issued twenty-two PMRs for six drugs. Nine studies are ongoing, and the final report was submitted for ten studies. Three studies have not been initiated, however, according to FDA classification, these have not met formal requirements for delay (i.e., the original projected date for initiation of patient accrual or initiation of animal dosing has not passed). A total of seventy PMRs were issued to GSK for fourteen drugs and seventeen vaccines. The FDA canceled four PMRs. Of the remaining sixty-six, thirty-four studies are uninitiated (no explanation has been provided for six pending PMRs), fourteen studies are ongoing, and eighteen have been completed with reports submitted. One of the pending studies was required in 2008. Merck had sixty-nine PMRs for eleven drugs and eight vaccines. As of June 2013, twenty-eight studies were pending, twenty-seven completed, and ten were ongoing. One hundred eighteen PMRs were issued to Novartis for seventeen drugs

Figure 2: Summary of Postmarket Requirements (PMR) 2010-2013*

*Source: FDA “Postmarket Requirements and Commitments”. www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
and twenty vaccines.\textsuperscript{131} The FDA canceled the PMRs for Zelnorm: the drug was withdrawn from the market. Of the remaining PMRs, sixty-one are uninitiated, twenty-five studies are ongoing, and twenty-nine have been completed with reports submitted.\textsuperscript{132} The completion date for one of the delayed studies was originally set for 2009.\textsuperscript{133} Pfizer was issued fifty-two PMRs for seven drugs. The company has fifteen studies ongoing, submitted the final report for five, and twenty-four studies are uninitiated.\textsuperscript{134} Additional data are given in Appendix 2.

**DISCUSSION**

We found that corporate governance has clear implications for pharmacovigilance. Values promoting drug safety begin in the boardroom, yet tensions between corporate responsibility to shareholders and CSR to a broader range of stakeholders may impede a culture of pharmacovigilance.\textsuperscript{135,136} Maennl (2008), found that effective corporate pharmacovigilance requires a culture of safety that aligns safety and risk management with corporate business strategy. This culture does not exist in most pharmaceutical companies, a finding supported by our research.\textsuperscript{137}

Although the company documents analyzed claimed that each GPC was working to achieve Millennium Development Goals (MDGs) to increase access to medicines, their commitment to pharmacovigilance was not found to be commensurate. Nearly all of the companies included in our study received low AMI ratings for their efforts to strengthen national pharmacovigilance systems.\textsuperscript{138} Postmarket drug safety in low and LMI countries such as India is further compromised when corporate governance that advances pharmacovigilance is absent, and healthcare system resources and pharmacovigilance capacity are limited.\textsuperscript{139}

**GPCS AND POSTMARKET DRUG SAFETY IN INDIA**

India’s population increasingly has access to new and older pharmaceuticals.\textsuperscript{140} However, the population is vulnerable to adverse effects linked to brand name and generic pharmaceuticals voluntarily withdrawn by GPCs in other countries. As recently as April 2013, a parliamentary standing committee on health charged the government with procrastination in following through with a pledge made to suspend market authorization for all drugs prohibited for sale in the US, Canada, EU, Australia and other countries and accused the ministry of, “collusion with the intention to save the guilty.”\textsuperscript{141} It was not until June 2013 that India’s Ministry of Health and Family Welfare took action to ban the analgesic Analgin (metamizole), the antidepressant Deanxit (flupentixol + melitracene), and the generic antidiabetic pioglitazone.\textsuperscript{142,143,144} All three drugs, produced by GPCs (Sanofi, Sanofi India and Lundbeck Italy), including generic pioglitazone, had been banned in other countries years earlier.\textsuperscript{145} Tesagerod, withdrawn by the FDA in 2007, and not banned in India until 2011, was found on drug outlet shelves in June 2011 during a Drugs Controller General of India (DCGI) inspection.\textsuperscript{146} Without a fulltime drug controller general since 2012, the DCGI’s capacity to monitor pharmacovigilance compliance has been limited.\textsuperscript{147} A survey of 230 Delhi pharmacists, community, hospital and medical representatives (from thirty-three GPCs including Eli Lilly, Pfizer, Aventis, GSK, and Astra Zeneca), assessed the knowledge, skills and attitudes about pharmacovigilance and ADR reporting. It found that medical
representatives had the least awareness of pharmacovigilance (35.48%), and only 14.51% of the medical representatives claimed they had ever reported ADRs despite Central Drugs Standard Control Organization guidelines that all ADRs should be reported.148

PHARMACOVIGILANCE AND CORPORATE GOVERNANCE: DIVERGENT STANDARDS

Our research found GPC’s had divergent integration of pharmacovigilance and corporate governance. Parent company and Indian subsidiary standards also diverged. Abbott, Merck, Novartis, and Pfizer’s publicly stated positions on regulatory requirements differed from SEC filings. GPC’s characterization of regulations requiring 1) postmarket testing, 2) documentation of safety and efficacy, and 3) greater scrutiny of compliance with product manufacture, as regulatory and safety hurdles because they can harm the company’s reputation, result in product recall, withdrawal or litigation, is an impediment to pharmacovigilance governance. The push for speedy review and regulatory approval for the purpose of early access to markets, as described in GSK India’s annual report, is not aligned with the precautionary principle which suggests that marketing should be delayed until sufficient safety information is compiled. Rather than strengthening pharmacovigilance regimes in low and LMI countries, as recommended by the AMI, GPC’s support for supranational positions (e.g., EFPIA) to limit additional national requirements suggests that they would be unlikely to lead efforts to implement stringent pharmacovigilance strategies.149,150

Research findings suggest that a corporate culture of pharmacovigilance is a determinant for PMR completion and the resolution of outstanding product safety issues. Eli Lilly, which comes closest to Maennl’s model for corporate culture of pharmacovigilance, had fewer uninitiated or delayed PMRs than Merck, Pfizer, Novartis, and GSK.151 GSK, Pfizer, and Novartis had the highest level of pending or uninitiated PMRs and the lowest level of study completion. Eli Lilly had a product withdrawn from the US, EU, or Indian market between 2010 and 2013, as did the other GPCs. Abbott and Merck, which described postmarket drug safety regulations as a threat in their corporate annual report, marketed their products in India after the drugs were withdrawn from US or EU markets. They exposed patients in India to medicines for which serious adverse events were known. Abbott India continued to market Leptos (sibutramine) until it was banned in India, one year after it was withdrawn from EU and US markets.152 Abbott and Merck cold products, reformulated in the US, continue to contain PPA in India. This suggests not only a failure of pharmacovigilance governance but also a double standard for postmarket drug safety in the developing countries, as compared to developed countries. Similarly, GSK has divergent standards for the use of comparator drugs in clinical trials in developing and developed countries.153 If GSK has divergent standards for clinical trials, it may also have a double standard for drug safety.

Public access to information about pharmacovigilance and drug safety is limited for GPC Indian subsidiaries. Pharmacovigilance is not described in the GSK India or Novartis India annual reports, and Abbott India describes drug safety relative to counterfeit drugs. Merck and Pfizer’s Indian subsidiaries reference their parent company policies and do not explicitly discuss corporate governance pertaining to pharmacovigilance. When the link to information about Merck’s safety monitoring is clicked, the viewer is directed outside the Merck India website and warned that MSD is
not responsible for the content. Information is posted to the Eli Lilly (India) website. However, the company’s corporate annual report is not publicly available to verify internal consistency between stated positions. The lack of public information by GPC Indian subsidiaries has implications for accountability for postmarket drug safety in India.

**CONCLUSION**

We found an inverse relationship between GPC integration of pharmacovigilance into corporate governance and outstanding product safety issues. The lack of integration has resulted in the perception that postmarket commitments are a threat rather than an opportunity to build value for the company. Our research suggests that the MDGs for access to medicines are insufficient to assure access to safe medicines. The ranking of GPCs for integration of pharmacovigilance and corporate governance varied between our study continuum and the AMI. Whereas Eli Lilly was ranked highest in our research, it was ranked fourteenth in the AMI. A possible explanation could be that pharmacovigilance is but one of the indicators of Capability Advancement in Product Development & Distribution, an area that received only 10% weighting by the Access to Medicine Foundation in the construction of the AMI. Further research is needed to better understand the inverse company ranking.

GPC Indian subsidiaries’ integration of drug safety and corporate governance is limited. Pharmacovigilance is unlikely to be supported solely by GPCs without robust policy incentives. Supranational standards requiring GPCs to strengthen capacity for pharmacovigilance in under-resourced areas and exceed minimum standards, as measured by the AMI, would enhance postmarket safety. GPCs currently abide by some supranational standards promoted by the International Conference on Harmonization. Rebates (or fines) based upon meeting (or not meeting) the highest pharmacovigilance standards, when country differences exist, would incentivize GPCs. Incentives that assure that drugs withdrawn from US, European and other major markets do not continue to be marketed in developing countries should be implemented. Employee bonuses based on innovation supporting pharmacovigilance would also incentivize postmarket drug safety.

Corporate governance that strengthens pharmacovigilance and builds capacity to monitor and enforce regulatory compliance will enhance postmarket drug safety and reduce corporate reputational risk related to product safety issues. Independent monitoring by the national drug regulatory authority supported by international regulatory authorities (e.g., FDA and EMA) and global health institutions such as the WHO is recommended to hold GPCs accountable for postmarket drug safety.

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Appendix 1: Corporate Governance Codebook

<table>
<thead>
<tr>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacovigilance described as a corporate value</td>
<td>Postmarket drug safety and safety monitoring is described as integrated within the global quality system and a Corporate social responsibility</td>
</tr>
<tr>
<td>Pharmacovigilance flow chart or safety framework published</td>
<td>Flow charts show passive and active pharmacovigilance activities e.g. pharmacosurveillance and postmarket clinical trials</td>
</tr>
<tr>
<td>Pharmacovigilance position publically available</td>
<td>Position papers posted on website</td>
</tr>
<tr>
<td>Drug safety practices described CSR or Global Citizen</td>
<td>Record of drug safety activities in reported in Annual Corporate Social Responsibility Report or Annual Global Citizenship Report</td>
</tr>
<tr>
<td>Participates in extramural pharmacovigilance activities</td>
<td>Member of external body engaged in improving pharmacovigilance</td>
</tr>
</tbody>
</table>

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GLOBAL HEALTH GOVERNANCE, VOLUME VII, NO. 1 (FALL 2013) http://www.ghgj.org
(PROTECT)...is a collaborative European project aimed at addressing the limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance. The EMA is the coordinator of PROTECT and GSK is the deputy coordinator.-GSK position paper on pharmacovigilance (2011)

<table>
<thead>
<tr>
<th>Complies with regulator reporting requirements</th>
<th>Submits reports of Suspected Unexpected Serious Adverse Reactions (SUSARS) and annual Periodic Safety Update Reports (PSURs).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-market drug safety described as a threat</td>
<td>Regulations requiring post-market safety studies described as a threat to corporate profits due to cost of clinical trials, risk for market withdrawal, or loss of market share.</td>
</tr>
</tbody>
</table>

[The] country manager is responsible for the collection of safety information and reporting issues in PSURs and discussing proposed action to mitigate risks with regulatory authorities.-GSK Global Public Policy Issues-Position on Pharmacovigilance

The post-approval regulatory burden on pharmaceutical companies has also been growing. ...post-approval Phase IV clinical trials to gather detailed safety and other data on products...further heighten the risk of recalls, product withdrawals, or loss of market share. - Novartis 2010 Corporate Annual Report

We are confronted by increasing regulatory scrutiny of drug safety and efficacy ... even when we view data as sufficient to support the safety and/or effectiveness of a product candidate or a new indication for an in-line product, regulatory authorities may not share our views and may require additional data or may deny approval altogether. – Pfizer Annual Report 2010 Appendix A 2010 Financial Report

...emerging markets have been increasing their regulatory expectations based on their own national interpretations of US and EU standards. Stricter regulatory controls heighten the risk of changes in product profile or withdrawal by regulators on the
basis of post-approval concerns over product safety, which could reduce revenues and result in product recalls and product liability lawsuits.—GSK 2012

| Action taken against corporation due to safety issues with drug product(s) | Product(s) withdrawn, labelling changes required for safety issues, Application Integrity Policy invoked, or litigation filed within past 3 years | Our businesses have been subject to significant civil litigation as well as governmental investigations and information requests by regulatory authorities—Novartis 2010

Beginning in December 2008, purported class actions were filed against us ...under Canadian product liability law, including with respect to the safety and efficacy of Champix—Pfizer Annual Report 2010 Appendix A 2010 Financial Report

Pharmacovigilance or drug safety not described in Annual Report | Description of corporate policies or governance related to pharmacovigilance or drug safety omitted

Appendix 2: Summary of Postmarket Requirements 2010-2013a

<table>
<thead>
<tr>
<th>Drug Name(s)</th>
<th>Studies not initiated, pending or delayed b</th>
<th>Studies Submitted or fulfilled</th>
<th>Final report past milestone</th>
<th>Ongoing Studies</th>
<th>Type of Study</th>
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</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>1</td>
<td>Depakote</td>
<td>0</td>
<td>1</td>
<td>Drug interaction between Depakote + olanzapine</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>22</td>
<td>Prozac, Effient, Zyprexa, Forteo, Cymbalta, Symbiya</td>
<td>3</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>70c</td>
<td>Arzerra, Horizant, Altabax, Votriant, Advair diskus, Zofran, Zyban, Potiga, Arixtra, Veramyst, Alli, Promacta, Flonase and Nicorette studies were released</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Company</th>
<th>PMR</th>
<th>Vaccines</th>
<th>Common Name</th>
<th>FDA Study</th>
<th>Zelnorm Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck</td>
<td>69d</td>
<td>11</td>
<td>Lamictal, Lamictal ODT &amp; CD, Requip XL, (+17 vaccines)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>118e</td>
<td>17</td>
<td>TOBI Podhaler, TOBI, Signifor, Reclast, Neoral, Tyzeka, Foradil, Fanapt, Coartem, Lioresal, Gleevec, Afinitor, Gilenya, Exjade, Tasigna, Voltaren gel, Nexcedex (+20 vaccines)</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>Pfizer</td>
<td>52f</td>
<td>7</td>
<td>Advil Allergy &amp; Congestion Relief, Advil, Zithromax, Vfend, Revatio, Chantix/Champix, Geodeon</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

b FDA Criteria of delay not met
c FDA released GSK from four PMR requirements
d FDA released Merck & Co from five PMR requirements
e FDA released Novartis from three PMR requirements
f FDA released Pfizer from eight PMR requirements (All "released" studies pertained to dosing of phenylephrine in children 2-12 yrs. The drug is no longer labeled for use in children under 12 years and has been removed from OTC drugs for children (Advil Allergy & Congestion Relief, Advil)
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48 Ibid., p.2.
50 Ibid., p.22.
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52 FDA, "Inspections, Compliance, Enforcement, and Criminal Investigations- Merck, Sharpe, and Dohme Warning Letter," in Ref: 12-HFD-47-02-0 (Silver Springs, MD: Department of Health and Human Services, February 17, 2012).
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The GSK statement on pharmacovigilance is available online at: [http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-pharmacovigilance.pdf](http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-pharmacovigilance.pdf)


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149 GlaxoSmithKline, "Clinical Trials in the Developing World."
150 GlaxoSmithKline, "Global Public Policy Issues- GlaxoSmithKline's Position on Pharmacovigilance."
151 Maennl, "Pharmacovigilance: a company-wide challenge: truly integrated risk management requires breaking down silos and strong business leadership from the top."
152 Central Drugs Standard Control Organization, "Drugs Banned in the Country."
153 GlaxoSmithKline, "Clinical Trials in the Developing World."
154 The link to more information about Merck India safety monitoring [http://www.msdindia.in/about/views-and-positions/Pages/quality-and-safety.aspx](http://www.msdindia.in/about/views-and-positions/Pages/quality-and-safety.aspx)