Pharmacogovernance in Low- and Middle-Income Countries: a case study of Brazil and Kenya

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Adverse drug reactions (ADRs) are a global public health threat leading to illness, disability and death. Yet, few countries have a framework to guide postmarket drug safety policy despite increasing access to pharmaceuticals worldwide and the growing trend of gathering information about medicines in the postmarket (rather than the premarket) period.

This gap is addressed by ‘pharmacogovernance’, a new theoretical concept that is introduced in this thesis. Pharmacogovernance is defined as the manner in which governing structures; policy instruments; and institutional authority (e.g., ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests for patient safety and protection from ADRs. An analytic framework for examining pharmacogovernance is presented that clarifies the relationship between governance and pharmacovigilance in order to explain how pharmacogovernance influences pharmacovigilance.

The research investigates how and why the State (at all levels), global actors and the pharmaceutical industry interact to affect pharmacogovernance and ultimately postmarket drug safety in a low and upper-middle income country (Kenya and Brazil); and how patterns of governance (e.g., devolved and decentralized) affect pharmacovigilance. A new application for
Network Governance Theory is presented to explain state and non-state actors’ interactions regarding pharmacovigilance.

Qualitative research methods that included key informant interviews, document analyses and a scoping review were conducted. Key findings show that the pharmacogovernance framework can guide policy making for postmarket drug safety. Policy, law and regulations are important for advancing pharmacovigilance and ensuring enforcement however gaps in other pharmacogovernance domains may impede pharmacovigilance in areas such as risk communication and regional equity in postmarket surveillance. The current funding model for pharmacovigilance in Brazil and Kenya is inadequate leading to ad hoc investment in pharmacovigilance and fluctuating priorities. Positive interdependency between pharmacogovernance structure, institutions and networks comprised of global actors can enhance pharmacogovernance and pharmacovigilance.

Research results illuminate how in Brazil and Kenya investments in pharmacogovernance processes, institutions and network engagement may further improve pharmacovigilance. Investments include: strengthening medicines regulatory authorities; establishing a sustainable funding model for pharmacovigilance; strengthening social participation and inclusion in regulatory decisions pertaining to pharmacovigilance; and increasing interdependency amongst pharmacogovernance structure, institutions, and networks.
Acknowledgments

The journey to completing a doctorate is an arduous one made easier by a league of mentors, family and friends. I have many people to thank for the guidance and assistance they provided along my journey.

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Next, I would like to thank my family for encouraging me throughout my journey. A special thank you goes to my husband Dr. Gervan Fearon who was instrumental in encouraging me to pursue a doctoral degree. He supported me in many ways during the past five years by accompanying me to late night study and writing sessions at coffee shops, reading numerous drafts of my thesis and providing constructive feedback.

I would like to thank my sister Dr. Susan Moscou. Susie is the first person in my family to earn a PhD. She has been a fabulous mentor and role model. She set the bar for my family that we can pursue and achieve a doctoral degree.

I am extremely proud of my daughter Dr. Gyasi Moscou-Jackson who received her PhD in nursing this past year. Gyasi and I enrolled in doctoral studies simultaneously. It has been an incredible mother-daughter bonding experience to walk this path together. While encouraging her and advising her through roadblocks in her doctoral journey, I have on occasion found that my words of advice were invaluable to me in overcoming similar setbacks.

I would also like to thank my parents for encouraging their children to think about how to make a contribution to the betterment of society at large, thus influencing my decision to conduct research on pharmacogovernance.

Lastly, I would like to thank Dr. Paola Casalvina and João Batista Da Silva Junior for their contribution to the scoping review.
Table of Contents

Acknowledgments.......................................................................................................................... iv

Table of Contents ........................................................................................................................... v

List of Tables ................................................................................................................................... x

List of Figures ................................................................................................................................ xi

List of Appendices ........................................................................................................................ xii

List of Abbreviations ................................................................................................................... xiv

Chapter One: Introduction ...............................................................................................................1

1.1 Context........................................................................................................................................ 1

1.2 Background................................................................................................................................. 1

1.2.1 Postmarket drug safety issues in LMI countries................................................................. 2

1.2.2 Pharmacovigilance in LMI countries.................................................................................. 5

1.2.3 Governance and postmarket drug safety......................................................................... 6

1.2.4 Global actors and the spread of pharmacovigilance policy norms............................... 9

1.3 Statement of the problem.......................................................................................................... 10

1.3.1 Rationale for Examining Pharmacogovernance in LMI countries......................... 10

1.3.2 Rationale for Investigating Pharmacogovernance in Brazil and Kenya.................... 11

1.3.3 Decentralization and devolved governance................................................................. 13

1.4 Rationale for the research....................................................................................................... 13

1.5 Purpose of the research.......................................................................................................... 15

1.6 Theoretical Framework.......................................................................................................... 16

1.7 Overview of thesis chapters.................................................................................................... 22

Chapter Two: Methods .................................................................................................................. 26
Chapter Three: “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety”

3.1 Preamble .................................................................46
3.2 Abstract .........................................................................47
3.3 Background .......................................................................48
3.4 Pharmacogovernance Framework .......................................49
3.5 Methods .........................................................................55
3.6 Results ............................................................................56
   3.6.1 Pharmacogovernance variables .......................................56
   3.6.2 Pharmacovigilance and pharmacogovernance institutions in Brazil and Kenya ...57
3.7 Discussion ........................................................................73
3.8 Conclusion ........................................................................77

Chapter Four: Exogenous Factors Influencing on Pharmacogovernance and Pharmacovigilance in Brazil and Kenya

4.1 Preamble........................................................................79
Chapter 4a: “Governance and pharmacovigilance in Brazil: a scoping review” ........................................80

4a.1 Abstract ..............................................................................................................................81

4a.2 Introduction .......................................................................................................................83

4a.3 Background .......................................................................................................................86

4a.4 Methods .............................................................................................................................89

4a.4.1 Search Methods ..............................................................................................................91

4a.4.2 Criteria for selecting studies .......................................................................................93

4a.4.3 Types of studies included ...........................................................................................93

4a.4.4 Data extraction and management ..............................................................................95

4a.5 Results ...............................................................................................................................96

4a.5.1 Literature describing ANVISA’s regulatory reforms and policy instruments ..........101

4a.5.2 Literature describing ANVISA’s regulatory governance ...........................................101

4a.5.3 Literature describing global actors’ influence on norms in Brazil pertaining to governance or pharmacovigilance .........................................................................................102

4a.5.4 Literature describing ANVISA and Pharmacogovernance ........................................104

4a.6 Discussion .......................................................................................................................113

4a.7 Conclusion ......................................................................................................................116

Chapter 4b: “Matching Safety to Access: Pharmacogovernance in Kenya” ...................................118

4b.1 Abstract ...........................................................................................................................119

4b.2 Introduction .....................................................................................................................121

4b.3 Background .....................................................................................................................122

4b.3.1 Pharmacogovernance and medicines safety in Kenya .............................................122

4b.3.2 Pharmacovigilance and Exogenous actors in Kenya ...............................................125

4b.3.3 Kenya’s governance and exogenous actors ...............................................................127

4b.4 Methods ...........................................................................................................................132

4b.5 Results .............................................................................................................................134
4b.5.1 Exogenous actors’ interest in pharmacovigilance in Kenya ..................................134
4b.5.2 State and exogenous actors’ perceptions of pharmacogovernance and drug safety ....................................................................................................................138
4b.5.3 Patterns of interactions among state, non-state, and external actors’ influencing pharmacogovernance and pharmacovigilance ..................................140
4b.6 Discussion ...........................................................................................................167
4b.7 Conclusions ...........................................................................................................171

Chapter Five: Conclusions .......................................................................................175
5.1 Preamble ..............................................................................................................175
5.2 Summary of key findings .....................................................................................176
5.3 Emerging theoretical framework ..........................................................................179
5.3.1 Pharmacogovernance structure ....................................................................180
5.3.2 Pharmacogovernance institutions ..................................................................183
5.3.3 Pharmacogovernance networks ....................................................................189
5.4 Conclusion and Policy recommendations ............................................................191
5.4.1 Sustainable funding model for pharmacovigilance ........................................193
5.4.2 Strengthening social participation, representation and inclusion .................195
5.4.3 Strengthening Regulatory Authorities ............................................................196
5.4.4 Interdependent engagement between pharmacogovernance structure, institutions, and networks ...............................................................197
5.4.5 Networking between pharmacogovernance structures and institutions ..........198
5.5 Implications for governance in newly evolving arenas ........................................199
5.6 Limitations ..........................................................................................................199
5.7 Future research ....................................................................................................199

References ..............................................................................................................201

Appendix A. Paper: Corporate governance and medicines safety ..............................218
Appendix B1. Ethics Approval - University of Toronto ..............................................243
Appendix B2. Ethics Approval – Kenya......................................................................................246
Appendix B3. Ethics Approval - Brazil.......................................................................................248
Appendix C. Invitation to participate in the study.................................................................251
Appendix D1. Letter of consent - English ..............................................................................253
Appendix D2. Letter of consent - Portuguese.................................................................258
Appendix E1. Interview Guide: National Regulatory Authority - ANVISA.........................264
Appendix E2. Interview Guide: National Regulatory Authority - Kenya Pharmacy and Poisons Board .................................................................269
Appendix F. Interview guide: State pharmacovigilance Centre - Brazil .........................272
Appendix G. Interview guide: County pharmacovigilance official - Kenya .....................278
Appendix H. Interview guide: Multinational corporation ..................................................281
Appendix I. Interview guide: Domestic pharmaceutical company....................................284
Appendix J. Interview guide: IGO or INGO representative ................................................289
Appendix K. Governance and pharmacovigilance codebook ............................................292
Appendix L. Scoping review search terminology.................................................................299
Appendix M. Global institutions pharmacovigilance norms adopted in Brazil...............300
Appendix N. Global institutions pharmacovigilance norms adopted in Kenya..................304
Copyright Acknowledgements............................................................................................308
List of Tables

Table 1. Brazil and Kenya Country Profiles

Table 2. List of Key Informants

Table 3. Pharmacogovernance Domain Definitions

Table 4. Factors Influencing Pharmacovigilance

Table 5. Comparison of Pharmacogovernance Models and the Affect on Pharmacovigilance

Table 6. Scoping Review Structured According to STARLITE Principles

Table 7. Characteristics of Literature Screened for Inclusion or Exclusion

Table 8. Typology of Literature Included in the Scoping Review

Table 9. Analysis of the Modes of Engagement between Domestic and Exogenous Actors and the Affect on Pharmacogovernance

Table 10. Comparison of Pharmacovigilance Priorities Between State and Exogenous Actors
List of Figures

Figure 1. Pharmacogovernance Institutions in Brazil

Figure 2. Pharmacogovernance Institutions in Kenya

Figure 3. Factors Influencing Pharmacovigilance in Brazil

Figure 4. Scoping Review Flowchart

Figure 5. Pharmacogovernance Framework

Figure 6. Framework for a National Pharmacovigilance System in LMICs

Figure 7. Patterns of interactions Between Domestic and Exogenous Actors Affecting Pharmacovigilance

Figure 8. Patterns of Interactions Between state Domestic and Exogenous Actors Affecting Pharmacogovernance

Figure 9. Tripartite Model for Pharmacogovernance
List of Appendices

Appendix A. Paper 4: Corporate Governance and Medicines Safety

Appendix B1. Ethics Approval – University of Toronto

Appendix B2. Ethics Approval – Moi University, Kenya

Appendix B3. Ethics Approval – Comissão Nacional de Ética em Pesquisa (CONEP), Brazil

Appendix C. Invitation to participate in the study

Appendix D1. Letter of Consent- English

Appendix D2. Letter of Consent- Portuguese

Appendix E1. Interview Guide: National Regulatory Authority- ANVISA

Appendix E2. Interview Guide: National Regulatory Authority- Kenya Pharmacy and Poisons Board

Appendix F. Interview guide: State pharmacovigilance centre- Brazil

Appendix G. Interview guide: County pharmacovigilance official- Kenya

Appendix H. Interview guide: Multinational corporation

Appendix I. Interview guide: Domestic pharmaceutical company

Appendix J. Interview guide: Intergovernmental Organization (IGO) or International Nongovernmental Organization (INGO)
Appendix K. Governance and pharmacovigilance codebook

Appendix L. Scoping review search terminology

Appendix M. Global institutions pharmacovigilance norms adopted in Brazil

Appendix N. Global institutions pharmacovigilance norms adopted in Kenya
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AMRH</td>
<td>African Medicines Regulatory Harmonization</td>
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<tr>
<td>ANVISA</td>
<td>Agência Nacional de Vigilância Sanitária</td>
<td></td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
<td></td>
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<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
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<tr>
<td>CEM</td>
<td>Cohort Event Monitoring</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
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<tr>
<td>CSO</td>
<td>Civil Society Organization</td>
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<tr>
<td>IPAT</td>
<td>Indicator-based Pharmacovigilance Assessment Tool</td>
<td></td>
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<tr>
<td>KEMSA</td>
<td>Kenya Medical Supply Agency</td>
<td></td>
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<tr>
<td>DANIDA</td>
<td>Danish International Development Agency</td>
<td></td>
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<tr>
<td>DfID</td>
<td>Department for International Development [UK]</td>
<td></td>
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<tr>
<td>EAC</td>
<td>East African Community</td>
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<tr>
<td>FBO</td>
<td>Faith-Based Organization</td>
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<tr>
<td>FDCSA</td>
<td>Food, Drug and Chemical Substance Act</td>
<td></td>
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<tr>
<td>HIV/AIDS</td>
<td>Human Immuno-deficiency Virus/Acquired Immunodeficiency Syndrome</td>
<td></td>
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<tr>
<td>IGO</td>
<td>Intergovernmental Organization</td>
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<tr>
<td>INGO</td>
<td>International Nongovernmental Organization</td>
<td></td>
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<tr>
<td>NGO</td>
<td>Nongovernmental organization</td>
<td></td>
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<tr>
<td>NPS</td>
<td>National Pharmacovigilance System</td>
<td></td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
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<tr>
<td>KHPF</td>
<td>Kenya’s Health Policy Framework</td>
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<tr>
<td>KHSSP</td>
<td>Kenya Health Sector Strategic and Investment Plan</td>
<td></td>
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<tr>
<td>KNPP</td>
<td>Kenya National Pharmaceutical Policy</td>
<td></td>
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<tr>
<td>LMIC</td>
<td>Low and middle income country</td>
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<tr>
<td>LPV/r</td>
<td>Lopinavir/ritonavir</td>
<td></td>
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<tr>
<td>MEDS</td>
<td>Mission for Essential Drugs and Supplies</td>
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<tr>
<td>MNC</td>
<td>Multi-National Corporation</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health</td>
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<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
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<tr>
<td>NEPAD</td>
<td>New Partnership for Africa’s Development</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TSR</td>
<td>Targeted Spontaneous Reporting</td>
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<tr>
<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
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<tr>
<td>OGA</td>
<td>Office of the U.S. Global AIDS Coordinator</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>PANDRH</td>
<td>Pan American Network for Drug Regulatory Harmonization</td>
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<tr>
<td>PBO</td>
<td>Public Benefit Organization</td>
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<tr>
<td>PMI</td>
<td>President’s Malaria Initiative</td>
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<tr>
<td>PPA</td>
<td>Pharmacy and Poisons Act</td>
<td></td>
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<tr>
<td>PPB</td>
<td>Pharmacy and Poisons Board</td>
<td></td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
<td></td>
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<tr>
<td>QPPV</td>
<td>Qualified Person for Pharmacovigilance</td>
<td></td>
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<tr>
<td>RCORE</td>
<td>Regional Centres of Regulatory Excellence</td>
<td></td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Chapter 1
Chapter One: Introduction

1.1 Context

Pharmaceuticals have important benefits in the treatment of disease however without pharmacovigilance: the activities to detect, assess, understand and prevent drug-related problems pertaining to marketed drugs the benefits will not be achieved. Adverse drug reactions (ADRs), the noxious and unintended effects of a drug that occur at normal therapeutic doses, are a global public health threat leading to illness, disability and death (World Health Organization, 2004, 2016). Drug safety involves much more than prescribing the correct drug for the diagnosis and taking the drug appropriately. Equally important is understanding whether the benefit:harm ratio of the drug justifies the prescription.

The opportunity to improve pharmacovigilance globally and in particular in low and middle-income countries, by improving our understanding of the relationship between governance and pharmacovigilance creates an opportunity to achieve global equity in drug safety and motivates this research.

1.2 Background

Access to essential medicines for the treatment for AIDS, TB, malaria and non-communicable chronic diseases has grown substantially in low and middle-income (LMI) countries (Strengthening Pharmaceutical Systems, 2011). In sub-Saharan Africa alone, the number of people with access to antiretroviral therapy (ART) grew for 50,000 in 2002 to 7.6 million in
2012 (Strengthening Pharmaceutical Systems, 2011; UNAIDS, 2013). In 2013, it was estimated that more than 40% of the adult population living with HIV in Kenya and Brazil had access to ARTs (UNAIDS, 2014). Knowledge about the safety and real-world effectiveness of essential medicines in LMI settings has lagged behind access.

Some uncertainty is inherent regarding the risks of medicines. The real life risks associated with newly marketed drugs are unknown. Pre-market trials are too short and too small to determine adverse events that occur only after long term use, appear only once millions of patients have taken the drug, occur when the drug is taken concurrently with other prescription or non-prescription drugs or appear in patient groups not part of the premarket testing (e.g., children and the elderly).

1.2.1 Postmarket drug safety issues in LMI countries

In all countries there is a general gap in knowledge about the real-world effectiveness and safety of medications. LMI countries face additional postmarket drug safety issues, moreover pharmacovigilance has not kept pace with the increasing access to medicines as the examples in this thesis illustrate (Olsson, Pal, Stergachis, & Couper, 2010; S. Pal, Dodoo, Mantel, & Olsson, 2011; Strengthening Pharmaceutical Systems, 2011; World Health Organization, 2002). As a result, information is incomplete regarding the safety of marketed fixed dose combination drugs; medicines use in patients with illnesses not studied in clinical trials; and the scope of poor quality medicines in the supply chain.

1.2.1.1 Unapproved, banned and withdrawn drugs found in the marketplace

Unapproved, banned and withdrawn drugs are marketed in LMI countries. In India, drugs that were unapproved by its national regulator were manufactured and distributed under licenses
granted by state drug authorities (Mukherjee, April 27, 2013). The weight loss drug sibutramine was withdrawn from the market in Europe and the United States but is marketed in Brazil. In Kenya, banned antimalarials and other drugs have also been marketed for sale ("Alarm over banned drugs still on sale," 2011; "Board admits bad drugs in the market," 2011).

1.2.1.2 Fixed dose combination drugs and ADRs

Fixed dose combination drugs (e.g., Coartem®) are marketed in Kenya, Brazil and other LMI countries for the treatment of malaria, HIV/AIDS, tuberculosis and minor ailments. Fixed dose combination drugs contain more than one therapeutic agent. Fixed dose combination drugs used to treat HIV/AIDS, TB and malaria have been formulated to reduce drug resistance and improve adherence.

Fixed dose combination (FDC) products have been associated with stability issues that reduce quality in Kenya and other LMI countries. Pharmacovigilance studies are ongoing to gather information about the conditions that undermine the stability of FDC anti-tuberculosis drugs in government facilities in some Kenyan counties (Njue, 2013). The rationale for some fixed dose combinations (e.g., for the treatment of minor ailments) has been questioned (McGettigan, Roderick, Mahajan, Kadam, & Pollock, May 12, 2015; Mukherjee, July 4, 2013). For example, India’s regulatory authority banned from sale 294 fixed dose combinations whose safety and efficacy had not been tested (unapproved) by the national regulator (McGettigan et al., May 12, 2015).

Many fixed dose combination drugs are available without prescription in Kenya, Ghana, Nigeria and other LMI countries (Oshikoya, 2010; Strengthening Pharmaceutical Systems, 2011). A person taking the combination drug may experience an adverse event to a single ingredient or a
combination of the drug ingredients and dosage adjustments of individual ingredients cannot be made.

1.2.1.3 ADRs and drugs treating endemic tropical diseases

There is a gap in knowledge about drug therapy used to treat endemic diseases such as malaria, particularly when used by pregnant women and children. Knowledge about the use of medicines in patients who have comorbid tropical diseases (e.g., antiretrovirals in patients with malaria) is incomplete because clinical trials have not been conducted in the countries where malaria is endemic (Mehta, Allen, & Barnes, 2010). In Brazil, the prevalence of people with both TB and HIV is 23 percent and in Kenya TB-HIV co-infection rate is 37 percent (Kenya NTLD Unit, 2013; World Health Organization, 2012a).1,2

Little is known about the risk for ADRs when prescription medicines are used concurrently with traditional medicines (Yadav, 2008) and according to the World Health Organization (WHO), up to 80 percent of the population in some African countries use traditional medicines for primary care (World Health Organization, 2008). Herbal medicines are also used widely in some Brazilian states. One study examining herbal therapy use in primary health care settings in Ceará, Brazil found that 63.7 percent of patients had previously used herbal medication to treat their conditions (M. Silva, Sousa, & Gondim, 2005).

1 In Kenya, 106,083 new cases of TB were reported in 2010. It is estimated that up to 82% of HIV infected persons in sub-Saharan Africa have latent TB infections (World Health Organization, 2011).

2 The co-infection rate represents the percentage of persons that have TB that are also HIV positive.
1.2.1.4 Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medicinal products

The risk for ADRs caused by Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medicinal products obtained through formal and informal sectors are also a threat to drug safety (Attaran et al., 2012; Stockholm, Torstensson, & Pugatch, 2010; World Health Organization, 2016). A substandard drug is defined as a ‘genuine medicine produced by manufacturers authorized by the National Medicines Regulatory Authority which does not meet quality specifications set for them by National standards’, by the World Health Organization. In contrast, ‘a counterfeit medicine is deliberately and fraudulently mislabelled with respect to identity and/or source’ according to the World Health Organization. See http://www.who.int/medicines/regulation/ssffc/definitions/en/. Up to 18 percent of drugs tested in Brazil in the public, private and NGO sectors were found to be substandard (Stockholm et al., 2010), increasing the risk for ADRs and treatment failures. The National Quality Control Laboratories and Pharmacy and Poisons Board in Kenya found that nearly 30 percent of drugs in Kenya were counterfeit and were valued between US $65-130 million annually (Editor K, 2011; Strengthening Pharmaceutical Systems, 2011). Poor-quality antimalarials contributed to the deaths of an estimated 122,350 children under 5 years old in 39 sub-Saharan African countries in 2013 (Nayyar, Breman, & Herrington, 2015). Worldwide, falsified medicines are estimated to produce $75 billion in illegal annual revenues (Nayyar et al., 2015).

1.2.2 Pharmacovigilance in LMI countries

Pharmacovigilance is increasingly cited as important by governments and non-governmental actors in LMI countries, particularly in response to Substandard, Spurious, Falsely labelled, Falsified and Counterfeit medicinal products and treatments for AIDS, TB and malaria (ANVISA, nd-c; Kenya PPB, 2009; PAHO, 2011; S. Pal et al., 2011; Strengthening
Pharmaceutical Systems, 2011). However, its prioritization remains low (Olsson et al., 2010; S. Pal et al., 2011; Strengthening Pharmaceutical Systems, 2011). Many LMI countries lack a national pharmacovigilance system and have limited infrastructure, human resources, training and capacity to detect and analyze drug safety signals (Olsson et al., 2010).

1.2.3 Governance and postmarket drug safety

How national, state and county governments establish priorities, make policy and allocate resources is shaped by governance. Governance is defined by the United Nations Economic and Social Council as the ‘exercise of economic, political and administrative authority to manage a country’s affairs at all levels. It comprises the mechanisms, processes and institutions through which citizens and groups articulate their interests, exercise their legal rights, meet their obligations and mediate their differences’ (UN Economic and Social Council, 2006, p. 3). Governance influences national and subnational policy choices (or lack thereof) and resource allocation. Pharmacogovernance, formally defined in this research as the manner in which governing structures; policy instruments; and institutional authority (e.g., ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests for patient safety and protection from adverse drug events should have vital implications for medicine safety, the incidence of ADRs, patient health, and health care costs associated with the treatment of adverse drug events.

To date, much of the research related to governance and pharmacovigilance has focused on developed industrial countries and regions (e.g., European Union, United States, Canada, etc.) The research is categorized into three thematic areas: institutional authority, policy instruments and transparent decisions.
1.2.3.1 Regulatory Authority and pharmacovigilance norms

The breadth of the regulatory authority’s powers, pharmacovigilance norms, enforcement and regulatory capture have been studied and debated in the literature. The expansion of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) authority to require drug companies to submit a Risk Management Plan (RMP) for drugs that have market authorization in European Union Member States and a Risk Evaluation and Mitigation Strategy (REMS) for drug that have market authorization in the United States has been described as advancing pharmacovigilance by regulators. On the other hand, Wiktorowicz et al. (2012) and Davis & Abraham (2011) have suggested that RMPs and REMS have hindered pharmacovigilance because within the same timeframe, FDA and EMA requirements for market renewal of medicines were relaxed.

Policy norms that tie funding of pharmacovigilance by the industry to drug approval times, has been deliberated in the European Union, Canada, and the United States (Cruz, 2010; Frau, Pous, Luppino, & Conforti, 2010; Lundh A, Sismondo S, Lexchin J, Busuioc OA, & L, 2012; Vernon, Golec, Randall Lutterd, & Nardinelli, 2009; Wieseler, McGauran, Kerekes, & Kaiser, 2012; Wiktorowicz, Lexchin, & Moscou, 2012). Critics of the Prescription Drug User Fee Act (PDUFA), which allows the U.S. Food and Drug Administration to collect fees in exchange for expedited premarket review, have argued that drug approval times have shortened since the passage of PDUFA (Frank et al., 2014). Instead of picking up safety data in the premarket phase, there is a greater reliance on gathering data about adverse drug events and other drug safety issues in the postmarket period.

Carpenter’s (2004) study of the conditions for regulatory capture found that regulator’s decisions are influenced by the regulator-industry relationship; the firm’s brand recognition; perceptions of
safety and information asymmetry between the drug company and regulator. Carpenter’s findings have implications for regulator’s decisions to renew product registration or require postmarket safety studies.

Wiktorowicz et al (2012) suggested that mechanisms for independent review are needed because of industry bias in reporting of study results. Lundh et al. (2012) found that industry-sponsored studies produced more favorable results than non-industry funded studies. The studies suggest that regulatory norms regarding the use of industry-conducted safety studies as a basis for decisions pertaining to postmarket requirements are needed.

1.2.3.2 Policy instruments

The effectiveness of pharmacovigilance policy instruments (e.g., RMPs and REMS) have been deliberated in the literature. Davis & Abraham (2011) and Frau, Pous, Luppino, & Conforti (2010), investigated the effectiveness of risk management plans as a policy instrument for improving postmarket drug safety. The study found that risk management plans expedited drug approvals and legitimized the collection of safety information in the postmarket period rather than in pre-market trials.

1.2.3.3 Transparency

Transparent decision making and enforcement ‘follows rules and regulations, information is freely available and directly accessible to those who will be affected by such decisions and their enforcement’(United Nations Economic and Social Commission for Asia and the Pacific, nd). Transparency in regards to drug approval and postmarket surveillance decisions has been studied. The literature suggests that transparency can improve public understanding of the benefit:harm ratio of medicines and facilitate provincial drug benefit managers’ decisions to list medication on drug benefit plans (Lexchin, Wiktorowicz, Moscou, & Silversides, 2011;
Wiktorowicz, Lexchin, Moscou, Silversides, & Eggertson, 2010). Transparent policies might include requiring public access to meeting minutes in which drug approval deliberations are undertaken or data upon which drug approval, re-approval and withdrawal decisions are made.

### 1.2.4 Global actors and the spread of pharmacovigilance policy norms

The prioritization of pharmacovigilance, adoption of pharmacovigilance policies and the spread of related policy norms in many LMI countries has been a dynamic process influenced by exogenous actors (Arrais, 1999; Rigo & Nishiyama, 2005; UNAIDS | WHO, 2011). Exogenous (non-state) actors are broadly defined for the purposes of this paper as agents motivated to influence public policy in multiple countries such as the World Health Organization (WHO)/Pan American Health Organization (PAHO), US Food and Drug Administration (FDA), Global Fund, European Medicines Agency (EMA), and US Agency for International Development (USAID) and global pharmaceutical corporations.

Renn et al. (2011) have suggested that the responsibility for managing risks should be shared between multiple state and non-state actors, thereby expanding the plurality of stakeholders involved in governance. Postmarket drug safety is multijurisdictional therefore global actors have an interest in disseminating knowledge about regulatory governance, pharmacovigilance guidelines and pharmacovigilance norms. Pharmacovigilance norms such as pharmacosurveillance (the collection of reports and monitoring for safety signals of a possible causal relationship between an adverse event and a drug) have been disseminated along with membership in the International Centre for Drug Monitoring, also known as the Uppsala Monitoring Centre (UMC). Pharmacovigilance has been promoted in order to expand the global data pool of ADR reports. (PAHO, 2011; S. Pal et al., 2011). UMC membership is contingent on providing evidence of the capacity for pharmacosurveillance.
1.3 Statement of the problem

Few countries have a governance framework to guide regulations and policy making pertaining to medicines safety. A pharmacogovernance framework would guide the establishment of norms for pharmacovigilance policy, law for enforcement and resources to assure equity in monitoring and surveillance nationally. It would also establish norms for inclusive representation in determining policy.

1.3.1 Rationale for Examining Pharmacogovernance in LMI countries

This research aims at expanding the scope of literature on governance and drug safety in LMI countries. A greater understanding of the factors and actors that influence pharmacogovernance is needed in developing countries where uncertain economies, weak legal controls, unstable political regimes, low per capita incomes and high morbidity and mortality due to communicable and non-communicable diseases are characteristic (Mulili, 2011).

In the absence of a pharmacogovernance framework, many LMI countries do not have a legal requirement for ADR reporting or postmarket surveillance by pharmaceutical manufacturers (Strengthening Pharmaceutical Systems, 2011). A survey of sub-Saharan countries found that fewer than one third had laws and regulations to mandate pharmacovigilance activities, although 78 percent have a National Medicines Policy (Strengthening Pharmaceutical Systems, 2011). Although Brazil has a national pharmacovigilance system and Kenya has proposed a national guideline, the implementation of the guidelines and use of policy instruments have been inadequate in preventing falsified antiretrovirals (ARVs) from entering the medicines supply chain in Kenya (Attaran et al., 2012). Falsified ARVs, that entered the medicines supply chain in Kenya, were inadvertently distributed to patients by Médicins Sans Frontières. The falsified
medicines were visually indistinguishable from the actual generic product but differed in product deterioration. In Brazil, drugs such as sibutramine (a weight loss medicine) remain on the market despite being withdrawn in Europe and the United States because clinical trial data indicated that use increases the risk of heart attack and stroke.

1.3.2 Rationale for Investigating Pharmacogovernance in Brazil and Kenya
In Brazil, the existing literature has largely described the history of the rise of national regulatory authorities and norms for governance, including global actors’ interventions to spread norms for regulatory governance (e.g., transparency and accountability) (Brass, 2012; Cruz, 2009, 2010; de Mello & Ramalho, 2009; Miranda, 2010; Rigo & Nishiyama, 2005). Pharmacovigilance has not been the focus of studies about governance in Kenya. Brass (2012) however, has described the impact of global actors’ in shaping policy ideas in Kenya.

This research expands the scope of literature on pharmacogovernance in LMI countries by examining pharmacogovernance through a case study of Brazil and Kenya. A cross-case analysis of pharmacogovernance in a representative lower income and upper-middle income economy enables identification of variants of pharmacogovernance. It was hypothesized that Kenya and Brazil would represent contrasting variations of pharmacogovernance because of differences in each country’s experience with pharmacovigilance, representative decision-making, and the strength of their pharmaceutical industries. The rationale for selection of Brazil and Kenya for the case study is briefly discussed below and fully described in Chapter 2.

Brazil and Kenya are rich locations for examining domestic factors influencing pharmacogovernance and pharmacovigilance such as the economy, domestic pharmaceutical industry and national governance. Kenya is classified by the World Bank as a lower income
economy. Brazil is classified as an upper-middle income economy. Both countries have a domestic pharmaceutical industry. The countries are a rich site for examining how decentralized/devolved governance effects pharmacogovernance and pharmacovigilance.

The countries are also rich locations for examining exogenous (non-state) factors influencing regulatory governance and pharmacovigilance because of each country’s historical and contemporary engagement with global actors. Additionally, both countries have been selected as regional centres of excellence related to pharmacovigilance by the Pan American Regulatory Harmonization (Brazil) and the African Medicines Harmonization (Kenya).

Table 1. Brazil and Kenya Country Profiles*

<table>
<thead>
<tr>
<th></th>
<th>Brazil</th>
<th>Kenya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size</td>
<td>204 million</td>
<td>45.9 million</td>
</tr>
<tr>
<td>Federal Districts</td>
<td>26 States</td>
<td>47 Counties</td>
</tr>
<tr>
<td>National Governance</td>
<td>Decentralized</td>
<td>Devolved</td>
</tr>
<tr>
<td>GDP per capita (2015 est.)</td>
<td>$15,800</td>
<td>$3,300</td>
</tr>
<tr>
<td>GNI per capita (2013)</td>
<td>$11,003 USD</td>
<td>$1,218 USD</td>
</tr>
<tr>
<td>% population below poverty line</td>
<td>21.4%</td>
<td>43.4%</td>
</tr>
<tr>
<td>World Bank country classification</td>
<td>Upper middle-income</td>
<td>Low income</td>
</tr>
<tr>
<td>National Regulatory Authority</td>
<td>Agencia Nacional de Vigilancia Sanitaria (ANVISA)</td>
<td>Pharmacy and Poisons Board</td>
</tr>
<tr>
<td>Total Pharmaceutical expenditures (2016 forecast)</td>
<td>$20 billion USD BRL66.8 billion</td>
<td>$797 million USD (KES83.84 billion)</td>
</tr>
</tbody>
</table>

1.3.3 Decentralization and devolved governance

Brazil and Kenya are federal republics. Brazil is comprised of a federal district and twenty-six states; each with its own government structure (Department of Foreign Affairs & Trade, 2014). Biaculli (2013) suggests that in Brazil, governance in which independent regulatory authorities exercise authority in different sectors at the federal, state, and municipal level gives rise to decentralization of powers. ‘Decentralization and devolution within the regulatory landscape requires governments to be more responsive to state and municipal demands’ (Bianculli 2013, p 551). Kenya is a federal republic comprised of forty-seven counties and a federal district. The country amended its constitution in 2010 to create devolved governance (Republic of Kenya, 2010). In Brazil and Kenya policy is established at the federal level, implemented at the state level (Brazil) and county level (Kenya). Priorities established at the subnational (regional) level are limited by scarce state and municipal fiscal and human resources as well as lack of coordination mechanisms to respond to regulatory needs (Bianculli 2013). This suggests that pharmacogovernance will be affected by Brazil and Kenya’s federal system of governance and national pharmacovigilance policy implemented at the subnational level subject to regional priorities and resources.

1.4 Rationale for the research

This research narrows the gap in our understanding of the characteristics of pharmacogovernance; the factors influencing pharmacogovernance; and the relationship between pharmacogovernance and postmarket drug safety in LMI countries. It is important to close this gap because pharmacogovernance affects public policy and resource allocation needed to assure capacity for drug surveillance and assessment of drug-related problems; equity in application of pharmacovigilance, nationally; policy, law and regulations to reduce risks for adverse drug
events; representation in decision making regarding drug safety; accountability for risk communication; and decision making that affects the quality of drugs entering the supply chain.

The research contributes to the emerging body of literature on pharmacogovernance by investigating: 1) how the State (at all levels), global actors (non-state) and the pharmaceutical industry interact to affect pharmacogovernance and ultimately postmarket drug safety in LMI countries; and 2) how patterns of governance (e.g., devolved\(^3\), decentralized\(^4\), corporate\(^5\)) affect pharmacovigilance.

A pharmacogovernance framework is used to guide the analyses of pharmacogovernance in Brazil and Kenya. The pharmacogovernance domains are: Policy, Law and Regulation; Accountability and Transparency; Equity and Inclusion; Participation and Representation; Effectiveness and Efficiency; Intelligence and Information; Stakeholder Coordination; Ethics; and Responsiveness. The pharmacogovernance domains and the pharmacogovernance framework are described in detail in Chapter 3. A framework for a national pharmacovigilance system in LMICs has also been developed as a result of this research.

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\(^3\) In Kenya, devolved governance is defined as national and county levels that are distinct and inter-dependent and conduct their mutual relations on the basis of consultation and cooperation [Kenya constitution 2010 6(2)].

\(^4\) Decentralized governance is a process through which subnational governments increasingly partake in deciding on and administering essential public policies (Saito, 2011).

\(^5\) Corporate governance in relation to medicines is the process of setting and monitoring business goals and strategies by the board of trustees, directors, and shareholders that advance pharmacovigilance and support postmarket drug safety.
1.5 Purpose of the research

The purpose of this research is to examine the relationship between pharmacogovernance and pharmacovigilance in order to better understand the factors that contribute to the betterment of pharmacovigilance in LMI countries. \(^6\)

The research objectives are:

1. To determine how pharmacogovernance shapes pharmacovigilance;
2. To determine how pharmacogovernance institutions impact pharmacovigilance; and,
3. To determine how and why state and non-state actors interact to influence pharmacogovernance and pharmacovigilance.

The research objectives are addressed through the following specific research questions in this thesis:

1. How do patterns of governance (e.g., devolved or decentralized) influence pharmacogovernance and pharmacovigilance?
2. How do pharmacogovernance institutions enable or hinder pharmacovigilance?
3. Which pharmacogovernance domains have the greatest influence on pharmacovigilance and why?
4. How does pharmacogovernance affect pharmacovigilance equity nationwide?
5. How do patterns of engagement between national, subnational and exogenous policy actors shape pharmacogovernance and pharmacovigilance?

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Two theoretical propositions are made \textit{a priori} in this research of pharmacogovernance in Brazil and Kenya. A theoretical proposition, as defined for case study research, is a working hypothesis pertaining to the phenomenon being studied (Yin, 2014). The theoretical propositions are:

1. Endogenous and exogenous factors contribute to pharmacogovernance;
2. Interactions between governance networks (supranational, national and subnational)\footnote{In Brazil and Kenya, the national pharmacovigilance policy is established at the federal level and implemented at the state level (Brazil) and county level (Kenya). States and counties may set priorities for pharmacovigilance locally.} influence the articulation and implementation of pharmacovigilance policies affecting equity in pharmacovigilance nationally and regionally.

\section*{1.6 Theoretical Framework}

This research is grounded in theories pertaining to shared governance (\textit{Network Governance Theory}) and the dispersion of ideas (\textit{Ideation Theory}). It is based on the supposition that governance affects public policy and the resources requisite to address systemic issues pertaining to drug safety. An investigation of the relationship between governance and pharmacovigilance is particularly relevant to Brazil and Kenya because both countries have multijurisdictional governance structures (decentralized, devolved) responsible for creating and implementing pharmaceutical policy.

Before describing the specific governance theory underlying this research, it is first necessary to define governance. There are varying definitions of governance; each describes characteristics that include how power is exercised, who has a voice in decision making, and how interactions
between actors produce policies and practices to manage a country’s affairs. Governance has been defined as:

- The informal and formal processes and institutions that guide and restrain the collective activities of a group (R. O. Keohane & Nye, 2000);
- The ‘processes and interactions through which actors and social interests combine to produce the policies, practices and patterns of rule’ (Bevir, 2011, pp. 1-2);
- The institutions, processes and conventions in a society, which determine ‘who has power, who makes decisions, how other players make their voice heard and how account is rendered’ (Institute of Governance, 2015); and
- The ‘exercise of economic, political and administrative authority to manage a country’s affairs at all levels. It comprises the mechanisms, processes and institutions through which citizens and groups articulate their interests, exercise their legal rights, meet their obligations and mediate their differences’ (UN Economic and Social Council, 2006, p. 3).

The definition of governance used in this research is a conceptual blend of the Bevir (2011), Institute of Governance (2015) and UN Economic and Social Council (2006) definitions presented above. This amalgamated definition acknowledges that the organization and management of society extends beyond government to also include structures, processes and collective decision-making by government and non-government actors. It also suggests that politics and resources influence priority setting and implementation of policy, processes and norms, particularly at supranational, national and subnational levels.

The theoretical frameworks underpinning this research are Network Governance Theory and Ideation Theory. Network Governance Theory is an explanatory theory for understanding how
and why governance networks, comprised of state, civil society and exogenous actors form and interact. Governance networks are autonomous, interdependent actors that contribute to the production of public governance (Torfing, 2012). The policy actors comprising the networks have divergent interests but converge around a common discourse that shapes the way problems are defined and how challenges are understood (Blanco, Lowndes, & Pratchett, 2011; Torfing, 2012). The basis for the formation of the network is the members’ recognition of their mutual dependence.

Torfing (2012) and Jacobsen (2015) characterize governance networks as institutionalized policy networks that form to address complex policy problems that are uncertain, require specialized knowledge, have potential for high risk of conflict and involve multiple relevant stakeholders because individual members cannot solve the problem(s) alone. In contrast, policy networks are characterized as a feature of government whereby policy making is supported by actors representing ‘policy-domain specific subsystems’ (Blanco et al., 2011). Both are described as an alternative policy making paradigm (Blanco et al., 2011). The literature has shown that governance networks and policy networks contribute to problem solving and fill policy and capacity gaps (Blanco et al., 2011; Jacobsen, 2015; Torfing, 2012).

Governance networks contribute to risk governance of medicines where risk is multi-jurisdictional and the real-life risk of pharmaceuticals is unknown.8 Risk governance is a

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8 Risk governance is defined as: “(1) the critical study of complex, interacting networks in which choices and decisions are made around risks and (2) a set of normative principles which can inform all relevant actors of society how to deal responsibly with risks” [van Asselt and Renn 2011, p 443].
normative framework that promotes societal norms for dealing with uncertain, complex and/or ambiguous risks (van Asselt and Renn 2011). Norms to assure access to safe medicines, health products and services include the establishment of national regulatory authorities and policy, law and regulation that enable their institutional authority. ‘Policy, law and regulation’ is one of the nine domains in the pharmacogovernance framework. Van Asselt and Renn (2011) posit that a risk governance framework is essential for understanding how governance networks influence policy choices and how decisions are made about risks.

The engagement of multiple stakeholders contributes to a comprehensive characterization of risk from varied perspectives that shapes the way problems are defined and which solutions are considered. De Marchi (2003), Renn et al. (2011) and McLaverty (2011) suggest that who participates in decision making (representation) and how participants are selected (closed list, expertise, volunteer) has implications for the legitimacy of the process. Participation is an important component of governance (ANVISA, 2009, nd-b; Cruz, 2010; De Marchi, 2003; Miranda, 2010; Renn, Klinke, & van Asselt, 2011; G. H. Silva, 2011). Participation and representation of key stakeholders in decision making (participatory governance) contributes to better policy making (McLaverty, 2011).

This research also draws insights from Ideation Theory to explain how and why specific ideas and norms pertaining to regulatory governance and pharmacovigilance have gained traction in Brazil and Kenya. The literature suggests that non-state actors have been instrumental in disseminating knowledge about pharmacovigilance.
Ideation Theory posits that global actors are able to leverage their expertise to influence multilateral and state policy-making (R. Keohane & Nye, 1972; Reich, 1995; Willis, 2005) by creating a platform for the exchange of ideas and best practices (Béland & Orenstein, 2010; Jordana & Levi-Faur, 2005; Reich, 1995; Risse, 2004) and the resources, connections and financing necessary to push their policy ideas (Béland & Orenstein, 2010; Jeffares, 2007; Klotz, 2002; Reich, 1995). Béland and Orenstein (2010) suggest that: 1) influence on policy occurs by active mechanisms, 2) the interaction between actors is important to bargaining and uptake of policy solutions, 3) ideational processes are key to the spread of ideas that promote norms and influence policy, 4) policy uptake usually requires collaboration with national actors along with technical and financial support from transnational policy actors, and 5) policy ideas are accepted more readily when they can accommodate many interpretations and hold broad meaning.

Ideation theory suggests that the interaction between actors is important to policy uptake (Béland & Orenstein, 2010; Dufwenberg, 2011). Collaboration that results in technical and financial support from transnational policy actors in under-resourced LMI countries creates incentives for the implementation of ideas (Béland & Orenstein, 2010). Policy transfer between heterogeneous actors may be asymmetrical and involve power imbalances (Tannenwald, 2005). A key feature of governance networks that include non-state actors is that they employ soft power (e.g., persuasion) to promote norms and sway state adoption of their strategic interests (Keck & Sikkink, 1998; Stone, 2004; Torfing, 2012). The power imbalance between actors may provide

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9 Soft power is a persuasive approach to shaping or co-opting government policy preferences or public opinion. Power rests in perceived legitimacy or shared values.
an explanation for whose ideas matter and can be used to explain why some norms or policies are not adopted.

Alternate explanations for idea adoption are also investigated in this research. For example, national drug regulatory authorities in Kenya and Brazil and their parallel county and state authorities have agency, therefore merely suggesting ideas for policy change is insufficient for adoption. They may adopt or adapt (localize) suggested pharmacovigilance norms.

To analyze the relationship between governance and medicine safety in Brazil and Kenya a pharmacogovernance framework was developed. The pharmacogovernance framework domains are: Policy, Law, and Regulation; Transparency and Accountability; Participation and Representation; Equity and Inclusiveness; Effectiveness and Efficiency; Intelligence and Information; Ethics; Responsiveness; and Stakeholder Coordination. The framework, adapted from the WHO matrix for health governance\textsuperscript{10}, is reconstructed on the basis of theories of network governance (Blanco et al., 2011; Jacobsen, 2015; Torfing, 2012), risk governance (Renn et al., 2011), participatory governance (Fischer, 2006), collaborative governance (Savage et al., 2010; Simmons, Iles, & Yolles, 2005) and corporate governance (Donaldson & Dunfee, 1994). The literature suggests that each of the domains is important to policies and processes that advance pharmacovigilance and assuring that medicines users nationwide benefit.

\textsuperscript{10} WHO international Case Study, Confronting the Challenge of Governance of the Health System, available at: gis.emro.who.int/.../Governance%20case%20study.doc, Accessed 9-21-14
The multijurisdictional authority over the production, distribution and use of medicines creates complexities in policy setting and regulation of pharmaceuticals (Renn, Klinke, and van Asselt 2011). Network Governance Theory has been used as an explanatory framework for examining shared governance in areas ranging from the environment in Brazil (Da Costa & Mertens, 2015; van Laerhoven, 2014) and health care pertaining to high-risk health insurance programs in the United States (Joaquin & Meyers). This research examines the relevance of Network Governance Theory to medicines governance.

New models for medicines governance are needed that integrate multiple stakeholders, multi-governance systems and multiple jurisdictions. This research contributes to the identification and measurement of the variables that represent a new theoretical concept “pharmacogovernance”. The model for measuring pharmacogovernance, the pharmacogovernance framework, integrates Network Governance Theory and Ideation Theory in order to analyze the relationship between governance and pharmacovigilance. This research aims to contribute to theories of integrated governance by examining the impact of governance that is shared by domestic and exogenous actors on pharmacovigilance in LMI countries. It contributes to theory on network interactions by exploring the modes of engagement between network actors that enable and hinder pharmacovigilance.

1.7 Overview of thesis chapters

This thesis examines the underlying relationship between pharmacogovernance, the manner in which governing structures; policy instruments; and institutional authority (ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests
for patient safety and protection from adverse drug events, and pharmacovigilance in Brazil and Kenya. The thesis is comprised of five chapters. The papers that comprise this thesis (Chapter 3, Chapter 4a and Chapter 4b) investigate unique aspects of pharmacogovernance. The papers address each of the research objectives, specifically to determine how pharmacogovernance influences pharmacovigilance, how state and non-state actors interact to influence pharmacogovernance and how patterns of governance (e.g., devolved or decentralized) influence pharmacogovernance and ultimately pharmacovigilance. The organization is described below:

- Chapter 1 gives a brief introduction to the problem, the rationale for the research and the research objectives.
- Chapter 2 describes the research methods used to investigate the research objectives and answer the research questions.
- Pharmacogovernance is defined in Chapter 3 and the pharmacogovernance framework used to analyze pharmacogovernance in Brazil and Kenya is described. Paper 1, “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety” examines pharmacogovernance in Brazil and Kenya and assesses whether it is sufficient to assure postmarket drug safety nationally. The Agência Nacional de Vigilância Sanitária (ANVISA) and Pharmacy and Poisons Board regulatory agenda and pharmacovigilance policies are analyzed to explain the relationship between pharmacogovernance and pharmacovigilance.
- Chapter 4 is comprised of two papers (Chapter 4a and Chapter 4b). Each investigates exogenous actors’ influence on pharmacogovernance and postmarket drug safety policy. The first paper, “Governance and Pharmacovigilance in Brazil: A scoping review” (Chapter 4a), investigates the relationship between regulatory governance, pharmacogovernance and pharmacovigilance by examining ANVISA’s regulatory agenda, pharmacovigilance policies, and governance. A scoping review of the literature pertaining to global institutions was
undertaken to illustrate how transnational policy ideas for regulatory governance (e.g., transparency and accountability) have been integrated and translated into pharmacogovernance in Brazil.

The paper “Matching Access to Safety: Pharmacogovernance in Kenya” (Chapter 4b) is a case study investigating exogenous actors’ interactions pertaining to pharmacogovernance which is important because Kenya’s national governance permits the delegation of authority to create infrastructure and implement domestic programs to non-state implementing partners. The research analyzes the relationship between pharmacogovernance and specific types of interactions (e.g., collaboration) between exogenous actors and state actors in Kenya. The research also analyzes the affects of specific types of engagement between state and non-state actors on postmarket drug safety. The analyses address the research question: which type or pattern(s) of engagement among state and exogenous actors enables or hinders pharmacogovernance and pharmacovigilance?

- Chapter 5 summarizes the key findings from each of the papers and discusses how the findings relate to each other and previously published work. The thesis concludes by making recommendations to improve pharmacogovernance, thereby enhancing pharmacovigilance and taking a step toward achieving the goal of global equity in drug safety. The strengths and limitations of the research as a whole are described and recommendations are made for future research.

The article “Corporate governance and medicines safety” is found in Appendix A. The research investigated the integration of pharmacovigilance into corporate governance in multinational and domestic pharmaceutical companies operating in a low income country (India). A document analysis of corporate annual reports was conducted for this research. The study found that
pharmacovigilance was not well integrated into pharmaceutical corporations’ governance (Moscou, Kohler, & Lexchin, 2013).
Chapter 2
Chapter Two: Methods

2.1 Preamble

The goal of this research is to examine the relationship between pharmacogovernance and pharmacovigilance, particularly in LMI countries. Drug safety issues are broad and the strategies to mitigate them involve a range of stakeholders. Chapter One sets the stage for understanding why this research was undertaken and why understanding the characteristics of pharmacogovernance, factors influencing pharmacogovernance and the relationship between pharmacogovernance and postmarket drug safety in LMI countries are important.

Chapter Two describes the qualitative research methods used in this research. The in-depth description of the research methods expands the abbreviated description provided in each of the published and submitted papers. The chapter also describes the sources of data analyzed and method of analysis. A discussion of the case study methodology and rationale for its use to achieve the research aims is presented.

2.2 Research Methods

Qualitative methods employed in this research consist of a case study and scoping review. The research methodology and methods for data analysis that were used are described herein. Triangulation of research methods and data analyses increases the robustness of the research and is a cross-check of contestable assertions, descriptions, and alternate interpretations of events and documents (Stake, 1995; Yin, 2003).
2.2.1 Case Study

This research is a case study of pharmacogovernance. The case study is conducted to explain: how pharmacogovernance influences pharmacovigilance; how and why non-state and state actors influence pharmacogovernance, and how patterns of governance influence pharmacogovernance and pharmacovigilance. Case studies are useful in research because they seek to explain how and why a specific phenomenon exists (Baxter & Jack, 2008; Yin, 2003).

Pharmacogovernance requires interactions between multijurisdictional actors because drug safety risks are complex. Greenhalgh, et al. (2011) argued that the case study approach is needed when there are complex initiatives involving multiple stakeholders. A case study is also preferred when the research involves the identification and measurement of variables that represent theoretical concepts (George & Bennett, 2005). In this research, ‘pharmacogovernance’ and ‘influence’ are theoretical concepts. Thus, for all of these reasons a case study design is appropriate for this research.

A case study is a bounded system in which the phenomena of interest is studied (Stake, 2005). This case study of pharmacogovernance is bounded in Brazil and Kenya. The phenomena of interest are:

- **Types of endogenous and exogenous factors** influencing pharmacogovernance.
- **Patterns of interactions** between governance networks at supranational, federal, state, and county levels influencing pharmacogovernance and pharmacovigilance.
- **Levels of variation between individual pharmacogovernance domains** and the impact on overall pharmacogovernance.
Kenya and Brazil were selected for this case study of pharmacogovernance for seven key reasons. First, the countries represent examples of a low-income and an upper middle income country. Second, the countries are at different stages of development related to pharmacovigilance. Pharmacovigilance policies in Kenya have been gaining priority only since 2007. In contrast, Brazil has a more established history of pharmacovigilance (since the late 1990s). Third, Kenya and Brazil have each received substantial funding and/or other resources from a broad range of transnational actors to support pharmacovigilance as the following examples demonstrate. For example, Kenya’s pharmacovigilance guidelines were developed as part of a joint initiative between the WHO and Kenya’s Pharmacy and Poisons Board (Mbindyo, Okello, & Kimani, 2010). The Pan American Health Organization (PAHO) has supported conferences to promote pharmacovigilance in Brazil. Fourth, both countries have a domestic pharmaceutical industry that supplies medicines to other low and middle income countries. Brazil is a pharmerging market and the largest pharmaceutical producer in Latin America. Kenya has 42 domestic pharmaceutical corporations and produces a fixed combination of lamivudine + zidovudine that was prequalified by WHO for procurement by international agencies for distribution in resource-limited countries in 2011 (World Health Organization, 2010, 2012b). Fifth, both countries have been recognized as regional centres of excellence for pharmacovigilance. Brazil was selected as a regional centre for pharmacovigilance by the Pan American Regulatory Harmonization

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11 A Pharmaceutical + (e)merging or pharmerging market is defined as a country with a high compound annual growth rate economic growth rate, a transitional disease profile, growing access to medicines and expanding public health programs. The 17 pharmerging markets are divided into 3 tiers. Tier 1 is solely comprised of China, India, Brazil and Russia are categorized in tier 2 and tier 3 is comprised of Argentina, Mexico, Poland, Turkey, Venezuela, Vietnam, South Africa, Thailand, Indonesia, Romania, Egypt, Pakistan and the Ukraine (IMS Health, 2010). Brazil may no longer be pharmerging given its serious economic problems.
(PANDRH) and Kenya was selected as a regional centre for regulatory excellence by the African Medicines Regulatory Harmonization. As regional centres of excellence, Brazil and Kenya present an interesting case study of peer learning by neighboring LMICs. Sixth, both countries are federal republics with decentralized (Brazil) and devolved (Kenya) governance that has implications for pharmacogovernance within each country. Lastly, Substandard, Spurious, Falsely labelled, Falsified and Counterfeit medicines have been found in the supply chain in Brazil (18%) and Kenya (30%), suggesting that research is needed that will improve pharmacovigilance in both countries.

The two-case study was designed as a cross-case analysis of pharmagovernance in order to investigate the variants of pharmacogovernance. It was hypothesized that Kenya and Brazil would represent contrasting variations of pharmacogovernance because of differences in each country’s experience with pharmacovigilance, representative decision-making, and the strength of their pharmaceutical industries.

2.3 Data Sources and Methods of Data Collection

The data analyzed in the studies that comprise this body of research were extracted from key informant interviews, publically available government documents, peer review and grey literature, newspapers archives and corporate annual reports. Triangulation of data sources increases the validity of the research findings (Yin, 2014). Converging lines of inquiry arising from the multiple data sources within each setting and across multiple settings also strengthen the validity of research results (Baxter & Jack, 2008; Stake, 1995; Yin, 2003). In this research, the convergence of perceptions of pharmacogovernance and pharmacovigilance found in the
literature and across key informants representing various sectors (federal, state, county
government and industry) was investigated through the diversity of data sources.

2.3.1 Semi-structured interviews

The key informants interviewed for this research included endogenous actors that were representative of rural, urban, highly resourced and poorly resourced regions of Brazil and Kenya. They represented the regulatory, government and industry sectors. The key informants also included exogenous or global actors (e.g., USAID, WHO/PAHO) that have provided resources and ideology regarding pharmacogovernance or pharmacovigilance in Brazil and Kenya. Semi-structured interviews were conducted with these key informants to:

- Aid in the identification of indicators for pharmacogovernance;
- Obtain key informants’ perspectives on the relationship between pharmacovigilance and pharmacogovernance; and,
- Explore key informants’ perspectives about the state/non-state relationship pertaining to pharmacogovernance and pharmacovigilance.

Key informant perspectives about the relationship between the sociopolitical, economic, historical factors, and strategic interests underpinning pharmacovigilance policy was also sought in order to provide context for how and why the national pharmacovigilance system has evolved in Kenya and Brazil. Probes were used in the interviews to tease out additional information.

2.3.1.1 Participants

The study participants were engaged in pharmacovigilance at the supranational, federal, state and county levels. Twenty-six key informants were interviewed. The key informants represented
the national regulatory authority, state pharmacovigilance units, county health executives, county pharmacy directors, multinational pharmaceutical corporations, domestic pharmaceutical companies, intergovernmental organizations (IGOs) and international non-governmental organizations (INGOs). Interviews were conducted between March 2014 and January 2015, following ethics approval from the University of Toronto, Canada; Moi University, Kenya; and Brazil’s National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa (CONEP). Interviews were conducted until saturation was reached. Saturation is described as the point of informational redundancy or when no additional data are found (Bernard & Ryan, 2010; Sandelowski, 1995) The concept of saturation has been operationalized ‘as the point in data collection and analysis when new information produces little or no change to the codebook’ (Guest, Bunce, & Johnson, 2006).

The key informants that were interviewed are categorized in Table 2.

<table>
<thead>
<tr>
<th>Table 2. List of key informants</th>
</tr>
</thead>
</table>
| **National Regulatory Authority** | • ANVISA (Brazil)  
| | • Pharmacy and Poisons Board (Kenya) |
| **Multinational pharmaceutical corporation** | • MSD  
| | • Bayer |
| **Domestic pharmaceutical company** | • Europharma (Brazil)  
| | • Farmanguinhos/Fiocruz (Brazil)  
| | • Teuto-Pfizer (Brazil)  
| | • Universal Corporation, Ltd. (Kenya) |
| **State pharmacovigilance** | • São Paulo  
<p>| | • Ceará |</p>
<table>
<thead>
<tr>
<th>(Brazil)</th>
<th>• Rio de Janeiro</th>
</tr>
</thead>
<tbody>
<tr>
<td>County pharmacovigilance (Kenya)</td>
<td>• Kwale</td>
</tr>
<tr>
<td></td>
<td>• Mombasa</td>
</tr>
<tr>
<td></td>
<td>• Turkana</td>
</tr>
<tr>
<td></td>
<td>• Uasin Gishu</td>
</tr>
<tr>
<td>Intergovernmental Organization (IGO) and Non-governmental organization (NGO)</td>
<td>• Pan American Health Organization</td>
</tr>
<tr>
<td></td>
<td>• World Health Organization Collaborating Centre for International Drug Monitoring-Uppsala</td>
</tr>
<tr>
<td></td>
<td>• Uppsala Monitoring Centre- Africa</td>
</tr>
<tr>
<td></td>
<td>• United States Agency for International Development</td>
</tr>
<tr>
<td></td>
<td>• Medicines Sciences for Health</td>
</tr>
</tbody>
</table>

### 2.3.1.2 Participant recruitment

Purposive and reputational sampling strategies were employed to select participants who were able to provide rich data about pharmacovigilance systems in Kenya and Brazil and who were representative of the various organizational viewpoints held. Purposive sampling was conducted to ensure that the sample embodied specific characteristics such as experience with policy development or policy implementation and abroad range of organizational perspectives was included in the research (Patton, 1987).

Reputational sampling is a ‘snow-balling’ process in which the key informants suggest others that should be interviewed based upon their likelihood of providing additional insight and expertise about the research topic (Snow, Hutcheson, & Prather, 1981). Reputational or chain sampling enabled quick identification of information-rich key informants. The participants,
identified via the ‘snow-balling’ process, were emailed a letter of invitation to participate in the study.

2.3.1.3 Sample size

Quota sampling, a non-probabilistic sampling method, was used to determine the sample size for this case study. The quota sampling method is designed to maximize the selection of a minimum representative sample of information-rich key informants needed to characterize the research environment (Trost, 1986). The minimum sample size is calculated by multiplying the number of variable strata by the independent variables (Trost, 1986). The principle independent variable for this case study is country (Brazil and Kenya) and thirteen variable strata consisting of location (rural, urban), pharmacovigilance resources (high resourced, low resourced) and sector representation (regulatory), government (national, foreign), pharmaceutical manufacturer, global institution, non-governmental organization (national, international). Based on multiplying the independent country variable (two) by 13 variable strata, the minimum sample size is 26. The per group sample size is as follows for each country: Regulatory sector (1) National government regional public health authority (2) foreign government (2) pharmaceutical manufacturer (3) global institution (2) and non-governmental organization (3). The sample included key informants from urban, rural, high resourced and low resourced regions. This sample size is consistent with PhD theses using qualitative research methods (Mason, 2010). Mason (2010) found that sample size for case studies ranged from 1 to 95.

2.3.1.4 Interview Protocol

An invitation to participate in the study was emailed to each potential key informant (Appendix C). Respondents who agreed to participate were emailed the informed consent letter outlining the purpose of the study, study procedures, benefits and risks to study participants, protection of
privacy and confidentiality (Appendix D). One-to-one semi-structured interviews were conducted with key informants who consented in writing to participate in the research. The interviews were conducted in-person, by SKYPETM, or by telephone. Two of the interviews in Brazil were conducted in Portuguese with the aid of a translator. During the approximately 60-90 minute interview, the key informants were asked to comment on issues pertaining to postmarket drug safety (pharmacovigilance) in their country, specific jurisdiction (state or county), and company (for multinational and domestic pharmaceutical companies). The key informants were also asked to comment on actions taken by various national and transnational actors pertaining to pharmacovigilance policies.

A separate interview guide was developed for each category of key informant (e.g., national regulatory authority, state pharmacovigilance, county pharmacovigilance, multinational corporations, domestic pharmaceutical company, and IGO or INGO) (Appendix E - Appendix J). The initial interview guide was based on the study objectives, review of the literature, information posted to regulatory authority and company websites, and publically available policy documents. The interview guides were continuously updated to probe additional relevant information that was uncovered during interviews with preceding key informants. Interviews with national regulatory authorities (Appendix E1 and Appendix E2) focused on:

- The national regulatory authority’s priorities for pharmacovigilance and how priorities are determined;
- How resources are allocated for pharmacovigilance and what are sources of funding;
- Their perceptions about how decentralization/devolution influences pharmacovigilance;
- The factors and stakeholders that have influenced pharmacovigilance or continue to influence pharmacovigilance;
• How global actors influence pharmacovigilance; and,

• Their perceptions about who is accountable for pharmacovigilance in the country and how is pharmacovigilance enforced.

Interviews with state and county pharmacovigilance actors (Appendix F and Appendix G) focused on:

• The state/county priorities for pharmacovigilance and how priorities are determined;

• How resources are allocated for pharmacovigilance and what are sources of funding;

• Differences between national and state/county priorities for pharmacovigilance;

• Their perceptions about how decentralization/devolution influences pharmacovigilance;

• Who are the stakeholders that participate in decision making pertaining to pharmacovigilance and how do they influence pharmacovigilance;

• How global actors influence pharmacovigilance; and

• Perceptions about who is accountable for pharmacovigilance in their state/county.

Interviews with multinational and domestic pharmaceutical companies (Appendix H and Appendix I) focused on:

• How does the company engage with the national regulatory authority, state or county health authorities, and faith-based healthcare systems pertaining to pharmacovigilance;

• How is pharmacovigilance integrated into corporate governance;

• How does resource allocation for pharmacovigilance compare to other departments (e.g., research and development) and why do differences exist; and

• What are the company’s local pharmacovigilance practices, how do they compare to the multinational policies/practices in other countries/regions (e.g., United States and Europe) and why do differences exist?
Interviews with IGOs and NGOs (Appendix J) focused on:

- IGO/NGO priorities for pharmacovigilance and how priorities are determined;
- How and why the IGO/NGO has aimed to influence pharmacovigilance in Kenya and/or Brazil;
- Specific examples of IGO/NGO norms, policies, standard operating procedures, frameworks, and/or guidelines for pharmacovigilance promoted in Brazil and/or Kenya;
- Factors influencing resources allocated to supporting global pharmacovigilance and type of support provided to Brazil and/or Kenya;
- Their perceptions about how decentralization/devolution has influenced pharmacovigilance; and
- Who are the stakeholders that participate in decision making pertaining to pharmacovigilance and how do they coordinate their activities (or not)?

The key informants responded to some questions as a free flow stream; sometimes combining the answers for two or three questions into one. When the combined question was reached on the interview guide, the question was repeated and probes used to see if the key informant had additional information to provide related to the question.

2.3.1.5 Limitations

Some of the key informants that were identified declined to be interviewed. For example, two of the potential key informants agreed to in-person interviews in Kenya but were unwilling or unable to conduct the interview by telephone or SKYPE. While it is possible that these key informants may have contributed to the key findings, interviews were conducted until saturation was achieved. The data obtained from alternate sources suggests the case study findings were valid.
Two key informants in Brazil requested the interview be conducted in Portuguese. Portuguese is the primary language in Brazil. All other key informants agreed to participate in an interview that was conducted in English. The depth of the responses provided by some Brazilian key informants providing English language interviews was somewhat less than interviewees whose primary language was English.

2.3.2 Documentary Evidence

Administrative documents, (e.g., corporate annual reports and agency progress reports), legislative documents (e.g., the Federal constitution of Brazil, the Constitution of the Republic of Kenya, and federal law), intergovernmental and nongovernmental organization policy papers, newspaper articles and grey literature were read to explore discourse pertaining to pharmacogovernance. These documents were selected for analysis because the rationale for policy adoption is often based on strategically crafted arguments which may be found buried within government reports, corporate annual reports, policy papers, and newspaper articles (Campbell, 2002; Lupton, 1992; Shaw, 2010).

A scoping review of the literature and policy papers was conducted to identify publications describing the endogenous and exogenous factors that influence pharmacogovernance in Brazil and Kenya and to obtain a contextual understanding of how and why these policies may affect pharmacogovernance.
2.3.3 Scoping Review

A scoping review is a methodical search of the literature about a phenomenon of interest. It is characterized by ‘a clearly stated set of objectives with pre-defined eligibility criteria for studies; and an explicit, reproducible methodology’ (The Cochrane Collaboration, 2011). A scoping review is conducted utilizing a fixed protocol for searching the literature, in order to identify all studies that meet the pre-defined eligibility criteria, then data is extracted according to a systematic approach (The Cochrane Collaboration, 2011).

The search terms used in the scoping review were entered into thirteen relevant databases of peer reviewed and grey literature (see Chapter 4a). Literature from pharmacy, political science, the social sciences and health databases was searched. The databases that were searched included Ovid MEDLINE(R), Ovid OLDMEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid Healthstar, Embase, Classic+Embase, International Pharmaceutical Abstracts, International Political Science Abstract, Journals@Ovid Full Text, Embase, LILACS, PubMed, EBSCO and SciELO. The diversity of databases searched, included two Latin American databases (LILACS and SciELO), to overcome non-inclusion bias. Non-inclusion of publications in scoping reviews can lead to an incomplete database and biased conclusions (Wieseler et al., 2012).

2.3.3.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were established to select the publications included in the studies (see Table 7, Chapter 4a). Abstract titles were read by two researchers (KM, PC) who determined which papers to exclude in phase one and which to include in phase two of the scoping review. The full texts were read in phase two of the scoping review. Publications
meeting the inclusion criteria characterized global interventions pertaining to governance or pharmacovigilance; pharmacy regulatory authority governance (e.g., accountability and transparency); and pharmacogovernance in each country.

2.3.3.2. Data Extraction

A selective approach to data extraction was used to extract data from publications satisfying the inclusion criteria. When a selective approach to data extraction is used only data that meets a pre-specified quality, specific issue or specific question is extracted (Noyes & Lewin, 2011). In this research, the publications were read iteratively and data specifically related to any of the pharmacogovernance domains or global actors was extracted to address the research aim: to investigate the types of endogenous and exogenous factors influencing pharmacogovernance. The pharmacogovernance framework described in the paper “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety” (Chapter 3) was used to analyze the relationship between pharmacogovernance and pharmacovigilance. The pharmacogovernance domains were established a priori. This method of data extraction is consistent with extracting qualitative evidence in a scoping review (Noyes & Lewin, 2011).

2.3.3.3 Limitations

Potential limitations to the inclusion/exclusion criteria are as follows. Abstracts with titles that were perceived to be not relevant to the research were excluded. This is a potential limitation to the study because publications with non-meaningful titles but relevant content may have been excluded. Publications that have non-meaningful titles, has been cited as a challenge to the retrieval of qualitative research studies (Booth, 2011). Further, when neither the abstract nor the full text could be retrieved, the publication was excluded from the study because there was no
full article to read from which to extract data. This may have resulted in non-inclusion of a publication(s) relevant to the study.

### 2.4 Data Analysis

Two approaches to qualitative data analysis were employed. There were thematic analysis and semantic analysis.

#### 2.4.1 Thematic Analysis

Interview transcripts and documentary evidence were read and re-read iteratively and with reflexivity\(^\text{12}\). The textual data was then coded employing an open coding process and using codes created \textit{a priori}. Data coding and re-coding was an ongoing process because new and more refined themes emerged during the coding process (Bernard & Ryan, 2010). A codebook with operational definitions (Appendix K) was created to maintain consistency in the coding process and to check reliability and reproducibility of the categories (Bernard & Ryan, 2010).

The codes were then applied to all of the interview transcripts and documents to be analyzed. The coded text was analyzed to identify key themes emerging for the data. Related codes were categorized into code families that comprised emergent key themes and \textit{a priori} themes representing the pharmacogovernance domains. Eakin and Mykhalovskiy (2003) argue for “the

\(^{12}\) Reflexivity entails continuous self-reflection while reading the data to examine underlying assumptions and preconceptions. Reflexivity is based on the premise that there is an interrelationship between the researcher, the research, knowledge construction, and interpretation; therefore ‘knowledge cannot be separated from the knower’ (SAGE Dictionary of Qualitative Management Research, http://srmo.sagepub.com/view/the-sage-dictionary-of-qualitative-management-research/n86.xml).
treatment of ‘themes’ as relatively objective phenomena inherent in the data, that ‘emerge’ or self-identify” (p.190). Bernard and Ryan (2010) suggest that this method of coding represents both an inductive and deductive approach to analyzing the data.

2.4.2 Semantic Analysis

A semantic analysis investigates how words are used in context and their relationship to one another (Bernard & Ryan, 2010). A semantic analysis of key informant transcripts and other textual data was conducted to identify common words and dissimilar words used by key informants to describe pharmacovigilance priorities at federal, state, county, and corporate levels; the priority setting process; the nature of interactions among global, national, state, county and municipal actors pertaining to pharmacovigilance. Linguistic connectors, such as ‘because’ and ‘since’ were analyzed within the textual data to examine key informants perceptions of causality (Bernard & Ryan, 2010). Linguistic connectors were also analyzed for conditional relations (e.g., if-then, rather than), temporal relations (e.g., now, before) and contingent relations (e.g., as soon as). Co-occurring words were analyzed to investigate common words used together when describing governance or pharmacovigilance in order to identify any relationship between these key concepts (Bernard & Ryan, 2010).

2.5 Validity and Reliability

One of the tests used to judge the quality of case study research is construct validity. In this test, key findings and research results are validated by identifying convergence or non-convergence of evidence between multiple sources (Yin, 2014). In this research, the data were analyzed to identify convergence and non-convergence amongst the key informants’ perceptions of pharmacogovernance, the research findings reported in the literature and governments documents.
For example, the analysis of peer reviewed studies, federal law, constitutional amendments and key informant interviews pertaining to deliberative decision making in Brazil and Kenya, identified convergence regarding the lack of mechanisms for social participation in decision making forums in Brazil and Kenya. Construct validity was also established by asking key informants to confirm the accuracy of their transcribed interview (Yin, 2014).

Stake (1995) and Yin (2003) suggest that with careful attention to reporting accuracy, triangulation of contestable assertions or descriptions, and analysis of alternate interpretations for the phenomena, the validity of case study research is addressed. Greenhalgh et al. (2011) argue that through research reflexivity, thick description, dialog and debate that both the researcher and the reader are able to conclude whether the phenomenon described by the case is relevant and transferable to other settings.

Care was taken to attend to the consistency in data collection and analysis (i.e., reliability). To ensure consistency in coding the transcripts and other textual data a codebook with operational definitions was developed. The codebook and an anonymized transcript were given to a second researcher to check inter-coder agreement on coding of themes. Inter-coder agreement strengthens the reliability of the research (Bernard & Ryan, 2010; Miles, Huberman, & Saldaña, 2014). Inter-coder reliability was moderate for coding of a single unit of analysis (e.g., a single pharmacogovernance domain), ranging from 53-72% raw agreement and agreement was better than chance. Inter-coder agreement was slight (kappa 0.06) with less than 27% agreement when coders were asked to code as many themes as they thought were relevant to a specific paragraph. The weak inter-coder agreement was less than chance. Weak inter-coder agreement was
attributed to the secondary coders’ unfamiliarity with the topic and lack of specificity in the
definition of some codes.

In the scoping review, explicit inclusion and exclusion criterion were established for selection of
publications to be included in the study. Establishing an explicit protocol increases reliability of
publication retrieval process (Booth, 2011). Validity of a scoping review that is conducted by
one researcher can be increased by having a second researcher validate a sample of the data
extractions (Noyes & Lewin, 2011). In the scoping review conducted for this research, two
researchers (KM, PC) read through the abstracts to determine exclusion or inclusion in the study.

2.6 Ethical considerations

This research was approved by the University of Toronto Research Ethics Board protocols #
29254 and #28320 (Appendix B1), Moi University, Kenya IREC #0001151 (Appendix B2) and
Brazil’s National Research Ethics Commission CONEP Número do Parecer: 686.734 (Appendix
B3).13

All key informants received a letter of consent outlining the study procedures and methods used
in order to protect confidentiality (Appendix D). They were instructed that participation in this
doctoral research was voluntary, they could choose to decline to answer any question asked and
end the interview session at any time.

13 CONEP Ethics Approval was under Dr. Jillian Kohler’s protocol Título da Pesquisa: Avaliação da Governança,
Responsabilidade e Transparência no Sistema Farmacêutico Brasileiro, CAAE: 18428213.0.0000.5421, Número do
Parecer: 686.734 (See Appendix B3)
Prior written consent was received from all key informants before commencing the interview. The researcher conducted all but the two interviews that were conducted in Portuguese. The Portuguese interviews were conducted by a research assistant trained in the ethics protocol. All of the interviews were audio-recorded upon obtaining consent from the key informants.

Key informants were advised that they had the option to review the transcripts of their interview and a copy was emailed to each study participant. Two of the key informants that were interviewed provided additional information to clarify their answers. One study participant requested that the information they provided be excluded from published study results.

Measures were taken to protect confidentiality of the key informants. Interviewees for this thesis and submitted papers were identified by country and role (e.g., regulatory authority -Brazil, domestic pharmaceutical company, multinational pharmaceutical, state health -Brazil, county health -Kenya, etc.). In order to minimize the risk that the key informant would be identified when the number of people who could provide information-rich descriptions was small the key informant was not quoted, however their perspectives were incorporated in the analysis.
Chapter Three: “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety”

The research was conducted by Kathy Moscou who is also the sole author of the paper.
3.1 Preamble

The paper, titled “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety”, investigates the relationship between pharmacogovernance and pharmacovigilance in Brazil and Kenya. The paper presents a novel approach to analyzing the strengths and weaknesses of the national regulatory system in each country in advancing pharmacovigilance.
3.2 Abstract

**Objectives:** The purpose of this paper is to investigate the relationship between pharmacogovernance and pharmacovigilance in Brazil and Kenya. Pharmacogovernance is defined as the manner in which governing structures, policy instruments and institutional authority are managed to promote societal interests for patient safety from medication use.

**Methods:** Qualitative research methods were employed. They included a review of peer reviewed and grey literature and key informant interviews. An innovative pharmacogovernance framework was used to clarify the relationship between pharmacogovernance and pharmacovigilance in Brazil and Kenya. Using the pharmacogovernance framework, the strengths and weaknesses of ANVISA and Kenya Pharmacy and Poison Board pharmacovigilance policies, as implemented, were identified.

**Results:** The research finds that gaps in pharmacogovernance may hinder postmarket drug safety even when policy, laws, and regulations support the national regulatory authority’s mandate to ensure access to safe medicines and health products. The research found gaps in pharmacogovernance in Brazil and Kenya in the domains: representation and participation; equity and inclusiveness; effectiveness and efficiency; responsiveness; and intelligence and information.

**Conclusions:** Key findings suggest that the pharmacogovernance framework contributes to a holistic assessment of pharmacogovernance structures and institutions that may used to support decision making pertaining postmarket drug safety.
3.3 Background

In Brazil and Kenya their constitutions proclaim that “Health is the right”. The challenge before the Federal Government is to determine what governance, regulations and policy instruments best fulfill the right to health thereby assuring access to safe, effective quality medicines and nationwide equity in monitoring, assessing, and communicating, drug safety risk. Fulfilling this mandate is all the more complex given Brazil and Kenya’s national governance structures.

The purpose of this paper is to examine the relevance of a pharmacogovernance framework for investigating the relationship between pharmacogovernance and pharmacovigilance in Brazil and Kenya within the context of their national governance. Brazil and Kenya are federal Republics with decentralized (Brazil) and devolved (Kenya) governance.

The research specifically addresses the research questions:

1) What variables contribute to pharmacogovernance? and,

2) How is pharmacovigilance affected by pharmacogovernance institutions?

Pharmacogovernance is defined as the manner in which governing structures, policy instruments and institutional authority are managed to promote societal interests for patient safety from medication use. Pharmacogovernance advances pharmacovigilance because it

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14 Pharmacovigilance is defined as the activities to detect, assess, understand and prevent adverse effects and drug-related problems pertaining to marketed drugs.

15 In this research I define *decentralization* as a governing arrangement whereby subnational governments partake in deciding on and administering essential public policies. *Devolution* is defined as the statutory granting of powers by the national government to distinct and inter-dependent subnational (county/state) levels [see Kenya constitution 2010 6(2)].
endorses a culture that supports postmarket drug safety (e.g., drug safety signal detection and risk communication). Weak pharmacogovernance de-incentivizes adoption of legislation and norms for pharmacovigilance that may lead to poor quality medicines in formal and informal supply chains (Baghdadi-Sabiti, Cohen-Kohler, & Wondemagegnehu, 2009; Garuba, Kohler, & Huisman, 2009; MacKey & Liang, 2012) and institutional conflicts of interest that are at odds with public health needs (Gava, Bermudez, & Pepe, 2010; Miranda, 2010; G. H. Silva, 2011).

An innovative pharmacogovernance framework was used to investigate pharmacogovernance institutions in Brazil and Kenya for their impact on postmarket drug safety nationally.

3.4 Pharmacogovernance Framework

The pharmacogovernance framework was used to clarify the relationship between pharmacogovernance and pharmacovigilance. The pharmacogovernance framework is a conceptual model that incorporates concepts derived from the literature on risk governance and Network Governance Theory. The literature suggests that risk governance, is the critical study of complex, interacting networks that make policy choices and decisions to address potential risks that are multijurisdictional, complex and/or ambiguous, such as the risks posed by pharmaceuticals. (Marjolein B.A. van Asselt & Renn, 2011; Renn et al., 2011; Renn & Schweizer, 2009). Risk governance normative principles can inform relevant societal actors about how to deal responsibly with risks (Renn et al., 2011). Network Governance Theory explains how and why governance networks form to address complex policy problems that are uncertain and require specialized knowledge as posed by pharmaceuticals (Torfing, 2012).
In this research, the pharmacogovernance framework serves as a guide for making choices that advance pharmacovigilance. The domains of the pharmacogovernance framework are informed by the United Nations Economic and Social Commission for Asia and the Pacific (UNESCAP) characteristics of good governance. Good governance, according to UNESCAP, is participatory, consensus oriented, accountable, transparent, responsive, effective and efficient, equitable and inclusive and follows the rule of law (United Nations Economic and Social Commission for Asia and the Pacific, nd).

Global pharmacogovernance favours state and exogenous actors’ engagement to reduce drug safety risks by strengthening pharmacovigilance. As such, the pharmacogovernance framework used in this research is expanded to include the domains ‘Stakeholder Coordination’ and ‘Intelligence and Information’. The pharmacogovernance framework domains are: Policy, Law and Regulation; Transparency and Accountability; Participation and Representation; Equity and Inclusiveness; Effectiveness and Efficiency; Intelligence and Information; Ethics; Responsiveness; and Stakeholder Coordination. The domains of the framework were established a priori.

- **Policy, Law and Regulation**: According to UNESCAP, good governance follows the rule of law whereby ‘fair legal frameworks are enforced impartially’ requiring ‘an independent judiciary and an impartial and incorruptible police force’ (United Nations Economic and Social Commission for Asia and the Pacific, nd). The pharmacogovernance domain ‘Policy, Law and Regulation’ is defined as laws, bills and resolutions that are intended to support the regulatory authority mandate to assure access to safe medicines, health products and services.
• *Transparency* is defined in this research as sharing information and operating in a manner that makes it easy for others to see what actions have occurred. It is aligned with the UNESCAP definition of transparency which is ‘decisions taken and their enforcement are done in a manner that follows rules and regulations. Information is freely available and directly accessible to those who will be affected by such decisions and their enforcement. It also means that enough information is provided and that it is provided in easily understandable forms and media’ (United Nations Economic and Social Commission for Asia and the Pacific, nd).

In this research, accountability is defined as taking responsibility for individual or organizational activities. This would include activities to advance postmarket drug safety. An institution is ‘accountable to those who will be affected by its decisions or actions. Accountability cannot be enforced without transparency and the rule of law’ (United Nations Economic and Social Commission for Asia and the Pacific, nd).

• *Participation and Representation*: UNESCAP suggests that participation is a characteristic of good governance. ‘Participation could be either direct or through legitimate intermediate institutions or representatives. It is important to point out that representative democracy does not necessarily mean that the concerns of the most vulnerable in society would be taken into consideration in decision making’ (United Nations Economic and Social Commission for Asia and the Pacific, nd). In consideration of concerns that the voice of vulnerable populations may not be represented, this research uses the definition ‘inclusive representation’. The pharmacogovernance domain participation and representation is defined as involvement in decision making by the
public at regulatory authority and government public meetings pertaining to setting the regulatory agenda and rules for postmarket drug safety.

- **Equity and Inclusiveness**: UNESCAP defines equity and inclusiveness as ‘all members feel that they have a stake in it and do not feel excluded from the mainstream of society. This requires [that] all groups, but particularly the most vulnerable, have opportunities to improve or maintain their wellbeing’ (United Nations Economic and Social Commission for Asia and the Pacific, nd). Pharmacogovernance expands this definition beyond representation in decision making to include equitable allocation and distribution of resources to ensure that all regions within the country have access to safe medicines and resources to detect and act on drug safety signals.

- **Responsiveness**: In this research, ‘responsiveness’ is defined as policies and regulations that address drug safety issues within a reasonable timeframe. This definition is consistent with ‘responsiveness’ as defined by UNESCAP.16

- **Effectiveness and Efficiency**: Effectiveness and efficiency is defined as ‘processes and institutions that produce results that meet the needs of society while making the best use of resources at their disposal’ by the UNESCAP. As related to pharmacogovernance, effectiveness and efficiency is defined as the capacity to evaluate the utility of

16 Good governance requires that institutions and processes try to serve all stakeholders within a reasonable timeframe, according to the UNESCAP definition.
pharmacovigilance policies and monitor pharmaceutical industry compliance with policy, law and regulation pertaining to postmarket drug safety.

- **Ethics**: Embedded in the definition of the pharmacogovernance domain ‘Policy, Law and Regulation’ and UNESCAP definition of ‘Follows the Rule of Law’ is the fair and impartial enforcement of national pharmacy policy and national pharmacovigilance policy. This suggests that a separate domain of ‘Ethics’ may be warranted. ‘Ethics’ is defined in this research as respect for justice, autonomy, non-maleficence, and beneficence to safeguard patient interests, right to safe medicines and health.

- **Intelligence and Information** is defined as mechanisms to improve communication between national regulatory authorities, state pharmacovigilance centres, patients, healthcare professionals, policymakers and the general public with respect to supporting the safe use of medicines.

- **Stakeholder coordination**: The pharmacogovernance domain ‘Stakeholder Coordination’ is defined as domestic and global actors that coordinate activities for the purpose of strengthening the national regulatory authority and human resources to benefit pharmacovigilance.
Table 3. Pharmacogovernance domain definitions

<table>
<thead>
<tr>
<th>Pharmacogovernance Domain</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy, Law and Regulation</td>
<td>Laws, bills and resolutions that are intended to support regulatory authority mandate to assure access to safe medicines, health products and services.</td>
</tr>
<tr>
<td>Transparency and Accountability</td>
<td>Sharing information and operating in a manner that makes it easy for others to see what actions have occurred. Taking responsibility for individual or organizational activities. This would include activities to advance postmarket drug safety.</td>
</tr>
<tr>
<td>Participation and Representation</td>
<td>Involvement in decision making by the public at regulatory authority and government public meetings pertaining to setting the regulatory agenda and rules for postmarket drug safety.</td>
</tr>
<tr>
<td>Equity and Inclusiveness</td>
<td>Equitable allocation and distribution of resources to ensure that all regions within the country have access to safe medicines and resources to detect and act on drug safety signals. Public decision making spaces are accessible to all segments of the population.</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>Policies and regulations address drug safety issues within a reasonable timeframe.</td>
</tr>
<tr>
<td>Effectiveness and Efficiency</td>
<td>The capacity to evaluate the utility of pharmacovigilance policies and monitor pharmaceutical industry compliance with policy, law and regulation pertaining to postmarket drug safety.</td>
</tr>
<tr>
<td>Ethics</td>
<td>The fair and impartial enforcement of national pharmacy policy and national pharmacovigilance policy. Respect for justice, autonomy, non-maleficence, and beneficence to safeguard patient interests, right to safe medicines and health.</td>
</tr>
<tr>
<td>Intelligence and Information</td>
<td>Databases and mechanisms to improve communication between national regulatory authorities, state pharmacovigilance centres, patients, healthcare professionals, policymakers and the general public with respect to supporting safe use of medicines.</td>
</tr>
<tr>
<td>Stakeholder coordination</td>
<td>Domestic and global actors that coordinate activities for the purpose of strengthening the national regulatory authority and human resources to benefit pharmacovigilance.</td>
</tr>
</tbody>
</table>
3.5 Methods

Qualitative research methods were employed in this study. They included a literature review of peer reviewed and grey literature and key informant interviews. Twenty-five key informants participated in 60-90 minute semi-structured interviews, in-person or by SKYPE, following ethics approval from University of Toronto, Moi University, Kenya and Brazil’s National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa (CONEP)). See Appendix B1, B2 and B3. Key informants that consented to an interview were advised that their anonymity would be protected (Appendix D). The interviews were conducted between October 2014 and January 2015. Interviews were conducted until saturation was reached. Reputational or chain sampling was used to identify information-rich key informants. This is a non-probabilistic method whereby study participants are asked to identify other potential key informants via a ‘snow-balling’ process. The study sample represented state pharmacovigilance units, ANVISA, the Kenya Pharmacy and Poisons Board, pharmaceutical companies (domestic and multinational) and county health representatives. The Brazilian key informants represented the states of Rio de Janeiro, São Paulo, Ceará and Goiás. Kenyan key informants represented Turkana, Kwale, Mombasa, and Uasin Gishu counties.

Interview notes were taken and all interviews were audio recorded and transcribed verbatim. The transcribed interviews were coded using Atlas.ti Qualitative Data Analysis software v. 7.5.4 (2015). Content analysis was conducted by the principal investigator. Data were coded into key themes relevant to the pharmacogovernance domains which were established a priori and emergent themes.
3.6 Results

Key informant interviews were analyzed to identify key themes that were relevant to pharmacogovernance. The pharmacogovernance framework was used to clarify the relationship between pharmacogovernance and pharmacovigilance by identifying areas of strength and weakness in furthering pharmacovigilance.

3.6.1 Pharmacogovernance variables

Key informants in Brazil and Kenya described the factors that they perceived to enable pharmacovigilance. The results that are shown in Table 4 and are organized according to the pharmacogovernance domains.

**Table 4. Factors influencing pharmacovigilance**

<table>
<thead>
<tr>
<th>Policy, Law &amp; Regulation</th>
<th>Intelligence &amp; Information</th>
<th>Participation and Representation</th>
<th>Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Policy instruments (e.g., RIA)</td>
<td>• Access to information technology</td>
<td>• Global actor engagement</td>
<td>• Clinical studies and spontaneous reporting guidelines publically accessible</td>
</tr>
<tr>
<td>• Policy priorities</td>
<td>• Resource allocation</td>
<td>• Inclusive access</td>
<td></td>
</tr>
<tr>
<td>• Priority setting practices</td>
<td>• Global actor engagement</td>
<td>• Stakeholder representation</td>
<td>• Quality Assurance</td>
</tr>
<tr>
<td>• Global actor engagement</td>
<td>o Funding/resources</td>
<td>o PV expertise to support regulatory decisions</td>
<td>o Global actor engagement</td>
</tr>
<tr>
<td>• Enforcement (e.g., RDCs)</td>
<td>o Active surveillance</td>
<td>o Stakeholder coordination</td>
<td>o Regulatory authority responsibility</td>
</tr>
<tr>
<td>• Transparency laws</td>
<td>o Access to global PV database</td>
<td>• Stakeholder collaboration</td>
<td>• Conflicts of interest or cross purpose interests</td>
</tr>
<tr>
<td>Accountability</td>
<td>o Access to risk communication network</td>
<td>Responsiveness</td>
<td>• State/County responsibility</td>
</tr>
<tr>
<td>• Regulatory authority responsibility</td>
<td>o Member of global PV network</td>
<td>• Global actor engagement</td>
<td>• Transparency</td>
</tr>
<tr>
<td>o Quality Assurance</td>
<td>• Data management compatible with international standards</td>
<td>o Active surveillance</td>
<td>• Clinical studies and spontaneous reporting guidelines publically accessible</td>
</tr>
<tr>
<td>• Global actor engagement</td>
<td>• Data analysis to support PV decision-making</td>
<td>• Takes action upon ‘several’ ADR reports</td>
<td></td>
</tr>
<tr>
<td>o norms</td>
<td>• Generate PV information and disseminate throughout the country</td>
<td>o Devolution decreases response time</td>
<td>• Regulatory authority responsiveness to industry requests</td>
</tr>
<tr>
<td>• Policy instruments</td>
<td>• National, subnational and supranational data sharing</td>
<td>o Submit all reports vs. only submit if ‘trend’ identified</td>
<td>• System for handling complaints</td>
</tr>
<tr>
<td>• Conflicts of interest or cross purpose interests</td>
<td>• Regulatory authority feedback (e.g., ADR reports) to guide decision-making</td>
<td>• Rapid uptake of policy and norms</td>
<td>• Rapid uptake of policy and norms</td>
</tr>
<tr>
<td>• State/County responsibility</td>
<td>• Widespread communication to</td>
<td>• Regulatory authority responsiveness to industry requests</td>
<td></td>
</tr>
<tr>
<td>Legitimacy of accountability</td>
<td>all levels of government, health sectors (public, private donor), health professional councils (e.g., medical, pharmacy, dentistry, nursing), state, county, municipal health depts. and drug/vaccine vigilance</td>
<td>Optimize risk management</td>
<td></td>
</tr>
<tr>
<td>Data collected disseminated to Ministry and ‘others’</td>
<td>Media coordination for consumer drug safety information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Board meeting minutes publically accessible</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire population covered by PV activities</td>
</tr>
<tr>
<td>Engage CHWs in pharmacosurveillance</td>
</tr>
<tr>
<td>Strategies to address environmental barriers to risk communication</td>
</tr>
<tr>
<td>Human resources</td>
</tr>
<tr>
<td>Financial resources</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness/Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmonization</td>
</tr>
<tr>
<td>Global actor engagement</td>
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<tr>
<td>PV system strengthening PV priorities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence or absence of conflict of interest guidelines</td>
</tr>
<tr>
<td>Ethics committees</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to information technology</td>
</tr>
<tr>
<td>Access to regulatory authority decision-makers</td>
</tr>
<tr>
<td>Consumer ADR reporting</td>
</tr>
<tr>
<td>Information accessible online</td>
</tr>
<tr>
<td>Community health workers included</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stakeholder Coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity building</td>
</tr>
<tr>
<td>Communication and information</td>
</tr>
<tr>
<td>Coordinate resource alignment to bridge gaps</td>
</tr>
<tr>
<td>Partnerships</td>
</tr>
<tr>
<td>Development of pharmacovigilance programs</td>
</tr>
<tr>
<td>Pharmacovigilance services</td>
</tr>
<tr>
<td>Submission of ADR reports</td>
</tr>
</tbody>
</table>

3.6.2 Pharmacovigilance and pharmacogovernance institutions in Brazil and Kenya

In the previous section, key informants’ perceptions of the pharmacogovernance variables that influenced pharmacovigilance were outlined. In the next section, research results pertaining to how pharmacovigilance is affected by pharmacogovernance in Brazil and Kenya is presented.

Pharmacogovernance institutions in Brazil include: the national regulatory authority (Agência Nacional de Vigilância Sanitária (ANVISA)), state Ministry of Health, State Centros de
Vigilância Sanitária (CVS) and the municipal government (Figure 1). ANVISA was established to protect and promote population health and ensure access to safe medicines, health products and services (ANVISA, nd-a; Mastroianni & Lucchetta, 2011). It is an independent regulatory body with administrative and fiscal autonomy, under contract with the Ministry of Health (MoH) (ANVISA, nd-a; de Mello & Ramalho, 2009). It is also funded by annual pharmaceutical company and drug registration fees.

**Figure 1. Pharmacogovernance institutions in Brazil***

*Shared pharmacogovernance
ANVISA regulates health products and services as well as sectors unrelated to pharmaceuticals or medical devices such as food, tobacco, agricultural chemicals, airports, and border surveillance (ANVISA, nd-a). ANVISA’s regulation of pharmaceuticals includes market authorization and review of drug pricing. ANVISA also reviews drug patent applications to evaluate the impact of a pharmaceutical product from the point of view of public health (Mueller & Costa, 2014; Shadlen, 2011).¹⁷ ANVISA’s ‘prior consent’ is a key step in the pharmaceutical patent process.

At the central level, regulatory activities are organized and developed by the National Health Surveillance System, comprising the Union, States, Federal District and Municipalities in Brazil (ANVISA Interview_02, 2014). ANVISA develops its activities in cooperation with the States, Federal District and Municipalities. “It is expected that the [subnational pharmagovernance institutions] locally develop post-marketing activities, leaving the federal level to address these activities at the macro level” (ANVISA Interview_02, 2014)

In Kenya, the pharmacogovernance institutions include the national regulatory authority (Kenya Pharmacy and Poisons Board), the Ministry of Health and County Departments of Health (Figure 2).

¹⁷ ANVISA is one of two agencies involved in the patent review process. The National Institute of Industrial Property (INPI) is the other agency that is responsible for conducting the registration review and technical examination of a pharmaceutical patent application.
The Kenya Pharmacy and Poisons Board was established as a semi-independent regulatory agency to ‘safeguard the health of the public by ensuring that medicines and health products comply with acceptable standard of quality, safety and efficacy’ (PPB Kenya, 2015). Regulatory policy is established at the central level.

**Figure 2. Pharmacogovernance institutions in Kenya***

*Centralized pharmacogovernance*
Resources and funding were identified as variables contributing to pharmacovigilance. Key informants in Brazil and Kenya acknowledged that financial and human resources were inadequate to advance pharmacovigilance.

‘There is no specific budget that is directed to the Pharmacovigilance. Every year at ANVISA's annual planning [is] where financial resources are approved for each area to run all year. The percentage of this budget [that will go to] pharmacovigilance is variable from year to year... The lack of human resources to work with pharmacovigilance does not allow us to move forward in some important respects.’ (ANVISA Interview_02, 2014)

‘Each directorate is given funding to plan it for the whole year...then depending on what the Board now thinks is a bigger priority, then more money can be given there. As it is, money is never enough. If you ask me I’ll need maybe 10 times what we actually we are given... And you know we are short staffed. We don’t have enough [staff] to take care of clinical trials, pharmacovigilance, postmarket surveillance, and medicines information. Very [few] key members of staff are covering for 2 million Kenyans.’ (Kenya Interview_PPB 01, 2014)

The funding structure of ANVISA and PPB may contribute to this deficit. ANVISA and PPB were established as semi-autonomous regulatory authorities. Neither PPB nor ANVISA are fully government funded (ANVISA does receive some funding from Ministry of Health contracts). Both regulatory authorities receive funding from the registration of pharmacies, pharmaceutical manufacturers and pharmaceutical products and receive fees for services (See Figure 1 and Figure 2). There was disagreement amongst key informants in Kenya regarding pharmaceutical industry funding for pharmacovigilance. One key informant commented that product retention fees, paid by industry for renewal of their product’s registration, were used for
pharmacovigilance. Another key informant commented that industry did not provide funding for pharmacovigilance because that would be a conflict of interest.

The analysis of the affect of decentralized governance (Brazil) as compared to devolved governance (Kenya) found that national governance structure can affect pharmacogovernance.

The research results are shown in Table 5.

**Table 5. Comparison of pharmacogovernance models and the affect on pharmacovigilance**

<table>
<thead>
<tr>
<th>Resources for pharmacosurveillance</th>
<th>Decentralized/shared pharmacogovernance model</th>
<th>Devolved/centralized pharmacogovernance model</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Financial &amp; human resources lacking to support pharmacovigilance, especially in historically poor states</td>
<td>- Financial &amp; human resources lacking to support pharmacovigilance, especially in historically poor states</td>
<td></td>
</tr>
<tr>
<td>- Resource allocation delegated to states thus subnational-level priority setting influences implementation of federal policy</td>
<td>- Resource allocation delegated to counties thus subnational-level priority setting influences implementation of federal policy</td>
<td></td>
</tr>
<tr>
<td>- Funding vulnerable to ‘political’ priorities</td>
<td>- Funding vulnerable to ‘political’ priorities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Policy, law &amp; regulation</th>
<th>Decentralized/shared pharmacogovernance model</th>
<th>Devolved/centralized pharmacogovernance model</th>
</tr>
</thead>
<tbody>
<tr>
<td>- National pharmacovigilance policy</td>
<td>- No national pharmacovigilance policy</td>
<td></td>
</tr>
<tr>
<td>- Federal and state regulations to support pharmacovigilance</td>
<td>- Conflicting Federal regulations pertaining to pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>- Mandatory pharma industry ADR reporting</td>
<td>- No mandatory pharma industry ADR reporting</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intelligence and information</th>
<th>Decentralized/shared pharmacogovernance model</th>
<th>Devolved/centralized pharmacogovernance model</th>
</tr>
</thead>
<tbody>
<tr>
<td>- National and subnational level pharmacogovernance institutions communicate information about ADR risk</td>
<td>- Fragmented ADR risk communication between subnational levels of government and parallel service providers</td>
<td></td>
</tr>
<tr>
<td>- Lack of integrated informational systems to aid in signal detection</td>
<td>- E-reporting system that includes patient ADR submission</td>
<td></td>
</tr>
<tr>
<td>- E-reporting system excludes patient ADR submission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Description</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Responsiveness to safety issues</td>
<td>• Federal and state shared responsibility for pharmacovigilance</td>
<td>• Federal and county shared responsibility for pharmacovigilance</td>
</tr>
<tr>
<td>Stakeholder coordination</td>
<td>• CVS partnerships with universities to expand personnel that are able to address ADR reports</td>
<td>• PPB partnerships with universities to build health care provider capacity for pharmacovigilance</td>
</tr>
<tr>
<td>Equity</td>
<td>• Inequitable distribution of pharmacogovernance institutions to monitor and assess drug safety (e.g., sentinel sites)</td>
<td>• Inequitable distribution of pharmacogovernance institutions to monitor and assess drug safety (e.g., sentinel sites)</td>
</tr>
<tr>
<td>Ethics, Accountability and Transparency</td>
<td>• Lapses in ethics motivated by cross purpose interests (e.g., drug re-authorization)</td>
<td>• Lapses in ethics motivated by cross purpose interests (e.g., pharmaceuticals procurement)</td>
</tr>
</tbody>
</table>
| Participation and Representation | • Spaces for public participation in ANVISA and CVS agenda setting  
 • Industry representation in decision making public forums | • No mechanism for public participation in PPB agenda setting  
 • Industry and donor representation in PPB decision making |
| Effectiveness and Efficiency | • Lack of funding and resources are barriers to effectiveness and efficiency in some states | • Lack of funding and resources are barriers to effectiveness and efficiency in some counties |

The results of the analyses of pharmacogovernance in Brazil and Kenya using the pharmacogovernance framework are described in detail in the next section. Overall, results suggest that policy, laws and regulations enabled pharmacovigilance in Brazil however, gaps in other pharmacogovernance domains were found that hindered pharmacovigilance. Pharmacovigilance in Kenya was impeded by gaps in all of the pharmacogovernance domains.

### 3.6.2.1 Policy, law and regulation

Pharmacogovernance institutional authority over pharmacovigilance is enabled by legislation, regulation and policy in Brazil and Kenya. Brazil has enacted numerous laws, regulations and
policies to support pharmacovigilance (Appendix M). The legislation that has been passed include: a National Medicines Policy (Ordinance 3.916), national drug surveillance (Ministerial Decree 696/01), National Pharmacovigilance Policy (Law 8.080/90) and mandatory postmarket surveillance with industry reporting (Law 6.360 and RDC no 55). Regulations to strengthen pharmacovigilance in Brazil include: RDC nº4, Article 3 (2009) which requires pharmaceutical companies to establish a pharmacovigilance program (Freitas & Romano-Lieber, 2007). Federal law nº6.360/76 article 79, and RDC nº55 article 9 that require drug companies to report ADRs associated with their drugs within 60 days for class I (cause death or permanent damage) and 120 days for class II (cause temporary or reversible damage) to the competent health authority (Law 6.360, 1976; "Resolution-RDC 55," 2005; Vashisth, Singh, & Nanda, 2012). Freitas and Romano-Lieber (2007), reported that few domestic companies provided training to report ADRs which could explain why, “although we are talking about the whole pharmacovigilance system, the companies are still not aware that they have to report on side effects of drugs. So if something happens …I know it’s a side effect of drugs, they say no, this is part of the disease” (Brazil interview_State 03, 2014).

Kenya has enacted fewer laws pertaining to pharmacovigilance (Appendix N). The Kenya National Drug Policy (1994) was revised in 2008. The 2010 National Drug Policy is still in the draft stage. The Pharmacy and Poisons Act, Cap 244, 1957 Revised Edition 2012 [1989] requires drug company surveillance of ADRs but has no provision for mandatory reporting. In contrast to Brazil, Kenya does not have a national pharmacovigilance policy. A policy was drafted in 2009 but it has yet to be passed. The final adoption of the NPS has been delayed by the 2010 election which brought in a new government, new constitution and devolved governance to Kenya’s counties (IGO/INGO Interview_05, 2014). Kenya’s National
Pharmaceutical Policy Sessional Paper No. 4 (2012), which includes pharmacovigilance guidelines is awaiting Parliamentary approval (IGO/INGO Interview_05, 2014). Kenya also does not have a requirement for drug companies to report ADRs, nor is there a requirement for a qualified person for pharmacovigilance. This is in contrast to Brazil which mandates these requirements by law.

Although pharmacovigilance policy, law and regulation have been established at the federal level, decentralized/devolved governance delegates authority to the states and counties to set subnational priorities. Subnational priorities affect resource allocation, implementation and compliance enforcement in Kenya and Brazil. Subnational priorities are strongly influenced by the pharmacogovernance domains.

3.6.2.2 Transparency and accountability

National-level regulatory reforms adopted since 2007 have aimed to change the culture and practice of public administration (G. H. Silva, 2011) and according to a key informant from ANVISA to, “provide more transparency, predictability and efficiency in the regulatory process of ANVISA... also increase the participation of civil society...Citizens, organizations, and public and private entities can contribute to set the priority themes for ANVISA for 2015-2016” (ANVISA 01). Accountability and transparency are agency values, according to ANVISA’s website (ANVISA, nd-a).

The Regulatory Process Improvement Programme and Regulatory Impact Analysis (RIA) have been introduced as policy instruments for accountability to measure the effectiveness and efficiency of ANVISA’s policies and responsiveness in meeting the regulatory agenda (G. H.
Silva, 2011). “I do not have any data about [regulatory agenda and regulatory impact analysis] but I believe that it has had some impact, because the institution has sought to expand the communication channels with the Brazilian society, including public hearings at the institution, publishing editorials to discuss themes, etc.” (ANVISA Interview_01, 2014). Despite discourse for transparent, accountable, administrative procedures written in the literature describing ANVISA’s regulatory governance, Miranda (2010) found that inadequate transparency and participation persists. Regarding ANVISA’s regulatory reforms, one state pharmacovigilance centre representative commented, “ANVISA has some projects that have been implemented, (e.g., NOTIVISA), but there is no follow-up in the program. There is still some lack of transparency in these programs” (Brazil Interview_State 04, 2014).

Priorities for pharmacovigilance are determined by the states which “have no obligation to do one thing or another. In Parana and Sao Paulo they have a pharmacovigilance bureau…Rio de Janeiro has a pharmacovigilance program” (Brazil Interview_State 04, 2014). Similarly, priority setting occurs in Kenyan counties where “the county executive and the director, they’re the ones who set the agenda and at least for […] they have not been exposed to pharmacovigilance issues. So most of the times in our meetings, even though pharmacovigilance comes up sometimes it has not been taken as serious as other issues” (Kenya Interview_County 02, 2015).

3.6.2.3 Participation and representation

‘Participation and Representation’ is defined in this study as public involvement in regulatory authority and government meetings for setting the regulatory agenda and rules for drug safety. ANVISA’s regulatory governance includes spaces for social participation (e.g., public hearings and consultations) to debate its regulatory agenda as a mechanism for transparency and

Key informants had scant information regarding the affect of norms for social participation on pharmacovigilance. One key informant commented that it was too early to say anything about it. It was not dedicated to pharmacovigilance, however it could have a major role (Brazil interview_State 01, 2014). An ANVISA key informant reported that, “I believe that it has had a certain impact because we are able to see that the organization (ANVISA) has looked to increase the communication channels between them and the public, which includes holding public hearings at ANVISA to discuss a specific subject” (ANVISA Interview_01, 2014). Another key informant queried, “On the paper, it looks fantastic, fabulous... Now, does it really work?” (Brazil interview_State 03, 2014). “I don’t know how many people really call the federal government hotline and complain about a medication. Few, if any of the spontaneous reports come from lay people to ANVISA. I really think that is very, very rare. It’s so difficult to get a line through, you know. They give up I guess” (Brazil interview_State 03, 2014).

Although public participation in health-related decision making is described as a guiding principle in Kenya’s health policy (Ministry of Health, nd; Sessional Paper No 6 of 2012 on the Kenya Health Policy 2012–2030 (DRAFT) National Development and Vision 2030), none of the key informants interviewed for this study outlined mechanisms for public participation (e.g., public forums).
On the other hand, donors were widely represented in decision making spaces pertaining to pharmacovigilance in Kenya. IGOs and INGOs (e.g., USAID and Management Sciences for Health) participated in meetings with the PPB and county health priority-setting meetings.

3.6.2.4 Equity and Inclusiveness

The responsibility for pharmacovigilance is a shared between the Federal government and decentralized state governments (Brazil) and devolved county governments (Kenya). Yet, this research found inequitable distribution of pharmacogovernance institutions and resources to monitor and assess drug safety throughout Brazil and Kenya. A greater concentration of sentinel hospitals, that integrate drug surveillance and ADR reporting into clinical practice (ANVISA, 2005-2009), was found in the highly resourced and densely populated Brazilian states (e.g., São Paulo, Rio de Janeiro, and Minas Gerais) and Kenyan counties (e.g., Nairobi and Uasin Gishu).

Fewer sentinel sites were found in rural, less populated regions of Brazil (e.g., Acre) and Kenya (e.g., Turkana County). In Brazil, “Not all the states have PV centers.” (ANVISA 01) and “if you’ve got a state, a poor state in the northeast of Brazil, they’re not doing anything. They don’t do any vigilance” (Brazil interview_State 03, 2014). These regions have a high level of poverty. Up to 42% of the population in the state of Acre, Brazil live in poverty (IBGE, nd). Approximately 95% of the population of Turkana County, Kenya live below the poverty line (SoftKenya, nd).

In Brazil, several key informants described inequities in pharmacovigilance across the country. One key informant suggested that, “decentralization can undermine the interaction between the
different State PV Centers. We are vulnerable to political forces; therefore, some states may receive more benefits/resources than others” (Brazil Interview_State 04, 2014).

3.6.2.5 Effectiveness and Efficiency

When asked about barriers to effective pharmacovigilance, many key informants in Brazil and Kenya responded that capacity was lacking. “We can hardly identify safety signals, leaving only the routine. This lack of personnel occurs not only at the federal level but also at the decentralized level” (ANVISA Interview_02, 2014). In regards to Kenya, “We have 47 Counties ... it may take longer for them to come to us… In terms of staffing at the Pharmacy and Poisons Board...they need to maybe have more numbers of people who can reach out to the field”(Kenya Interview_County 03, 2014).

3.6.2.6 Intelligence and information

An overlap was observed in ANVISA and state actors’ description of their responsibilities for disseminating information about adverse drug reactions. According to key informants, ANVISA and the states are responsible for notifying federal health districts, municipal branches, institutions that may be affected, the state health departments, federal professional boards (e.g., medicine, pharmacy and dentistry board) (ANVISA Interview_01, 2014; Brazil interview_State 02, 2015; Brazil Interview_State 04, 2014). “There is active communication between ANVISA, state and local surveillance that occurs through different instruments, such as letters, e-mails, phones, regular meetings and in-person meetings, circular letters and visits” (ANVISA Interview_02, 2014) which is consistent with shared pharmacogovernance. The effectiveness of their risk communication strategies (internet, phone, mail and official publications) has not been
studied according to key informants interviewed. “I don’t know if there is any regional variation. It is difficult to control information to rural areas.” (Brazil interview_State 02, 2015).

Kenyan key informants developed strategies to overcome challenges linked to disseminating risk communications in rural areas. One county pharmacist reported that notification was easy. “Each county has got a pharmacist who is coordinating pharmaceutical services. So we communicate to that particular person and it is up to him or her to tell the other team members” (Kenya Interview_County 04, 2014). Another key informant stated, “Sometimes to reach people you have to use community health workers, because the majority of the population is nomadic...community health workers are embedded in those populations” (Kenya Interview_County 02, 2015).

While intrastate and intra-county communication was identified by this research, the analysis of ‘intelligence and information’ in Kenya and Brazil found that interstate and inter-county communication between pharmacogovernance institutions and parallel sectors providing pharmaceuticals in Brazil and Kenya was fragmented. In Brazil, the lack of integrated informational systems to aid in signal detection was perceived as an additional barrier to effective pharmacovigilance (ANVISA Interview_01, 2014; IGO/INGO Interview_04, 2014).

18 An example of a parallel sector includes the public and faith-based medicines distribution system (e.g. Kenya Medical Supply Agency (public) and Mission for Essential Drugs and Supplies (faith-based donor operated).
3.6.2.7 Ethics

Population expectations for access to safe, quality medicines and industry expectations for industry-friendly policies can diverge. Gava et al. (6, p. 3410), suggest that while ‘health authorities should act as mediators between the interests of drug manufacturers and the needs of public health… [they have a] duty to protect health’. The literature suggests that ANVISA must reconcile its dual mandate and strengthen its regulatory role (Miranda, 2010; G. H. Silva, 2011).

One key informant suggested that, “Brazil simplified the bureaucratic process to open competition for small business. This is not a policy for pharmacovigilance” (Brazil interview_State 01, 2014). This research suggests that gaps persist in the pharmacogovernance domain ‘Accountability’ despite ANVISA’s adoption of the Good Regulatory Practices Program (PRO-REG) because PRO-REG has not yet been applied to regulatory policy that is related to pharmacovigilance.

Pharmacogovernance institutions in Kenya have also exhibited lapses in ethics motivated by cross purpose interests, particularly in regards to pharmaceuticals procurement (Kenya Interview_County 04, 2014; Otieno, Odundo, & Rambo, 2014). “A lot of funds go to procurement of pharmaceutical products. In that we also find that certain people have interests in pharmaceutical products. It means that within the county, if policies have to be passed, anything to do with medicines or pharmaceutical supplies you can say there’s a lot of debate. The policies will not easily pass” (Kenya Interview_County 04, 2014). Newspaper articles suggest that PPB has also acted with cross purpose interest leading to policies that resulted in unregistered drugs in the marketplace ("Board admits bad drugs in the market," 2011).
### 3.6.2.8 Responsiveness

Some Brazilian key informants suggested that communication between ANVISA and the states was sluggish and non-responsive. One key informant expressed frustration with ANVISA regarding actions taken as a result of spontaneous ADR reports stating, “...they don’t do anything. It’s a loss of time for me to pick up the phone and tell them that there’s a side effect of a drug. They don’t take any action” (Brazil interview_State 03, 2014). Similarly, in Kenya one county key informant described an incident involving a drug that was withdrawn from the market in which there was a delay in risk communication. “That one took almost...quite some time, so people weren’t aware ‘cause they’re giving those to patients... they’re not getting any information. It took months” (Kenya Interview_County 03, 2014).

Many key informants interviewed agreed that pharmacovigilance in Brazil and Kenya was hindered by insufficient capacity to analyze the volume of ADRs reported. “We have a human resource deficiency designed to work with pharmacovigilance, considering the size of Brazil” (ANVISA Interview_02, 2014). A key informant in Kenya reported that, “in [...] County the majority of the health facilities don’t have pharmaceutical staff. PPB communications [related to pharmacovigilance] are directed to the pharmacist and pharmacy technologist” (Kenya Interview_County 02, 2015). Inadequate infrastructure hindered responsiveness in rural Kenya. “Not too many places have internet, even though the PPB has an online format where you can report directly... also in most parts there is no electricity. So they write physical [ADR] reports which come to the county by post” (Kenya Interview_County 02, 2015).
3.6.2.9 Stakeholder coordination

Decentralized governance necessitates coordination between federal and state stakeholders to assure effective pharmacovigilance across the nation. Key informants in Kenya diverged in their opinions regarding the impact of devolution on pharmacovigilance and the importance of stakeholder coordination to overcome deficits in capacity. While Kenyan county key informants were in support of the autonomy that they achieved through devolvement, they acknowledged that they were ill-prepared to advance pharmacovigilance. “There have been no changes. We have not factored pharmacovigilance. Activities will continue as before where only Pharmacy and Poisons Board is initiating, and then we take up” (Kenya Interview_County 04, 2014).

National and subnational pharmacogoverance institutions have responded to the capacity deficiency in various ways. In Brazil, state pharmacovigilance centres (e.g., Ceará) have partnered with universities to expand personnel that are able to address ADR reports. In Kenya too, the PPB and University of Nairobi have collaborated to develop pharmacovigilance resources and build capacity. Unlike Brazil, Kenya has placed a strong emphasis on IGO and NGO support for training to develop needed capacity.

3.7 Discussion

Government commitment to assuring strong pharmacogovernance helps to ensure the right to health and safe, effective medicines guaranteed by the constitution of Brazil and Kenya’s Bill of Rights. Decentralization/devolution gives subnational governments the responsibility for assuring pharmacovigilance through implementation of national policy, law and regulation. Subnational governments may also set individual pharmacovigilance priorities.
The research found that decentralized/devolved governance augmented the impact of the gaps in pharmacogovernance, particularly in under-resourced states (Brazil) and counties (Kenya). For example, the regional disparities in the distribution of resources for monitoring and assessing drug safety nationwide that were found in both Brazil and Kenya revealed gaps in ‘Equity’ that compromises pharmacovigilance. Risk communication was also found to be hampered by regional disparities.

*Network Governance Theory* suggests that policy networks would form to overcome the limitations of decentralization and devolvement that foster regional disparities. In Kenya, policy networks have formed that included state and non-state actors (e.g. USAID and WHO) that mobilized financial and human resources to support pharmacovigilance in under-resourced counties. On the other hand, inequities persisted perhaps because policy networks in Kenya lacked representation of medicines users to advocate for equitable distribution of pharmacovigilance across the country. Similarly, consumers were under-represented in policy making spaces in Brazil.

Inequities in pharmacovigilance might be addressed by inclusion of the public in drug safety policymaking forums. Pharmacogovernance that expands consumer representation in the agenda setting process has the potential to increase accountability and reduce political forces that skew decision-making. Kohler & Martinez (2015) suggest that, to be effective, citizens must receive training and education about deliberative governance.

This research suggests that stable federal and state funding is needed that is specifically targeted for pharmacovigilance. The ANVISA and PPB funding models may leave the regulatory
authorities under-resourced because funding varies annually, adjusting with changes in priorities. Key informants reported that resources for pharmacosurveillance and other pharmacovigilance activities were insufficient. Moreover, some regions were allocated greater resources than others. Some states had no pharmacovigilance centres at all (Brazil interview_State 02, 2015; Kenya Interview_County 02, 2015). This finding is consistent with the literature that suggests poor service delivery in under-resourced municipalities is in part, due to lack of human resources.

The ANVISA and PPB funding model, whereby agency funding is principally derived from fees for service and registration fees may also leave the regulatory agencies vulnerable to industry interests (Figure 1 and Figure 2). The literature suggests that industry may influence regulators’ decisions regarding postmarket drug safety, skewing decisions toward industry interests (Davis & Abraham, 2011; Frank et al., 2014). A study of the impact of the Prescription Drug User Fee Act (PDUFA) in the United States, which ties funding for pharmacovigilance to expedited product approvals, found that there were more drug withdrawals and product warnings, after the passage of the Act (Frank et al., 2014). The Prescription Drug User Fee Act (PDUFA) was enacted in 1992 and renewed in 1997, 2002, 2007 and 2012. In Kenya, the collection of product retention fees for registration renewal, may lead conflicts of interest that result in PPB’s renewal of products with suspected safety issues.

Moreover, industry has both access and representation in decision making spaces in Brazil and Kenya. Whereas a code of ethics attempts to minimize conflicts of interest by limiting industry direct access to ANVISA policy makers in Brazil, industry representatives reported that they had relatively easy access to PPB representatives in Kenya.
Findings also suggest there are also gaps in the pharmacogovernance domain ‘Ethics’. Conflicts of interest have been described in the literature and were reported by key informants that were related to pharmaceutical approval process and procurement (Baghdadi-Sabeti et al., 2009; Garuba et al., 2009; Gava et al., 2010). This research suggests that drug procurement decisions may be political (de Lima, 2013; Gava et al., 2010; Kenya Interview_County 03, 2014; Kenya Interview_County 04, 2014; Otieno et al., 2014). Political forces within subnational governments influenced pharmacovigilance priorities and allocation of resources for postmarket drug safety, according to some key informants. Corruption is endemic in Kenya and Brazil leading to service delivery skewed to ‘politically loyal key decision makers’ and procurement malpractice whereby tenders were awarded to “politically connected bidders” (Baghdadi-Sabeti et al., 2009; Garuba et al., 2009; Otieno et al., 2014; Rich & Gomez, 2012). Drug procurement decisions made on the basis of politics may result in poor quality medicines in the supply chain, substandard therapies and increased ADRs.

Gaps in pharmacogovernance related to information and intelligence were augmented by decentralized or devolved governance because interstate (Brazil) and inter-county (Kenya) communication between subnational pharmacogovernance institutions was fragmented. State CVS’ in Brazil and county health departments in Kenya did not typically communicate with each other. Similarly, communication among parallel sectors providing pharmaceuticals (e.g. public, private and faith-based institutions) was fragmented in Kenya. This led to delays in risk communication regarding adverse drug reactions. This finding is consistent with the literature. Miranda (2010) argued that decentralization led to fragmentation of the healthcare system.
3.8 Conclusion

This research suggests that the pharmacogovernance framework can contribute to a holistic assessment pharmacogovernance structures and pharmacogovernance institutions that impact pharmacovigilance. Moreover, the research contributes to our understanding of the variables that influence pharmacovigilance in Brazil in Kenya.

Using the pharmacogovernance framework, the research found similar enablers and hindrances to pharmacovigilance in decentralized/shared governance and devolved/centralized pharmacogovernance models. In both models pharmacovigilance was hindered by insufficient resources (human and financial). Insufficient resources may negatively impact capacity for passive and active pharmacosurveillance. Unanticipated was a finding that subnational level priority setting may negatively impact the allocation of resources for pharmacovigilance.

Policy, regulation and enforcement were identified as variables that influence pharmacovigilance. When national governance was devolved and pharmacogovernance was centralized, pharmacovigilance was hindered by the lack of a national pharmacovigilance policy and regulation to enforce pharmaceutical company reporting of ADRs in Kenya. In contrast, when national governance was decentralized and pharmacogovernance shared as in Brazil, the research suggests that pharmacovigilance may be hindered by the absence of a centralized ADR reporting system for patients.

The research suggests that pharmacovigilance may be enabled when national and subnational level pharmacogovernance institutions share responsibility for pharmacovigilance and share risk
communication. Regardless of the model of pharmacogovernance, research findings suggest that stakeholder coordination that involves university partnerships can strengthen pharmacovigilance capacity building and activities.
Chapter 4

Chapter Four: Exogenous Factors Influencing on Pharmacogovernance and Pharmacovigilance in Brazil and Kenya

4.1 Preamble

The papers in chapter 4 investigate exogenous actors’ influence on pharmacogovernance in Brazil and Kenya.

The article, titled “Governance and Pharmacovigilance in Brazil: A scoping review”, investigates the relationship between governance, pharmacovigilance, and Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil; important given ANVISA’s coordination of the national pharmacovigilance system and authority over Brazil’s national pharmaceutical policy. The paper examines the literature pertaining to global institutions to investigate how transnational policy ideas for regulatory governance have been integrated and translated into pharmacogovernance in Brazil.

The paper, titled “Matching Access to Safety: Pharmacogovernance in Kenya”, is a case study investigating exogenous actors’ interactions pertaining to pharmacogovernance. The study addresses the research question: which type or pattern(s) of interactions among exogenous actors, the Kenya Pharmacy and Poisons Board and County actors enable or hinder pharmacogovernance and pharmacovigilance.
Chapter 4a: “Governance and pharmacovigilance in Brazil: a scoping review”

This chapter is a reprint of:


The research design and analysis was conducted by Kathy Moscou. Co-authors Dr. Jillian C. Kohler and Dr. Anita McGahan read and contributed article drafts. The abstracts retrieved by the scoping review were read by two researchers (KM, PC).
4a.1 Abstract

**Background:** This scoping review investigates the relationship between governance, pharmacovigilance, and Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil, which has authority over Brazil's national pharmaceutical policy, drug registration and coordination of the national pharmacovigilance system. The purpose is to investigate opportunities for effective pharmacovigilance.

**Methods:** Sixty-three terms pertaining to pharmacovigilance in Brazil and ANVISA, global institutions, pharmaceutical industry, and civil society were searched in thirteen relevant databases on November 17-18, 2013. Using a pharmacogovernance framework we analyzed ANVISA's pharmacogovernance: the manner in which governing structures, policy instruments, and institutional authority are managed to promote societal interests for patient safety due to medication use. The integration of transnational policy ideas for regulatory governance into pharmacogovernance in Brazil was also investigated.

**Results:** Brazil's policy, laws, and regulations support ANVISA's authority to ensure access to safe medicines and health products however ANVISA's broad mandate and gaps in pharmacogovernance account for regional disparities in monitoring and assessing drug safety. Gaps in pharmacogovernance include: equity and inclusiveness; stakeholder coordination; effectiveness and efficiency; responsiveness; and intelligence and information.

**Conclusions:** Pharmacogovernance that addresses 1) regional resource disparities, 2) federal and state lack of coordination of pharmacovigilance regulations, 3) asymmetric representation in the
pharmaceutical regulatory agenda and which 4) disaggregates regulatory authority over health and commercial sectors would strengthen pharmacovigilance in Brazil.

Key words: Brazil, drug safety, governance, pharmacovigilance, regulation, pharmaceutical policy
4a.2 Introduction

Pursuant to Article 196 of the Brazilian Constitution, all Brazilians have the right to health (Biehl, Petryna, Gertner, Amon, & Picon, 2009; Constituição da República, 1988; Mastroianni & Lucchetta, 2011). The Constitutional commitment to health for its population includes access to safe, effective, quality essential medicines; guidelines to promote rational use; and cost control (Mastroianni & Lucchetta, 2011) as expressed in Brazil’s National Medicines Policy (NMP). One key challenge the Federal government has faced is how to determine what governance, regulations and policy instruments best fulfill Brazilian’s constitutional right to health; including assuring nationwide equity in monitoring, assessing, and communicating drug safety risk.

Accordingly, we investigate pharmacogovernance in Brazil and the Agência Nacional de Vigilância Sanitária (ANVISA) regulatory governance for their impact on pharmacovigilance (the science and activities relating to detecting, assessing, understanding and preventing adverse effects or other possible drug-related problems).

We define pharmacogovernance as the manner in which governing structures; policy instruments and institutional authority (ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests for patient safety and protection from adverse drug events. Pharmacogovernance embraces a culture that supports drug safety and contributes to maintaining a healthy population, which the state and corporate sector advances as aligned with pharmacovigilance (Moscou et al., 2013). The absence of strong pharmacogovernance undermines stewardship for postmarket drug safety, safety signal detection, risk communication and rational medicine use. Weak pharmacogovernance therefore entails a lack of oversight and accountability that may negatively affect pharmacovigilance by:
• Creating opportunities for corruption to emerge (Baghdadi-Sabeti et al., 2009; Garuba et al., 2009; Mackey & Liang, 2012);
• Creating institutional conflicts of interest, whereby regulators are dually responsible for protecting patient safety and industry competitiveness (Gava et al., 2010; Miranda, 2010; G. H. Silva, 2011);
• De-incentivizing adoption of legislation and norms for pharmacovigilance; and
• De-incentivizing detection of adverse drug reactions (ADR) (Baghdadi-Sabeti et al., 2009; Garuba et al., 2009; Mackey & Liang, 2012).

These negative outcomes of deficient pharmacogovernance are at odds with public health needs and the constitutional right to health in Brazil.

We also investigated whether governance by the Agência Nacional de Vigilância Sanitária (ANVISA) and support from the international community are sufficient to ensure postmarket drug safety across Brazil. Specifically, we investigated how global actors’ policy ideas for regulatory governance (e.g., transparency and accountability) were integrated into pharmacogovernance in Brazil. Global actors were broadly defined as agents that influence public policy in multiple countries. They included employees of the World Health Organization/Pan American Health Organization (WHO/PAHO), US Food and Drug Administration (FDA), Global Fund, European Medicines Agency (EMA) and others that have provided pharmacovigilance guidelines, best practices, training, regulatory norms, technical expertise and access to global knowledge networks (Coêlho, Arrais, & Gomes, 1999; PAHO, 2011; Rigo & Nishiyama, 2005; UMC, 1998, 2001; UNAIDS | WHO, 2011).
We employ *Ideation Theory* to frame our understanding of how and why global actors’ policy ideas and norms pertaining to pharmacovigilance have gained traction in Brazil. *Ideation Theory* suggests that a meaningful feature of global actors is their capacity to convert ‘soft power’ into ‘hard power’ whereby global actors’ policy ideas and knowledge influence the policy agendas, policy tools, legislation, and practices of recipient countries (Stone, 2004). Soft power represents a persuasive approach that is taken to shape or co-opt government policy preferences or public opinion. The power to influence rests in perceived legitimacy or shared values (Nye, 2004). Norms are presented as a ‘toolbox’ from which countries choose according to perceived relevance.

Ideation Theory suggests that policy uptake usually requires collaboration between national and transnational policy actors’ with technical and financial support (Béland & Orenstein, 2010). New ideas (e.g., the use of policy tools for analyses of regulatory policy) are adopted to the extent that they respond to concrete policy problems, resonate with the interest and ideas of key actors and are brought to the attention of relevant public agencies that have the structural capacity to implement the new ideas (Hall, 1993). The policy ideas are reinforced through peer learning. Peer learning is used as a strategy for the diffusion of global development agencies’ policy ideas to poor and developing countries (Gaetani & Albuquerque, 2009; Stone, 2004).

Our manuscript is organized as follows. First, the evolution of pharmacovigilance and regulatory authority over postmarket drug safety in Brazil is described. Next, our search methodology is described following the STARLITE reporting criteria. Following, our research findings are reported for each of the literature typologies we identified. Lastly, recommendations to advance pharmacogovernance and pharmacovigilance in Brazil are provided.
4a.3 Background

The 1990’s was marked by a groundswell of discourse supporting pharmacovigilance by domestic and global actors. Support for pharmacovigilance grew in Brazil’s universities, consumer advocacy groups, drug information centers, and health professional associations during the 1990s (Mendes, Pinheiro, Avelar, Teixeira, & Silva, 2008). State pharmacovigilance centers and drug information centers (Centros de Informação de Medicamentos) were established in São Paulo, Ceará, Paraná and Mato Grosso do Sul during the period between 1989 and 1998 (Carvalho, 2011; Castro, 1999; Centro de Vigilância Sanitária, nd; Coêlho et al., 1999; Mendes et al., 2008). Pharmacovigilance was also the focus of the IV Brazilian Congress on the Surveillance of Drugs (1997), Conference of Brazilian Society of Hospital Pharmacy I and II, and the 1st Brazilian Seminar on Pharmacoepidemiology (Coêlho et al., 1999). Global actors’ policy ideas during this period, as later described in this manuscript, served as a catalyst for discussions regarding nationwide pharmacovigilance systems. The disseminated policy ideas influenced state pharmacovigilance initiatives in Brazil (Rigo & Nishiyama, 2005) (Figure 3).

ANVISA’s mandate is to protect and promote population health and ensure access to safe medicines, health products and services (ANVISA, nd-a; Mastroianni & Lucchetta, 2011). It is one of Brazil’s largest regulatory agencies; overseeing the implementation of aspects of Brazil’s NMP (Dias et al., 2002; Yadav, 2008).

ANVISA regulates products, sectors and services related to health and numerous areas not directly relevant to pharmaceuticals or medical devices (e.g., foods, tobacco, agricultural chemicals, airports, and border surveillance) although much of its resources are allocated to non-
health sectors (ANVISA, nd-a; de Mello & Ramalho, 2009). It regulates products and services that are valued at approximately 25 percent of Brazil’s gross domestic product (de Mello & Ramalho, 2009). ANVISA’s governance reflects the reform agenda championed by President Fernando Henrique Cardoso beginning in 1995 and continuing throughout his presidency.

**Figure 3. Factors influencing pharmacovigilance in Brazil**

Cardoso’s endorsement of regulatory oversight led to a surge in the creation of newly structured regulatory authorities (Cruz, 2009; Ramalho, 2009). ANVISA’s governance also reflected
global actors’ ideas for regulatory governance that were circulated during the 1990s (Cruz, 2009; de Mello & Ramalho, 2009).

The post 2000 period

Brazil’s National Pharmacovigilance System (NPS) was adopted in 2001. The NPS is managed by the Pharmacovigilance Unit (Yadav, 2008) and coordinated by ANVISA (Dias et al., 2002; Yadav, 2008). The National Center for Monitoring of Medicines (CNMM) was also created in 2001 following the meglumine tragedy (2000) that resulted in hundreds of fatal ADRs (Dias, 2002; Rigo & Nishiyama, 2005; Yadav, 2008). The emergence of yet another incident of serious and fatal ADRs resulting from the use of medicines (e.g., thalidomide in 1960) reinforced to the Federal government the need for governing structures and institutional authority over drug safety in Brazil. Today, the CNMM is headquartered in the Pharmacovigilance Unit and is responsible for planning, coordinating and supervising the formulation and implementation of operational guidelines and technical norms for medicines safety, rational use and surveillance.

Like many areas of the health system governance, responsibilities are shared at different levels. Both ANVISA and Brazilian state governments have responsibility for pharmacovigilance. State Centros de Vigilância Sanitária (CVS) are responsible for implementing policy and practices to reduce ADRs and poor quality medicines. Pharmacosurveillance, monitoring drug adverse-effects for signals of safety issues, is carried out by regional pharmacovigilance centers in 193 sentinel hospitals and sentinel pharmacies as part of the Notifying Pharmacies project (ANVISA, nd-d; Vashisth et al., 2012). The Notifying Pharmacy project (Farmácias Notificadoras), a partnership between the CVS and State Boards of Pharmacy, requires a pharmacist be present during pharmacy operating hours and submit reports of drug-related problems to the CNMM (ANVISA, nd-e).
4a.4 Methods

A scoping review of peer reviewed and grey literature from pharmacy, health, political science, and the social sciences, pertaining to global actors (e.g., WHO, Global Fund) and pharmacovigilance, regulatory governance, accountability and transparency in Brazil was conducted for this study of governance and pharmacovigilance in Brazil. The scoping review was used to map the existing literature and gather a holistic picture of pharmacogovernance in Brazil. Cochrane Collaboration guidelines for qualitative research were followed for searching, inclusion, and data extraction (Booth, 2011; Noyes & Lewin, 2011). The full search strategy is presented in Table 6 and follows the STARLITE reporting criteria (Booth, 2011). The acronym STARLITE represents sampling strategy, type of study, approaches, range of years, limits, inclusion and exclusions, terms used, and electronic sources. Although we narrowly defined the research question, pre-determined inclusion and exclusion criteria, and followed a strategy for data extraction- consistent with a scoping review, we did not apply quality filters and nor formally assess the quality of the literature included in our study- consistent with a scoping review (Armstrong, Hall, Doyle, & Waters, 2011).
Table 6. Scoping review structured according to STARLITE principles

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<th>STARLITE principles</th>
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<tr>
<td>S</td>
<td>Selective <strong>sampling strategy</strong>: Articles selected from pharmacy, health, political science, and the social sciences databases</td>
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<td>T</td>
<td>All <strong>types of studies</strong> were included (policy papers, qualitative studies, dissertations)</td>
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<tr>
<td>A</td>
<td><strong>Approaches</strong> Subject searching, citation searching, hand-searching, internet searching</td>
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<td>R</td>
<td><strong>Range</strong> (No restrictions): to the beginning of each database—to November 18, 2013</td>
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<td><strong>Limits</strong></td>
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<tr>
<td>I</td>
<td><strong>Inclusion</strong>: Global actors and pharmacovigilance, regulatory governance, accountability and transparency in Brazil; <strong>Exclusion</strong>: Studies describing: 1) vaccines, herbals or animal studies; 2) pre-market studies (phase I, II, and III); 3) pharmaceutics methods; 4) randomized controlled trials or observational studies pertaining to therapeutics or characterizing drug-specific ADRs or 5) did not describe pharmacovigilance in Brazil</td>
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<td>T</td>
<td><strong>Terms</strong> (See Appendix L)</td>
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<td>E</td>
<td><strong>Electronic sources</strong>: Ovid MEDLINE(R), Ovid OLDMEDLINE(R), Ovid MEDLINE(R) In-Process &amp; Other Non-Indexed Citations, Ovid Healthstar, Embase Classic+Embase, International Pharmaceutical Abstracts, International Political Science Abstract, Journals@Ovid Full Text, Embase, LILACS, PubMed, EBSCO, SciELO, GOOGLE Scholar</td>
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4a.4.1 Search Methods

Search methods included entering search terms into relevant databases, organizational websites (e.g., ANVISA) and hand searching. Sixty-three search terms were entered into 13 relevant databases on November 17-18, 2013 to identify literature pertaining to pharmacovigilance, governance, transparency, specific global actors, the pharmaceutical industry, ANVISA, and civil society (Appendix K). Acronyms and full text were entered as search terms, such as World Health Organization and WHO. All databases were searched for the same time period which was the beginning date of the database (e.g., OVID [1946] and International Pharmaceutical Abstracts [1970]) through November 18th, 2013. Data were only available through October 2013 for some of the databases searched. This date range was selected to capture literature describing global actors’ influence in Brazil in the years prior to the creation of ANVISA up to the date of the search. The databases searched were Ovid MEDLINE(R) 1946 to November Week 1 2013, Ovid OLDMEDLINE(R) 1946 to 1965, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 15, 2013, Ovid Healthstar 1966 to October 2013, Embase Classic+Embase 1947 to 2013 Week 46, International Pharmaceutical Abstracts 1970 to October 2013, International Political Science Abstract 1989 to October 2013, Journals@Ovid Full Text November 18, 2013, Embase 1974 to 2013 November 15, LILACS DATE 1st mentioned to November 18, 2013, PubMed 1st mention to November 18, 2013, EBSCO search Oct 16, 2013 and SciELO 1st mention to Nov 17, 2013. There were no search restrictions. English, Portuguese, and Spanish publications were included.
Figure 4. Scoping review flowchart

Records identified through database searching
\((N = 1137)\)

Records after duplicates removed
\((n = 362)\)

Records screened Phase 1
\((n = 362)\)

Records screened Phase 2
\((n = 128)\)

Full-text publications assessed for eligibility
\((n = 38)\)

Publications included in Scoping Review
\((n = 14)\)

Records excluded
\((n = 234)\)

Records pertaining to pharmacovigilance excluded
\((n = 90)\)
- Jurisdiction outside of Brazil
- Publications not specifically characterizing pharmacovigilance

Publications excluded
\((n = 24)\)
- Articles not pertaining to regulatory governance, pharmacogovernance accountability, transparency and global actors
The 1137 records retrieved were derived from: OVID/Embase (986), LILACS (57), PubMed (89) and EBSCO (5). After duplicates were removed 358 records remained. Data from ANVISA, WHO and PAHO websites (4) was included.

4a.4.2 Criteria for selecting studies

Two researchers (KM, PC) read through the titles and abstracts (all written in English) to determine relevance to this study. Phase I exclusion criteria comprised publications that described: 1) vaccines, herbals or animal studies; 2) pre-market studies (phase I, II, and III); 3) pharmaceutics methods; 4) randomized controlled trials or observational studies pertaining to therapeutics or characterizing drug-specific ADRs and 5) studies that were retrieved solely because the author was from Brazil, or a Brazilian reference was cited (Figure 4). In phase II, the full text was read to determine inclusion (Table 7). Full texts written in Portuguese and Spanish were read; then translated into English using Google translate; then re-read before determining inclusion. Publications not meeting inclusion criteria provided background information to contextualize Brazil’s experience with pharmacovigilance.

4a.4.3 Types of studies included

Fourteen publications met our inclusion criteria (Table 7). The publications that were included characterized: 1) global interventions in Brazil pertaining to governance or pharmacovigilance, 2) ANVISA regulatory governance (e.g., accountability and transparency), and 3) pharmacogovernance in Brazil. All of the publications that met the inclusion criteria were read iteratively by the principal author and data was extracted that was relevant to 1) how global actors, their policy ideas and instruments influenced Brazil’s regulatory governance and pharmacovigilance and 2) how ANVISA’s pharmacogovernance supports pharmacovigilance.
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<th>Type</th>
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<td>A</td>
<td>ADR studies: Prevalence and Characterization of ADRs</td>
<td>A1: Specific drug(s) [43]</td>
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<td>A2: Vaccines, herbals, phytopharmaceuticals, nutraceuticals, Over-the Counter [22]</td>
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<tr>
<td>B</td>
<td>Theoretical papers (Not Brazil specific)</td>
<td>B1: ADR reporting [3]</td>
<td>14</td>
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<td></td>
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<td>B2: Risk communication [1]</td>
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<td>B3: Regulatory harmonization [1]</td>
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<td>B4: Global actors’ norms or Global governance [6]</td>
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<td>B5 Pharmacovigilance regulatory authority Latin America [3]</td>
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<tr>
<td>C</td>
<td>Pharmacovigilance practices in Brazil</td>
<td>C1: Industry implementation of pharmacovigilance [2]</td>
<td>35</td>
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<tr>
<td></td>
<td></td>
<td>C2: Analysis of pharmacovigilance centres, sentinel hospitals &amp; notifying pharmacy ADR reports [9]</td>
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<td>C3: Pharmacovigilance Systems, regulations, or policies [20]</td>
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<td>C4: ADR prevention interventions [4]</td>
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<tr>
<td>D</td>
<td>Regulatory governance, pharmacogovernance and pharmacovigilance</td>
<td>D1: Transparency and/or Accountability [5]</td>
<td>14</td>
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<tr>
<td></td>
<td></td>
<td>D2: Global actors and Transparency and/or Accountability [3]</td>
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4a.4.4 Data extraction and management

A selective approach to data extraction was employed in this research. Data specifically related to the study question(s) are selectively extracted when using this approach (Noyes & Lewin, 2011). Data that were relevant to the pharmacogovernance domains was extracted for this research. A pharmacogovernance framework was used to analyze the relationship between pharmacogovernance and pharmacovigilance. The pharmacogovernance domains were established *a priori*. Our pharmacogovernance domains were: Policy, Law, and Regulation; Transparency and Accountability; Participation and Representation; Equity and Inclusiveness; Effectiveness and Efficiency; Intelligence and Information; Ethics; Responsiveness; and Stakeholder coordination (Figure 5). Quality of the literature included in this review was neither prioritized nor formally assessed.

**Figure 5. Pharmacogovernance Framework**
4a.5 Results

Our scoping review identified fourteen publications on the topic of governance and ANVISA in Brazil; nine specifically addressed accountability and/or transparency. From this sample, four referenced global institutions. Nearly half of the publications (4) were written by persons internal to ANVISA and described regulation and regulatory reforms in ANVISA. The publications that were analyzed were classified into 4 typologies. The typologies that were found were classified into the following areas: 1) ANVISA’s regulatory reforms and policy instruments; 2) ANVISA’s regulatory governance; 3) global actors’ influence on norms in Brazil pertaining to governance or pharmacovigilance; and 4) ANVISA and the pharmacogovernance domain(s) (Table 8).

Table 8. Typology of included literature

<table>
<thead>
<tr>
<th>Literature typology</th>
<th>Authorship and date</th>
<th>Types of literature</th>
<th>Article summary</th>
<th>Data extracted</th>
</tr>
</thead>
</table>
• Aims of regulatory management reform  
• The Regulatory Agenda as a policy instrument to strengthening regulatory governance through increased transparency and social participation  
• ANVISA’s ongoing experience with the regulatory reform |


<table>
<thead>
<tr>
<th>Literature describing ANVISA’s regulatory governance</th>
<th>ANVISA (2009)</th>
<th>Commissioned report: Regulation and Agency Regulators: Governance and analysis of regulatory impact (Chapter 5)</th>
<th>Factors influencing the development of regulatory authorities in Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANVISA (2009)</td>
<td>Commissioned report: Regulation and Agency Regulators: Governance and analysis of regulatory impact (Chapter 5)</td>
<td>Factors influencing the development of regulatory authorities in Brazil</td>
<td></td>
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<tr>
<td></td>
<td>ANVISA (2009)</td>
<td>Commissioned report: Regulation and Agency Regulators: Governance and analysis of regulatory impact (Chapter 5)</td>
<td>Factors influencing the development of regulatory authorities in Brazil</td>
</tr>
</tbody>
</table>

- Globalization and regulatory reform in Brazil
- Rationale for adoption of global actors’ policy ideas
- Policy, law and regulations adopted for regulatory improvement
- Characterization of RIA as a policy instrument to improve the regulatory decision-making
- ANVISA’s Regulatory Agenda as a policy tool for transparency
- Social participation as a mechanism for transparency
- Characterization of the political and economic conditions influencing regulatory reforms
- Description of enabling legislation for regulatory reform of 10 agencies— including ANVISA
- Global actors’ influence on ANVISA’s regulatory governance
- ANVISA’s characteristics and scope
- Relationship between ANVISA’s
<table>
<thead>
<tr>
<th>Literature describing global actors’ influence and norms in Brazil pertaining to governance or pharmacovigilance</th>
<th>ANVISA (2009)</th>
<th>Commissioned report: Regulation and Agency Regulators: Governance and analysis of regulatory impact (Chapter 2)</th>
<th>Factors influencing the development of regulatory authorities in Brazil</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PAHO. (2011)</td>
<td>Commissioned report:</td>
<td>Description of PAHO best practices for pharmacovigilance</td>
</tr>
<tr>
<td></td>
<td>Biehl, J., et al. (2009). Princeton University, Princeton</td>
<td>Commentary</td>
<td>Describes the growing trend of litigation to gain access to medicines in the context of incomplete</td>
</tr>
</tbody>
</table>

- Global actors’ influence on regulatory reform and ANVISA’s governance structure
- Rationale for adoption of global actors’ policy ideas
- Characterization of pharmacovigilance pertaining to efficiency and transparency
- Recommendations for supporting a culture of disclosure to advance pharmacovigilance
- PAHO norms for pharmacovigilance
- Need for transparency in drug approval process and placement of drugs on SUS formulary.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Type</th>
<th>Title</th>
<th>Key Points</th>
</tr>
</thead>
</table>
| Cruz, V.  | Journal Article | ANVISA is used as a case study of institutionalized mechanisms for accountability and transparency | • Civil society participation as a mechanism to increase regulatory accountability and transparency  
• Global actors’ influence on ANVISA’s regulatory governance  
• ANVISA’s management contract as an instrument of accountability |
| Freitas, M. & Romano-Lieber, N. | Journal Article | Laws pertaining to pharmacovigilance and industry | • Laws requiring ADR reporting by industry  
• Laws requiring industry pharmacovigilance departments  
• Evaluation of the effectiveness of laws |
| Gava, C., et al. | Journal Article | Medicines registration process for new and generic drugs | • Characterization of Brazil’s drug registration process  
• Description of processes lacking transparency |
| Miranda, A. | Dissertation | ANVISA’s experience with transparency in regulatory management | • Characterization of the conditions leading to drug safety reforms  
• Characterization of ANVISA’s scope and mandate  
• Social participation and transparency in regulatory management  
• Characterization of the effectiveness of ANVISA’s actions to include social |
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Type</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastroianni PC, Lucchetta RC. (2011)</td>
<td>Journal article</td>
<td>ANVISA and the drug approval process</td>
</tr>
</tbody>
</table>

- Participation in decision making
- ANVISA’s role in protecting medicines safety
- Drug registration and re-registration requirements
- Characterization of social participation as a mechanism of governance in Brazil
- ANVISA requirements for drug registration in Brazil
- Global actors’ influence on ANVISA’s regulatory reforms with emphasis on transparency and accountability
- Characterization of ANVISA’s Regulatory Process Improvement Programme including the Regulatory Agenda
- Analysis of the implementation of the Regulatory Agenda
- Characterization of effectiveness and remaining gaps
- Requirements for drug approval
- Characterization of effectiveness and gaps in pharmacovigilance
- Recommendations to strengthen pharmacovigilance (e.g., enforcement)
4a.5.1 Literature describing ANVISA’s regulatory reforms and policy instruments

ANVISA was one of the earliest regulatory authorities to take up reforms aimed to strengthen regulatory management processes (Gaetani & Albuquerque, 2009). The ANVISA Regulatory Process Improvement Programme or Good Regulatory Practices Program (PRO-REG) required mandatory implementation of a Regulatory Agenda (G. H. Silva, 2011).

ANVISA’s priority areas are adopted into an agenda that is established through participatory governance whereby the public is invited to participate in a consultation process (G. H. Silva, 2011). The general population and industry may participate in the public consultation. The Regulatory Impact Analysis (RIA) is another policy instrument to improve and strengthen the regulatory system (ANVISA, 2009; G. H. Silva, 2011). The RIA is described as a tool for accountability and transparency because it evaluates policy effectiveness, efficiency and responsiveness in meeting ANVISA’s regulatory agenda (Gaetani & Albuquerque, 2009; G. H. Silva, 2011). According to Ramalho (2009 p8), PRO-REG and RIA are tools for ANVISA to create an ‘institutional environment favourable to social and economic development of the country.’

4a.5.2 Literature describing ANVISA’s regulatory governance

Pharmacovigilance is integrated into Brazil’s national health care system. ANVISA was established as an independent regulatory body with administrative and fiscal autonomy, under contract with the Ministry of Health (MoH) (ANVISA, nd-a; de Mello & Ramalho, 2009). It also receives funding annually from pharmaceutical company registration and drug registration fees.
ANVISA is governed by a 5-member Collegiate Board of Directors that is accountable for the agency’s activities (ANVISA, nd-a). Its Advisory Board includes representation from industry, the scientific community, government and the public.

Brazil’s Federal Constitution gave legitimacy to public stakeholder engagement in decision-making spaces. Participatory governance was endorsed as a ‘strategy for strengthening governance and the legitimacy of regulatory action in the country’ (G. H. Silva, 2011) yet, consumer interests are represented by only two of ANVISA’s 12-member board (Instituto Brasileiro de Defesa do Consumidor and Fundação Procon/ São Paulo) (Miranda, 2010). ANVISA’s Ombudsmen, appointed by the Minister of Health and approved by president of Brazil, was established to respond to citizen issues; providing another mechanism to the public interests to be voiced.

4a.5.3 Literature describing global actors’ influence on norms in Brazil pertaining to governance or pharmacovigilance

Brazil’s pharmacogovernance, especially the adoption of regulatory agencies, drug safety policy and pharmacovigilance norms, has been shaped by national and transnational actors (Appendix M) (Biehl et al., 2009; Cruz, 2009, 2010; de Mello & Ramalho, 2009; Hoffmann, Fouretier, and, & Bertram, 2012; Miranda, 2010; Rigo & Nishiyama, 2005). They endorsed the establishment of National Regulatory Authorities (NRAs) such as ANVISA. Global actors, such as the Pan American Network for Drug Regulatory Harmonization (PANDRH) Working Group on Pharmacovigilance, endorsed ‘...qualification of the NRAs in the Region in accordance with criteria established by PAHO/WHO in order to establish reference Regulatory Authorities...’, in
Brazil and throughout Latin America to achieve access to quality, safe, and efficacious medicines (PANDRH Steering Committee, 2009, p. 1). Brazil was recognized by PAHO as one of 5 regional reference authorities (Prat, 2013).

Domestically, Carlos Luis Bresser-Pereira, Brazil’s Minister of Federal Administration and Reform of the State (1995-1998) championed regulatory reform to address ‘bureaucratic administration [that] is slow, [and has] little or nothing geared to meet the demands of citizens’ (Bresser-Pereira, 2001; Ramalho, 2009, p. 131). Silva (2011) and Ramalho (2009 p127) posited that regulatory reform in Brazil was also motivated by the desire to harmonize regulatory practices with global norms ‘especially as regards [to] conformation of bureaucracy and its interaction with the "outside world"’ and to increase Brazil’s acceptance into ‘the circle of countries with a modern regulatory system’ (Cruz, 2009, p. 56).

According to Silva (2011 p1) Brazil’s National Regulatory Agenda and ANVISA reforms have ‘mirrored most developed countries’. ANVISA’s Good Regulatory Practices Program (PRO-REG) is modeled after FDA, Health Canada, Australia Therapeutic Goods Administration, UK Medicines and Healthcare Products Regulatory Agency, and Portugal’s Instituto Nacional da Farmácia e do Medicamento (G. H. Silva, 2011). The PRO-REG has incorporated OECD norms for regulatory impact analysis and WHO principles for Good Governance in Medicines (GGM) (OECD, 2003). Although Brazil is not an active participant in the GGM programme, ANVISA has adopted many WHO/PAHO norms pertaining to pharmacovigilance. Specific norms include: good governance for supply chain management, code of ethics to prevent corruption, good manufacturing processes spontaneous ADR reporting and sentinel reporting sites (Anello,
We analyzed ANVISA’s pharmacogovernance in nine core domains: Policy, law and regulation; Transparency and Accountability; Responsiveness; Participation and Representation; Equity and Inclusiveness; Effectiveness and Efficiency; Intelligence and Information; Ethics and Stakeholder coordination.

4a.5.4.1 Policy, Law and Regulation

Brazil has well defined ‘policy, law, and regulation’ to enable pharmacovigilance. Existing laws grant the agency authority to regulate drug registration, ADR reporting, approve patent applications and drug pricing. Pharmaceutical companies desiring product registration in Brazil must submit proof of safety and efficacy (Mastroianni & Lucchetta, 2011); an EMA Certificate of Medicinal Product or Certificate of Pharmaceutical Product issued by FDA or country of origin; and may undergo manufacturing site inspection to assure ANVISA’s Good Manufacturing Practices are observed. Product registration must be renewed every five years (Mastroianni & Lucchetta, 2011). The renewal process requires submission of ADR reports, complaints, technical reports of therapeutic ineffectiveness, pharmacovigilance data, and product long-term stability studies (Mastroianni & Lucchetta, 2011). Generic drug registration requires submission of tests for pharmaceutical equivalence and bioavailability to their reference drug (Mastroianni & Lucchetta, 2011).

Drug manufacturers are required to establish a corporate pharmacovigilance program. Freitas and Romano-Leiber (2007) found that despite resolution RDC No. 4, Article 3 (2009) fewer than half
the companies responding to their survey (20) had implemented a program. Thirteen companies that implemented a pharmacovigilance program were multinational corporations and 7 were domestic companies (Freitas & Romano-Lieber, 2007). Market authorization holders are required by Federal law (nº 6,360/76 article 79) to report ADRs associated with their drugs to the competent health authority (Law 6.360, 1976; Vashisth et al., 2012), however Freitas and Romano-Lieber (2007) found that few domestic companies provided regular training for reporting ADRs. Compliance with international regulatory requirements and international harmonization was the rationale given for reporting by 25% of the pharmaceutical companies surveyed (Freitas & Romano-Lieber, 2007).

Despite policies, laws, and regulations intended to support ANVISA’s mandate to ensure access to safe medicines, health products and services (Appendix M), our study found literature describing a lack of standardization and regulation of medicines prior to the adoption of Brazil’s NMP (Samara Haddad Simões Machado, 2013) that still persists today.

4a.5.4.2 Transparency and Accountability

‘Transparency’ in the public pharmaceutical sector is defined as openness in sharing information. It is a ‘principle whereby those affected by administrative decisions should be informed, and it is the duty of civil servants, managers and trustees to act visibly, predictably and understandably’ (Baghdadi-Sabeti et al., 2009, p. 162). Information is publicly and easily accessible when regulatory decision making is transparent. Transparency aids in building understanding and trust from healthcare professionals in regulatory decisions and risk minimization measures (Bahri & Harrison-Woolrych, 2012). We define accountability as taking responsibility for postmarket drug safety policy outcomes.
Accountability and transparency were described as agency values on ANVISA’s website (ANVISA, nd-a). Norms for transparency were codified by Ministerial Decree nº 5.482/05. ANVISA’s regulatory agenda and management contract were described as instruments of accountability (Cruz 2010 and Silva 2011). Both aimed to address past issues that included a ‘lack of systematization and standards for the regulatory process; ... lack of predictability of regulatory actions; ...and inadequate mechanisms for transparency... and participation’ (G. H. Silva, 2011, p. 3). ANVISA’s 3-year management contract was described as a mechanism of administrative review of the agency’s performance (Cruz, 2010). The requirement for ANVISA to submit reports to its advisory board, the MoH, National Health Council and competent authorities to account for its activities was described as another mechanism of accountability. The integration of public participation in consultations and hearings to debate ANVISA’s regulatory agenda was also described in the literature as a mechanism for transparency and accountability (ANVISA, nd-b; Miranda, 2010).

The literature describing transparency, accountability in ANVISA’s administrative procedures has been contested. We identified literature that emphasized how transparency was needed in the drug approval process, drug surveillance and regulatory control of medicines (Biehl et al., 2009; Gava et al., 2010). ANVISA’s lack of transparency was noted in the 13th National Conference on Health report (Miranda, 2010). Gava et al. (2010) argued transparency was lacking in ANVISA’s approval of ‘me-too’ drugs that have little benefit over drugs currently marketed. A ‘me-too’ drug is a new molecular entity or biological equivalent, structurally similar to an existing drug (e.g., anti-cholesterol drugs atorvastatin and pravastatin). Gava et al. (2010) recommends a more transparent registration process whereby data is publicly available to inform
consumers, health professionals and health managers, about the true benefits and risks of drug treatment.

A behavioural impediment to a culture of transparency and disclosure was also described in the literature. Dainesi (2005) found that health care professionals’ reluctance to report errors, adverse events and treatment failures was an impediment to pharmacovigilance. ANVISA, industry and academia must each promote ‘values that should guide corporate governance’: a culture of transparency, justice, overall compliance with regulations, and accountability (Dainesi, 2005, p. 186).

4a.5.4.3 Participation and Representation

The pharmacogovernance domain ‘participation and representation’ pertains to public representation and involvement in decision making at regulatory authority and government public meetings to establish the regulatory agenda and rules for postmarket drug safety. ANVISA’s Regulatory Agenda is determined annually through what is reported to be a participatory process. Laws enacted to support social participation aim to get public input in regulatory decisions making.

We found literature that suggested that the general public was under represented in public decision making spaces (e.g., public forums). Public representation in Municipal Councils was described as largely comprised of citizens with higher education and income (Miranda, 2010); with lesser representation of minority and marginalized groups. (Pereira, 2010). Miranda (2010) found a gap in public knowledge of spaces for citizen participation. Whereas ANVISA described the Ombudsman's Office and the telephone exchange as spaces for public input some key
informants did not know how to use the services (e.g., where to submit a report). Additionally, Miranda (2010) found that key informants incorrectly identified the National System of Controlled Products Management (SNGPC) and Sistema de Notificações para a Vigilância Sanitária (NOTIVISA) as spaces for public participation. NOTIVISA is Brazil’s online system for reporting ADRs. Consumers may not submit reports to this online system. Only industry, health professionals, hospitals and pharmacies are permitted to submit reports to NOTIVISA.

4a.5.4.4 Equity and Inclusiveness

We define ‘inclusiveness’ as spaces for public participation in pharmacovigilance policy setting that are accessible to all segments of the population. ANVISA working papers describe agency actions to increase spaces for social participation in ANVISA’s decision making (ANVISA, 2009, nd-b; Cruz, 2010; Miranda, 2010; G. H. Silva, 2011). Citizen consultation in public hearings is required by ordinance prior to the adoption of new regulatory standards or rules changes (ANVISA, nd-b; Miranda, 2010). The literature suggests that although public policy and regulation in Brazil aims to encourage inclusive decision making, equity and inclusiveness has not yet been realized (Miranda, 2010; Pereira, 2010).

Miranda (2010) and Pereira (2010) found gaps in the public’s capacity to participate in ANVISA’s decision-making spaces that impede inclusive governance. Although advance notice of public meetings is posted to ANVISA’s website disparities exist in internet access. Up to 65% of the population in some Brazilian states has limited to no internet access (IBGE, nd; Miranda, 2010). Online notification fails to reach audiences without computer access. Meetings scheduled at times and locations that are not readily accessible to the public limits inclusion. The literature suggests that inclusion in ANVISA’s public consultation for its Regulatory Agenda is
asymmetric with greater participation by industry and wealthy individuals. ‘Information asymmetry between the government regulated sector and society’ compromises transparency and equity (Miranda, 2010, pp. 78-79).

We define ‘equity’ as economic and social resource allocation to ensure that all regions within the country have access to safe medicines and resources to detect and act on drug safety signals. Pharmacovigilance coverage in all regions is a measure of equity. The literature suggests that resources to monitor and assess drug safety are not distributed equitably nationwide. Although sentinel hospitals are located throughout the country, the number of sentinel sites is greatest in the most highly resourced and densely populated southeast region (includes São Paulo, Rio de Janeiro, and Minas Gerais) and the least in rural, less populated north and central-west regions with poverty levels up to 42 percent (IBGE, nd). While ANVISA’s Notifying Pharmacies project has the potential to expand pharmacosurveillance, participation has been low (Barreto & Simões, 2008; Vashisth et al., 2012).

4a.5.4.5 Effectiveness and Efficiency

Pharmacovigilance policy, law and regulations are defined as effective when they benefit patient safety. Actions to improve pharmacovigilance are efficient when they are undertaken in a timely manner. We found gaps in the literature pertaining ANVISA’s analysis of the effectiveness of pharmacovigilance policies and their capacity to monitor compliance with policy, law and regulation pertaining to postmarket drug safety.

Ramalho (2009) suggested that ANVISA’s effectiveness has been challenged by: 1) fragmented establishment of norms; 2) a culture of disregard for rules of the State; 3) unnecessary or
overlapping regulations; 4) ineffective monitoring and enforcement; and 5) poor design and/or implementation of norms leading to high costs for compliance. ANVISA's diverse portfolio was described as too expansive to "effectively monitor a pharmaceutical market with the size and growing demand of Brazil" (Vashisth et al., 2012, p. 141). Vashisth et al., (2012) argued that stronger enforcement mechanisms were needed to strengthen pharmacovigilance, particularly in regards to generic drugs registered before 2003 (prior to proof of bioequivalence requirements), although the extent of the problem of substandard generics was not reported.

4a.5.4.6 Intelligence and information

The pharmacogovernance domain ‘intelligence and information’ pertains to mechanisms that exist to improve communication among the national regulatory authority, state pharmacovigilance centers, healthcare professionals, policymakers, patients and the general public with respect to medicine safety. Risk communication about drugs with real and potential safety issues is important for enabling the safe use of medicines (Bahri & Harrison-Woolrych, 2012).

Our analysis of the literature describing ANVISA’s pharmacogovernance in the domain intelligence and information is limited. We found only three abstracts that described risk communication in Brazil. Two abstracts described ADR reporting mechanisms- ANVISA’s website, sentinel hospitals, and the CNMM (NR De Souza et al., 2005; N. R. De Souza et al., 2005). The third described the importance of training health professionals to report ADRs (NR De Souza et al., 2005). None of the abstracts described the process by which ANVISA communicates information about safety signals to the states or municipalities. Given the
inequities in the sentinel reporting site distribution, it is anticipated that corresponding inequities exist in risk communication.

Incompatibility between databases in Brazil was described as an impediment to data sharing of ADRs reported for medicines and immunizations [personal communication 2014]. Brazil does not submit case safety reports to the Uppsala Monitoring Centre using the UMC global reporting format. Moreover, Brazil’s domestic ADR reporting form collects less information than 13 countries studied (Bhatt & Singh, 2012).

4a.5.4.7 Ethics

‘Ethics’ is defined as respect for justice, autonomy, non-maleficence, and beneficence to safeguard patient interests, right to safe medicines and health. Miranda (2010) argues that ANVISA has a dual mandate: to increase the competitiveness of domestic industries under its purview and protect population health. The dual mandate undermines beneficence and patients’ rights to safe medicines and health. The literature challenges the assumption that ANVISA can balance incompatible societal interests in patient safety and industry interests (Miranda, 2010; G. H. Silva, 2011). Gava et al. (2010 p3410), suggest that while ‘...health authorities should act as mediators between the interests of drug manufacturers and the needs of public health... [they have a] duty to protect health’. Access to safe medicines may be compromised by ANVISA’s policy to evaluate the potential impact of regulatory action with regard to national competitiveness (G. H. Silva, 2011). Miranda (2010) and Silva (2011) concur that ANVISA must reconcile its dual mandate to ‘better withstand the volatile nature of conflicts of interest in relations of production and consumption, seeking to strengthen its regulatory role...’ (G. H. Silva, 2011, p. 20).
4a.5.4.8 Responsiveness

The pharmacogovernance domain ‘responsiveness’ is defined as promptly acting to address drug safety issues and enact pharmacovigilance policies/regulations. We found a gap in the literature pertaining to ANVISA’s responsiveness in addressing drug safety issues. Although we are aware that the agency has posted drug safety alerts on its website, we were unable to find literature of Regulatory Impact Analyses conducted of ANVISA’s risk communication policies for responding to drug safety issues. The literature regarding RIA was primarily descriptive; assessing whether ANVISA acted on an agenda item (G. H. Silva, 2011) rather than the impact of specific policies or regulation.

The first agenda items directly relevant to pharmacovigilance were added to the 2013-2014 agenda, five years after the Regulatory Agenda policy was implemented (ANVISA, 2014). They pertain to requirements for companies to communicate registration changes, product labeling risk communication, and rational use of medicines.

4a.5.4.9 Stakeholder coordination

The pharmacogovernance domain ‘stakeholder coordination’ describes actions by ANVISA and global actors to coordinate activities aimed to strengthen pharmacovigilance. The literature was searched for evidence of stakeholders’ efforts to coordinate initiatives and/or resources to strengthen postmarket drug safety. We found a gap in the literature regarding stakeholder coordination for the purpose of enabling pharmacovigilance. We identified literature describing global and domestic actors’ interventions, policy preferences and norms in Brazil, but not examples of stakeholder coordination pertaining to any specific pharmacovigilance intervention.
4a.6 Discussion

Regulatory governance and pharmacogovernance that best supports pharmacovigilance is still being debated globally (Cruz, 2010; Frau et al., 2010; Vernon et al., 2009; Wieseler et al., 2012; Wiktorowicz et al., 2012). Questions regarding governing structures, authority to implement and enforce norms, policies and processes to mitigate ADRs, the regulator-industry relationship, scope of regulatory authority, reliance on industry-produced studies, mechanisms for independent review and accountability for decision-making remain.

Our study found that the literature written by those internal to ANVISA was mostly favourable to the agency’s efforts to advance a culture of transparency and accountability. One study, written by an author external to ANVISA, suggested that greater transparency was needed regarding drug registration, reauthorization and ADR reporting to benefit patients served by Brazil’s National Health System (Sistema Único de Saúde [SUS]).

Transparency confers legitimacy, increases accountability in decision-making and is a basic requirement of good governance (Cruz, 2010; Miranda, 2010). The absence of transparency obfuscates the ability to identify whose interests are served by policy preferences adopted.

We found Brazil’s pharmacogovernance was strongest in the domain of policy and law. Existing regulations should effectively enable access to safe medicines (Prat, 2013). Gaps in other domains however disenabled postmarket drug safety and have led to regional disparities in pharmacovigilance between highly resourced states and under resourced Brazilian states.
Our findings regarding the pharmacogovernance domain ‘intelligence and information’ suggest that signal generation and risk communication may be impeded in Brazil. ‘Ethics’ is challenged by ANVISA’s excessively broad purview over disparate sectors (e.g., pharmaceuticals to airports) and dual industry-health mandate that threaten strong pharmacovigilance policies. Industrial interests and public health interests are not typically aligned. Conflicts arising from industry accountability to shareholders have been shown to create tensions that impede pharmacovigilance (Forman & Kohler, 2012; Maennl, 2008; Moscou et al., 2013). With ANVISA’s dual mandate, the balance between medicines safety, accessibility, and economic development, is largely unachievable. This could be mitigated by addressing concerns about transparency in drug approval and re-approval decisions raised in the literature.

ANVISA’s Regulatory Agenda and Regulatory Impact Analysis could advance pharmacogovernance. To be sure, since this study was conducted new norms and revisions of existing norms for medicines have been added to the agenda. However, ANVISA has not undertaken analysis of the impact of its pharmacovigilance system nor analyzed the effectiveness of parallel reporting systems between states and the federal government. Regulatory impact analyses of ANVISA’s stakeholder participation have not been conducted either. Greater public representation and participation would improve accountability and could in principal hold regulators and drug companies to account for their decisions pertaining to pharmacovigilance. Spaces for social participation must be accessible to be effective and our research found that strategies are needed to make public representation more inclusive (Miranda, 2010; Pereira, 2010).
Public participation in setting ANVISA’s Regulatory Agenda could enable the adoption of policies that focus on patients’ drug safety and advance pharmacovigilance. The absence of norms for inclusive stakeholder participation in decisions regarding pharmacovigilance is troubling and ANVISA’s expansive definition of ‘public’ opens public forums to industry as well as consumers; diluting the voice of consumers. This asymmetry may disenable decisions that improve equity in pharmacovigilance and compromise transparency (Cruz, 2010; Miranda, 2010).

ANVISA’s current governance and pharmacovigilance norms reflect global and domestic actors’ policy ideas. This has benefitted pharmacogovernance with respect to norms for pharmacovigilance systems, infrastructure, drug surveillance and regulatory accountability. Global actors’ influence on pharmaceutical policy has not always aimed to advance drug safety and access to medicines; therefore, Brazil has exercised autonomy in determining which norms to adopt. An example is Brazil’s decision to retain its 5-year product renewal requirement, unlike the EMA, which reversed its drug reauthorization policy to adopt the US model of continuous reauthorization (Mastroianni & Lucchetta, 2011; Wiktorowicz et al., 2008). Reauthorization permits periodic reassessment of drug registration that informs decisions to require post authorization studies, market withdrawal, or conditional re-approval. It shifts the onus to drug companies to show cause for why drug registration should be reauthorized rather than regulatory justification for why registration changes may be needed.

Policy uptake is strongly conditioned by country specific contexts including national traditions including the pattern of government-industry relations (Gaetani & Albuquerque, 2009; Wiktorowicz et al., 2012). Brazil’s prior confrontation with the World Trade Organization over
the TRIPS Agreement, may explain its reluctance to adopt all global actors’ policy ideas. More accountability for decision-making is desirable to assure public interests are protected from influence by unelected regulatory authorities (e.g., World Trade Organization, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

4a.7 Conclusion

The present study contributes to the literature on pharmacogovernance and the relationship between governance, pharmacovigilance and global institutions in Brazil. The few articles published are written in Portuguese limiting the transfer of knowledge about Brazil’s experience with pharmacogovernance. This is the first English language review of which we are aware.

Understanding the relationship between ANVISA’s governance and pharmacovigilance is important. Pharmacogovernance embraces a culture of postmarket drug safety. It assures that governing structures, policy instruments, authority to implement and enforce norms, policies and processes preserve societal interests for patient safety and protection from adverse drug events.

Our findings suggest that pharmacogovernance that addresses 1) regional disparities in the use of policy instruments and distribution of resources for monitoring and assessing drug safety nationwide, 2) federal and state incoordination of pharmacovigilance regulations, 3) asymmetric representation in public consultation for ANVISA’s regulatory agenda and which 4) disaggregates ANVISA’s health and commercial sector regulatory oversight is needed. Disaggregating ANVISA’s regulatory oversight of health and commercial sectors would mitigate
conflicts of interests and disincentives to adoption, implementation and enforcement of strong pharmacovigilance policies.

Further research is needed to better understand the relationship between pharmacogovernance and postmarket drug safety in decentralized, federal systems especially pertaining to accountability and equity. Scope for further research includes studies to answer: 1) How do decentralized state bodies, responsible for the implementation of pharmacovigilance policies, interact with the central regulatory authority policymakers?, 2) Who is accountable for pharmacovigilance where decentralized governance exists?, and 3) How does it balance accountability to consumers, industry, the Ministry of Health and global stakeholders?

The literature on pharmacogovernance establishes that, in Brazil, investments in pharmacogovernance processes have generated significant improvements in patient health through a number of mechanisms, including transparency, accountability, policy, law and regulation. The literature also points to a number of mechanisms by which pharmacogovernance may improve health that have not developed as fully in Brazil compared with other nations. Three such mechanisms include, first, comprehensive ethics processes for review of clinical trials for new drugs, proposals for post authorization safety studies and the distribution of drugs; second, the use of new data and analytics to reveal the prevalence of disease and to administer medical resources where they are urgently needed; and third, to improve the engagement of diverse stakeholders in decision-making about resource allocation for pharmacovigilance.
Chapter 4b: “Matching Safety to Access: Pharmacogovernance in Kenya”

This paper has been submitted to Globalization and Health. The paper is under review.

**Author contributions:** Kathy Moscou conceived the study design, conducted all key informant interviews, was responsible for data extraction, analysis, drafted the paper and made revisions suggested by the co-author. Dr. Jillian C. Kohler read and contributed to paper drafts. All authors read and approved the final paper.
4b.1 Abstract

Background: The Kenyan government has sought to address inadequacies in its National Pharmaceutical Policy and the Pharmacy and Poisons Board's (PPB) medicines governance by engaging with global actors (e.g., the World Health Organization). The state and non-state relationship in Kenya regarding pharmaceuticals has the potential to positively or negatively affect postmarket drug safety.

Methods: Qualitative research methods that included key informant interviews and document analysis were employed to investigate the relationship between global actors' patterns of engagement with national actors and the impact on pharmacogovernance in Kenya. We used purposive and reputational sampling methods to select key informants to interview. Interviews were conducted between March 2014 and January 2015 following ethics approval from the University of Toronto, Canada and Moi University, Kenya. Thirteen key informants representing intergovernmental and non-governmental organizations, Kenya PPB, county health and pharmacy administrators, domestic and multinational pharmaceutical companies were interviewed. The interviews were conducted until saturation was reached. Documentary data included newspaper archives, publically available government documents, peer reviewed and grey literature. Data were read iteratively and coded to identify themes regarding pharmacogovernance and patterns of engagement. A semantic analysis of the data was also conducted.

Results: Global actors' influence on pharmacogovernance and pharmacovigilance priorities in Kenya (e.g., legislation and adverse drug reaction surveillance) was positively perceived by key
informants. We found that global actors' engagement with state actors produced positive and negative outcomes. Engagement with the PPB and Ministry of Health (MOH) that was characterized as dependent (advocacy, empowerment, delegated) or interdependent (collaborative, cooperative, consultative) was mostly associated with positive outcomes such as capacity building; strengthening legislation and stakeholder coordination. Fragmentation (independent engagement) hindered risk communication between public, private, and NGO health programs.

**Conclusion:** The MOH and PPB should aim to strengthen national pharmacogovernance. The sole use of global actors to address Kenya's pharmacovigilance inadequacies leaves the country vulnerable to: 1) conflicts of interests; 2) pharmacovigilance fragmentation; 3) ad hoc drug surveillance; and 4) shifting priorities. Ideally, dependency on exogenous actors should be reduced while retaining consultative, collaborative, and cooperative engagement when interdependency is appropriate.

**Key words:** Kenya, drug safety, governance, pharmacovigilance, regulation
4b.2 Introduction

This case study of pharmacogovernance in Kenya investigates exogenous (non-state) actors’ impact on pharmacogovernance and pharmacovigilance (activities to detect, assess, understand and prevent adverse effects and drug-related problems). Exogenous actors are broadly defined as external and non-state actors (e.g., bilateral, nongovernmental and civil society organizations) that support national programs in Kenya. Examples are: the World Health Organization (WHO), UMC (Uppsala Monitoring Center), United States Agency for International Development (USAID), and Management Sciences for Health (MSH). The research investigates the relationship between specific modes of engagement among exogenous and domestic actors at the national and subnational level to identify the positive or negative effect on pharmacogovernance and pharmacovigilance. Pharmacogovernance is defined in this research as the manner in which governing structures; policy instruments; and institutional authority (e.g., ability to act, implement and enforce norms, policies and processes) are managed to promote societal interests for patient safety and protection from ADRs.

Kenya is a rich site to examine because of the numerous internationally funded NGOs in the country and their high level of integration into Kenya’s governance (Brass, 2012). In 2014, there were more than seven thousand NGOs registered in Kenya; most were funded by international donors (Brass, 2012).19 The Kenyan government has delegated to non-state implementing partners, the authority to create infrastructure and implement domestic programs.

19 In 2014, the Kenya National Council of NGOs published a list of 7083 members. (See www.thengocouncilkenya.org/index.php/resources-and-publications/downloads.htm)
Exogenous actors have the potential to profoundly influence pharmacogovernance given their representation in health policy networks therefore, it is important to understand the manifestation of their patterns of engagement (e.g., dependent, independent, and interdependent) with state actors in Kenya. For the purposes of this research, I define dependency as relying on others for financial or other support. Independence is defined as not depending on another's authority or financial support. In interdependent modes of engagement each partner benefits by reliance on each other. The research question addressed through this study is: which pattern(s) of engagement among exogenous actors, the Kenya Pharmacy and Poisons Board and county actors enable or hinder pharmacogovernance and pharmacovigilance?

4b.3 Background

4b.3.1 Pharmacogovernance and medicines safety in Kenya

The Ministry of Health governs safety of medicines. The Ministry delegates this responsibility to the Pharmacy and Poisons Board (PPB). The PPB was established by Parliament in 1957 under the Pharmacy and Poisons Act, Chapter 244 (Kenya PPB, 2009). It is a semi-independent regulatory authority (Ministry of Health, nd). The PPB’s stated mission is to ‘safeguard the health of the public by ensuring that medicines and health products comply with acceptable standards of quality, safety and efficacy.’ (PPB Kenya, 2015)

PPB’s mission complements the Kenya Health Policy and the Kenya constitution which states that ‘every person has the right to the highest attainable standard of health’ [Kenya Bill of Rights Article 43 (1)(a)], and ‘consumers have the right (a) to goods and services of reasonable quality; (b) to the information necessary for them to gain full benefit from goods and services; (c) to the

The PPB has six directorates. Pharmacovigilance is located within the Directorate of Medicines Information and Pharmacovigilance. There are four divisions within the Directorate of Medicines Information and Pharmacovigilance. They are postmarket surveillance and pharmacovigilance; clinical trials; medicines information and advert promotion. The other Directorates are Product Evaluation and Registration; Pharmacy Practice, Regulation and Training; Quality Control; Pharmaceutical Inspectorate, Surveillance and Enforcement; and Business Support (Ministry of Health, 2015).

Staffing is not apportioned equally to the Directorates. Staffing is greatest in the Directorates of Business Support (46) and Pharmaceutical Inspectorate, Surveillance, and Enforcement (62). In contrast, fewer staff are allocated to the Directorates of Medicine Information and Pharmacovigilance (5) and Quality Control (2) (Ministry of Health, 2015). Each Directorate is allocated an operating budget by PPB. Some Directorates receive greater funding than others depending on PPB and Ministry of Medical Services priorities.

Pursuant to the *Pharmacy and Poisons Act*, the PPB can generate revenues to support its functions by collecting fees for licensing and product registration as permitted by the Act. The PPB also receives funding from the national government and contributions from exogenous actors (e.g., WHO and MSH). The percentage of PPB’s funding that is allocated to pharmacovigilance is unknown. Funding levels needed to meet PPB’s strategic goals for
pharmacovigilance are not reported in the Pharmacy and Poisons Board Strategic Plan 2014-2019 (Ministry of Health, 2015).

PPB’s regulatory authority over pharmacovigilance has been hampered by a lack of enabling legislation to enhance and enforce pharmacovigilance; inadequate governance with respect to the relationship between national and subnational levels of government; insufficient human resources and inadequate financial resources for comprehensive regulatory coverage from pre-market approval to postmarket surveillance (Ministry of Health, 2015, Ministry of Health, nd; "The Pharmacy and Poisons (Amendment) Act, 2014", 2014). The 2008 Kenya National Pharmaceutical Policy (KNPP), Sessional Paper No. 1 of 2010, Sessional Paper No. 4 of 2012 on the National Pharmaceutical Policy and the Pharmacy and Poisons (Amendment) Act, 2014 (Rev. Cap 244) proposed reforms to establish a more effective pharmacovigilance and post market surveillance system and improve pharmacogovernance by providing the enabling legislation to restructure the Pharmacy and Poisons Board (PPB) into a new Pharmacy and Poison Authority (Kenya National Pharmaceutical Policy, 2008; "The Pharmacy and Poisons (Amendment) Act, 2014," 2014; Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). The Pharmacy and Poison Authority would have a structure that is similar to the US Food and Drug Administration with increased scope of authority and accountability ("House Team's Dilemma Over Proposed Parastatal ", 2013; Ministry of Health, nd; Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). The proposed changes to the Kenya National Pharmaceutical Policy would result in clearly delineated pharmaceutical sector governance structures apart from the Directorate of Medical Services (Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). Restructuring of the institutions responsible for regulating, distributing and analyzing the quality of medicines into autonomous authorities, as well as development of an institutional implementation
framework, have also been proposed (Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). The proposed policy and regulatory changes, if enacted, are anticipated to enable the implementation of the Pharmacy and Poisons Board Strategic Plan 2014-2019.

4b.3.2 Pharmacovigilance and Exogenous actors in Kenya

International donors have been described positively in the literature and in PPB policy documents as a potential resource to aid the implementation of Kenya’s proposed National Pharmacovigilance System; play a key role in analyzing safety signals; and enhance risk communication (Kenya PPB, 2009; Olsson, Pal, & Dodoo, 2015). The Kenyan government, under presidents Kibaki and Kenyatta, has sought engagement with exogenous actors to address inadequacies in Kenya’s National Pharmaceutical Policy and PPB’s pharmacogovernance in order to combat deficiencies that have left the country vulnerable to substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medicines entering the supply chain. For example, in 2011, counterfeit drugs that were found in Kenya’s supply chain included the oral contraceptive Postinor-2® (levonorgestrol) and 15,000 of batches of the antiretroviral Zidolam-N® (zidovudine) (Strengthening Pharmaceutical Systems (SPS) Program, 2011). Falsified antiretroviral medicines that entered the supply chain were inadvertently distributed to patients by Médicins Sans Frontières (Attaran et al., 2012).

Exogenous actors have provided pharmacovigilance training to build capacity for pharmacosurveillance. They have supported for the development of adverse drug reaction (ADR) reporting tools and USAID funded the development of PPB’s online ADR reporting system (Kenya PPB, 2009). Donor-run health programs enhanced pharmacovigilance posited Olsson, Pal, & Dodoo (2015) because the programs had pharmacovigilance requirements that were not
mandated by the public sector. Additionally, NGOs provided technical support and resources for active pharmacosurveillance employing cohort event monitoring and targeted spontaneous reporting. Academic Model Providing Access to Healthcare [AMPATH] is an example of an NGO that is conducting active pharmacosurveillance at Moi Teaching and Referral Hospital in Eldoret, Kenya.

On the other hand, it has been argued that donor operated public health and parallel faith-based and NGO-run vertical health programs have fragmented the healthcare system (Olsson et al., 2015). Pharmacovigilance has been impeded by fragmentation of communication between the parallel systems (Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). Examples of faith-based organizations providing health services in Kenya are Aga Khan Development Network and Christian Health Association of Kenya. Elisabeth Glaser Pediatric AIDS Foundation is an example of a NGO that provides health services. In addition to providing primary health care in parallel with the public sector, the faith-based sector operates medicines distribution warehouses (e.g., MEDS http://www.meds.or.ke/); operating in parallel to the Kenya Medical Supply Agency (KEMSA). The faith-based sector also operates its own WHO-prequalified quality assurance lab in parallel to the National Quality Control Lab.

A framework for a national pharmacovigilance system that integrates exogenous actors is shown in Figure 6. The pharmacovigilance system contains three key components. They are a system for collecting pharmacovigilance data; centre(s) for collecting, analyzing and evaluating case reports; and a system for communicating safety signals. Reports may be collected from patients, health care providers, pharmaceutical industry, and the national drug procurement center (e.g., KEMSA). If the country has regional pharmacovigilance centers, then reports may be submitted to the regional centre, processed and forwarded to the national regulatory authority.
4b.3.3 Kenya’s governance and exogenous actors

In order to boost regulatory governance in Africa, the New Partnership for Africa’s Development (NEPAD) African Medicines Regulatory Harmonization (AMRH) Programme created ten
Regional Centres of Regulatory Excellence (RCOREs). One RCORE has been designated specifically to address pharmacovigilance. AMRH has prioritized harmonization of medicines approval and reporting formats for ADR case reports (Olsson et al., 2015). The Kenya Pharmacy and Poisons Board and UMC-Africa have each received funding to create RCOREs for pharmacovigilance. Kenya is also a member of the East African Community (EAC), another regional network that has advocated for harmonization and regulatory convergence pertaining to pharmacovigilance (Doua & Van Geertruyden, 2014).

Kenya’s national governance permits the delegation of authority to exogenous actors, to create infrastructure and implement domestic programs that increase national capacity to provide services. The Kenya Health Sector Strategic and Investment Plan (KHSSP) implementation framework is comprised of three pillars: state actors, non-state actors, and external actors (Ministry of Health, nd). Two of the three pillars of this tripartite model are comprised of exogenous actors (i.e., external and non-state). External actors are defined by the government of Kenya, as bilateral, multilateral, or philanthropic actors that support national programs in Kenya, as part of their internal mandate. Non-state actors include faith-based organizations (FBOs), civil society organizations (CSOs), and nongovernmental organizations (NGOs). The government of Kenya recognizes three types of NGOs. They are distinguished by the origin of

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20 The AMRH regional economic partners are the East African Community (EAC), South African Development Community/Common Market for Eastern and Southern Africa (SADC/COMESA), Economic Community of Central African States (OCEAC/ECCAS), Economic Community of West African States-West African Health Organization/West African Economic and Monetary Union (ECOWAS-WAHO/UEMOA), and the Community of Sahel-Saharan States (CEN SAD/AMU). Kenya is a member of the EAC (Burundi, Kenya, Rwanda, Tanzania and Uganda).
their incorporation. National NGOs are incorporated and registered in Kenya. They work exclusively in and for Kenya. International NGOs are registered in Kenya but are incorporated in another country. Not-for-profit NGOs, voluntary private associations or individuals, may be organized nationally or internationally ("Non-governmental Organizations Co-ordination Act Chapter 134 Revised Edition 2012 [1990]"). International NGOs (INGOs), not-for-profit NGOs and external actors are described as ‘crucial partners, both as a source of financial resources for the health sector and as a way of ensuring programme delivery competencies’ to augment limited domestic resources in the Kenya Health Policy 2012-2030 strategic vision (nd; Sessional Paper No 6 of 2012 on the Kenya Health Policy 2012–2030 (DRAFT) National Development and Vision 2030, pp. 31-32).21

The NGO Coordination Act was enacted by the Moi government, which sought greater oversight over the activities of NGOs. The Act (1990) was revised in 2012 to facilitate and coordinate the work of national and international NGOs operating in Kenya, thereby reducing fragmentation in the healthcare system. The Act called for the establishment of a NGO Coordination Board to coordinate the activities of external actors and international NGOs, advise government on activities of NGOs and provide policy guidelines regarding harmonization of activities to the

21 Approximately fourteen percent of health care services are provided by faith-based organizations and NGOs in Kenya (Kagawa, Anglemyer, & Montagu, 2012; "Kenya Health Facilities list with services as of October 05, 2015"; National Coordinating Agency for Population and Development (NCAPD) [Kenya], 2011).

The state-NGO’s relationship is in a state of flux. The PBO Act, passed Jan. 2013, repealed the NGO Coordination Act. The PBO Act created a newly regulated category called Public Benefit Organization; requiring registration of all PBOs in Kenya (Churchill, 2013a, 2013b). While the country continues to recognize ‘the importance of mutual co-existence and the need to work together [with NGOs]’ ("Public Benefits Organizations Act Revised Edition 2014 [2013]" p. 38), editorial have suggested that President Uhuru Kenyatta’s Jubilee government has been pushing forward constitutional amendments to reduce exogenous actors’ sphere of influence. The passage of the Public Benefits Organizations (PBO) Act (2013), and limits placed on foreign donations to NGOs, is seen by some NGOs as a move to ‘shrink the political and legal space in which they operate’ (Menya, 2014).

Despite a stricter definition of PBO versus NGO, and

22 The rapid rise of NGOs in the 1980s resulted in a crackdown by the Moi government on what they perceived as NGO influence on partisan politics and questioning government’s perceived legitimacy (Brass, 2012).

23 The PBO Act does not become effective until it is officially published in the Kenya Gazette.

24 The PBO Act clearly defines what is and is not a PBO, also what type of activities that PBOs can and cannot engage in. For example, a trade union, political party or religious organization whose main purpose is worship may not be registered as a PBO. PBOs activities include: enhancing or promoting the economic, environmental, social or cultural development or protecting the environment or lobbying or advocating on issues of general public interest or the interest or well-being of the general public or a category of individuals or organizations ("Public Benefits Organizations Act Revised Edition 2014 [2013].")

25 Supporters of the PBO Act argue that the Kenyan government is right to limit the influence of unelected, unaccountable, exogenous actors, however some NGOs claim that the Act was passed to crack down on civil society
requirements to file annual returns, Part VII, Section 66(4) and Section 67 states that the
government shall invite PBOs in policy making and decision making on issues affecting them
("Public Benefits Organizations Act Revised Edition 2014 [2013] "). Therefore, they remain
represented in Kenya’s governance and are able to promote their policy preferences.

In such a fluid environment, it is important to understand the varied modes of engagement
among non-state actors, external actors, Pharmacy and Poisons Board and county governments
that pertain to pharmacogovernance. This study aims to identify the patterns of engagement that
enable or hinder pharmacogovernance and correspondingly pharmacovigilance. An
understanding of these patterns of engagement is important because of Kenya’s past and current
dependence on exogenous actors as implementing partners.

This paper is organized as follows. In the first section, exogenous actors’ motivation for
engaging with state actors to advance pharmacovigilance and pharmacogovernance are analyzed.
Next, state and exogenous actors’ perceptions of pharmacogovernance and drug safety are
analyzed. Finally, the patterns of engagement between state and exogenous actors are

because of its support for the International Criminal Court in The Hague case against president Uhuru Kenyatta;
accused of post-election violence (2008). Those opposed to the PBO Act point out NGOs provide billions (Ksh) in
funding and services in Kenya and Kenyans relying on those services will be hurt by the retreat of exogenous actors.
The PBO Act also effects IGOs e.g. USAID, UK DfID. The campaign to vilify NGOs, linking them to agents
seeking to over throw the government or terrorists, has had a chilling effect on donations to organizations that
[2013],").
characterized and analyzed for their impact on enabling or hindering pharmacogovernance or pharmacovigilance. The results of the analyses are organized within a pharmacogovernance framework. The pharmacogovernance framework guides state, non-state and external actors’ policy making pertaining to postmarket drug safety.

4b.4 Methods

Key informant interviews and a documentary analysis were conducted to investigate the patterns of engagement between state and exogenous actors affecting pharmacogovernance and pharmacovigilance in Kenya. Interviews were conducted between March 2014 and January 2015 following ethics approval from the University of Toronto, Canada (#29254) and Moi University, Kenya (#0001151). Informed consent was obtained from each study participant agreeing to participate in this research; including consent to publish the information they provided.

The minimum number of key informants to be interviewed was established by quota sample (Trost, 1986). The quota sample represented the types of the state and exogenous actors anticipated to influence pharmacogovernance or pharmacovigilance in Kenya. In all thirteen key informants were interviewed. They included representatives of the Kenya Pharmacy and Poisons Board, pharmacy and health administrators from Turkana County, Uasin Gishu County, Mombasa County and Kwale County, domestic and multinational pharmaceutical company representatives and four IGOs/NGOs.

Purposive and reputational sampling strategies were employed to select participants able to provide rich data about pharmacovigilance systems in Kenya. Reputational or chain sampling
enabled quick identification of information-rich key informants. The participants, identified via the ‘snow-balling’ process, were emailed a letter of invitation to participate in the study. The interviews were conducted in person or via SKYPE, a web-based communication platform. Interviews were conducted until saturation was reached. All interviews were audio recorded and transcribed verbatim.

Data for the document analysis were derived from publicly available government documents (e.g., the Kenya constitution (2010), the Pharmacy and Poisons Act and the NGO Coordination Act), peer reviewed and grey literature and newspapers archives. The documents and transcribed interviews were read iteratively and data extracted by the author. Data specifically related to any of the pharmacogovernance domains or global actors was extracted. The pharmacogovernance domains were Policy, Law, and Regulation; Participation and Representation; Ethics; Equity and Inclusion; Intelligence and Information; Responsiveness; Accountability and Transparency; Effectiveness and Efficiency; and Stakeholder Coordination. The pharmacogovernance domains were informed by the United Nations Economic and Social Commission for Asia and the Pacific (UNESCAP) characteristics of good governance. According to UNESCAP, good governance is participatory; concensus oriented; equitable and (United Nations Economic and Social Commission for Asia and the Pacific, nd). It was hypothesized that the pharmacogovernance domains would have an impact on the governing structures, policies, processes and the overall institutional authority to protect societal interests for drug safety.

Data were coded employing an open coding process using Atlas ti v. 7.5.9 (2015) qualitative software. Data coding and re-coding was an ongoing process as new and more refined patterns of engagement between exogenous and state actors emerged (Bernard & Ryan, 2010). A codebook
with operational definitions was created to maintain consistency in the coding process (Appendix K). Data were also coded to identify themes pertaining to pharmacogovernance in Kenya.

A semantic analysis of key informant transcripts and other textual data was conducted to identify words co-occurring with pharmacovigilance and governance. The data were analyzed to identify common words and dissimilar words used by key informants to describe pharmacovigilance. Linguistic connectors, such as ‘because’ and ‘since’ were analyzed within the transcribed interviews to examine key informants perceptions of causality (Bernard & Ryan, 2010). Additional linguistic connectors such as ‘if-then, rather than’; ‘as soon as’; and ‘before, now’ were analyzed to identify key informants perspectives of conditional relations, contingent relations and temporal relations. The interviews and documentary data were analyzed for converging lines of inquiry in order to strengthen the validity of findings (Baxter & Jack, 2008; Stake, 1995; Yin, 2003).

4b.5 Results

4b.5.1 Exogenous actors’ interest in pharmacovigilance in Kenya

Numerous non-state and external actors (e.g., MSH and USAID) are engaged in commodities management in Kenya particularly in areas relevant for medicines to treat AIDS, TB, and malaria. Pharmacovigilance falls under the category of commodities management in Kenya. According to the key informants interviewed, exogenous actors that have provided support to the pharmaceutical sector include: the WHO, UMC, USAID, MSH, Global Fund, Swedish International Development Agency, United Nations Children's Fund, Centers for Disease Control (CDC), United Nations Population Fund, Danish International Development Agency (DANIDA), US President’s Emergency Programme for AIDS Relief, and the Bill and Melinda Gates
Foundation (BMGF). The World Bank, Deutsche Gesellschaft für Technische Zusammenarbeit, Japanese International Cooperation Agency, DfID (Department for International Development [UK]) and faith based organizations such as Aga Khan Development Network (Mbindyo et al., 2010). Pharmaceutical sector support that is specifically targeted for pharmacovigilance includes funding for a country’s assessment of its pharmacovigilance system (Global Fund)\(^{26}\), tools for assessing the country pharmacovigilance systems (WHO and MSH), active surveillance studies to support decision making (WHO) and capacity building (USAID, MSH, European Commission). The exogenous actors that have contributed to initiatives to increase access to medicines in Kenya have also provided support for commodities management. Historically, their priorities for commodities management have focused on access to medicines rather than pharmacovigilance.

The semantic analysis of key informants interviewed suggested that exogenous actors have begun to prioritize pharmacovigilance and provide support to Kenya because of their interest in increasing the pool of data used to identify drug safety signals. According to one IGO/INGO interviewed, “There are very many good reasons to expand and extend the coverage of pharmacovigilance because the chance of finding rare adverse reactions is directly proportional to the population exposed and the danger that is being gathered. In terms of the variability of the problems, they will look very different in different populations and different cultural situations (IGO/INGO-2). For this reason, they have funded Cohort Event Monitoring (CEM)

\(^{26}\) The Global Fund has provided funding for pharmacovigilance since Round 8. Kenya’s Global Fund Round 10 proposal included a description of how countrywide systems for pharmacovigilance would be utilized for pharmaceutical and health product commodities management.
and Targeted Spontaneous Reporting (TSR) active surveillance studies. Kenya has also received support for capacity building and pharmacovigilance training from MSH, UMC-Sweden and UMC-Africa. As a member of the Uppsala Monitoring Centre, PPB has received access to data analyses of case reports and the Vigibase data management system. In addition to guidelines for pharmacovigilance system assessment (UNAIDS | WHO, 2011), they have supported the establishment of pharmacovigilance centres in Kenya and other countries in Africa and spread their policy norms. A ‘step by step’ approach to pharmacovigilance is described in WHO handbooks for medicines used in the treatment of AIDS, TB, malaria, and tropical diseases. An Indicator-based Pharmacovigilance Assessment Tool (IPAT) was developed by USAID/MSH (Management Sciences for Health, 2009). In 2015, the WHO published an up-to-date comprehensive tool for assessing pharmacovigilance systems (World Health Organization, 2015).

Exogenous actors’ engagement with government and the Pharmacy and Poisons Board has focused on strengthening pharmacovigilance in Kenya to enhance postmarket drug safety and shift priorities for essential medicines from ‘access only’ to include pharmacovigilance.

27 The WHO, AMPATH, Indiana University, Purdue University, Moi University and PPB collaborated on CEM and TSR studies conducted at Moi Teaching and Research Hospital. CEM is a prospective, observational study. Patients that are taking the study drug are routinely interviewed about ADR, changes in health status, poor quality medicine, etc., before treatment has commenced, during treatment and at the conclusion of therapy. TSR targets reporting of specific ADRs that may be life threatening or alter treatment (S. N. Pal et al., 2013).

28 The pharmacovigilance handbooks are available at http://pvtoolkit.org/pv-toolkit-2/resources-for-pv/#tab-id-1
“Our work plan is also strengthening those that have come on board or there is no point in being on board. And, helping them with systems issues like policies... So I came to them championing partnerships where they are drumming up support from those around them.” (IGO/INGO-3)

With the input of exogenous actors such as the WHO, the Pharmacy and Poisons Board priorities expanded to include medicines safety (Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010).

“There was a time when we wanted medicines to be available. That was the biggest want. But now we want to go past the availability debate to the safety of these drugs.”- (PPB 01)

International donors’ priorities for pharmacovigilance have also trickled down to the county level.

“There could be [a relationship between priorities for pharmacovigilance in the county and global actors] because many times when we conduct this postmarket surveillance we are funded. So there could be a connection in that these donors might be funding it.” - (Kenya Interview_County 04, 2014)

Research findings suggested that pharmaceutical companies’ interest in pharmacovigilance was motivated by a desire to expand markets while limiting reputational risk (i.e., damage to the company’s reputation caused by product safety issues). One multinational pharmaceutical company interviewed, reported that pharmacovigilance was important to their company’s aim “to increase our footprint in Africa. We want to ensure that at any given point in time, that the risk profile of any of our medications always remains at the tip-top balance for the patient” (Kenya Interview_Pharma 02, 2014).
Managing reputational risk, commented one IGO/INGO key informant, was basis for the Bill and Melinda Gates Foundation Safety Surveillance Working Group’s recommendation to develop a pharmacovigilance strategy for new vaccines and medicines planned to be launched in resource-limited countries (IGO/INGO Interview_02, 2015). The Bill and Melinda Gates Foundation Safety Surveillance Working Group’s recommended that the product launch date, anticipated risk, and country pharmacovigilance capacity be considered when developing a postmarket surveillance strategy (Bill & Melinda Gates Foundation, 2013). The key informant suggested that, “because they[BMGF] are focused on all the countries where their products will be introduced to make sure that their products are not stained with rumours about product safety... then all the other countries they leave behind and [others do] all the work for them” (IGO/INGO Interview_02, 2015).

4b.5.2 State and exogenous actors’ perceptions of pharmacogovernance and drug safety

Poor governance and political instability thwart efforts to establish sustainable pharmacovigilance systems, weaken regulatory oversight, impede access to technology and limit capacity to support pharmacovigilance (Mulili, 2011; Olsson et al., 2015). Kenya’s pharmaceutical sector has been characterized as having a weak infrastructure, conflicting laws and weak enforcement of laws governing pharmaceuticals (Mbindyo et al., 2010; Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). Enforcement of pharmacovigilance has been challenged by a lack of specificity in the law (PPB 02).

Key informants’ perceptions of governance and pharmacovigilance diverged. The words that they used to describe governance varied according to type of actor interviewed. Their perception of governance reflected their positionality and perceived accountability.
“The governance goes beyond [us]. There are higher levels...there is the OGA...Office of Global AIDS Health, something. It looks at how efficient US government agencies manage their HIV/AIDS portfolio. Within Kenya we have the USAID, CDC, US Department of Defense and a fourth one...Peace Corps. At one time the CDC supported postmarket surveillance for pharmacovigilance and I think antiretroviral (ARV) drugs. So there is a bigger, higher level body who is really directing the flow of funds.” - (IGO/INGO Interview_01, 2014)

International NGOs used the most words to describe governance. Words that reflected the process of governance co-occurred with the word governance in their response to interview questions. These words included accountability, transparency, budgets and funding, autonomy, leadership, contracts and directives.

“In terms of governance there’s accountability. We are also having transparency because whenever the centres collect [ADR reports] we will manage that data, under the leadership of PPB and disseminate that information in a transparent way...whoever asks for it [or] whether it is the Ministry.” - (IGO/INGO Interview_05, 2014)

Pharmaceutical companies used the fewest words to describe governance. In contrast to IGOs/INGOs, the multinational corporations (MNCs) responses included words that emphasized procedures rather than process.

“So with the corporate governance we’ve got policies and procedures, worldwide policy and procedures, we’ve got SOPs that are global.” - (Kenya Interview_Pharma 01, 2014)
Pharmacogovernance in Kenya is evolving. The 2010 Constitution heralded devolved governance, which is defined by stakeholders as governance operating at national and county levels that are distinct and interdependent whereby mutual relations are conducted on the basis of consultation and cooperation [Kenya constitution 2010 6(2)]. The change from centralized governance to devolved governance has had an impact on who makes decisions about pharmacovigilance, how pharmacovigilance is implemented, and how implementing partners interact with each other.

One non-state actor expressed frustration with the pace of change suggesting that it had hindered pharmacovigilance “because once it goes through Cabinet they change many things so there are many things that I have had to pull, because of these new changes as far as governance goes to tweak implementation. I can’t implement it under the previous budget because of new laws!” (IGO/NGO-5)

4b.5.3 Patterns of interactions among state, non-state, and external actors’ influencing pharmacogovernance and pharmacovigilance

Given Kenya’s dependence on non-state and external actors as implementing partners and donors, it is important to understand the relationship between specific patterns of engagement and pharmacogovernance. We examined how exogenous actors have influenced pharmacogovernance and pharmacovigilance by analyzing their patterns of engagement with state actors. We found examples of dependent, independent, and interdependent patterns of engagement between state and exogenous actors. State engagement with exogenous actors that was based on dependency included advocacy, delegation, empowerment and hierarchy.
Interdependent modes of engagement included collaboration, cooperation, and consultation. Autonomy and fragmentation were characterized as independent modes of engagement.

The study found that exogenous actors’ engagement with state actors in Kenya primarily enabled, but in some cases hindered pharmacogovernance. Dependent and interdependent patterns of engagement were found to be associated with strengthening pharmacovigilance through capacity building; pharmacovigilance priority setting; advocacy for policy, law, or regulation; stakeholder coordination; and local empowerment for pharmacovigilance. Delegation was associated with strengthening pharmacovigilance with respect to exogenous actors’ aim to develop Pharmacy and Poisons Board into a regional influence for pharmacovigilance for the purpose of transferring to Kenya the responsibility to build regional capacity. The effect of specific modes of engagement on pharmacogovernance is shown in Table 9.

Table 9. Analysis of the Modes of Engagement between Domestic and Exogenous Actors and the Affect on Pharmacogovernance

<table>
<thead>
<tr>
<th>Pharmacogovernance Domains</th>
<th>Advocacy</th>
<th>Autonomy</th>
<th>Collaborative</th>
<th>Consultative</th>
<th>Cooperative</th>
<th>Delegated</th>
<th>Empowerment</th>
<th>Fragmented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy, law, regulation (Governing structures, norms, policy instruments, practices, institutional authority)</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accountability &amp; Transparency</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Participation &amp; Representation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equity &amp; Inclusiveness (Distribution of resources for pharmacovigilance)</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Ethics (Policies to safeguard patient interests)</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness &amp; Efficiency (System integration &amp; communication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsiveness (Risk communication)</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intelligence &amp; Information (e-reporting technology, risk communication)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stakeholder Coordination (Pooled resources, network mobilization, communication network)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[+] Agreement between literature and key informants that the mode of engagement enabled pharmacovigilance policy or practice in the pharmacogovernance domain

[+/-]: Disagreement in the literature and among key informants regarding the impact of mode of engagement on pharmacovigilance policy or practice in the pharmacogovernance domain

[-]: Agreement between literature and key informants that the mode of engagement hindered pharmacovigilance policy or practice in the pharmacogovernance domain

Exogenous actors contributed to developing a cadre of advocates for pharmacovigilance whom they nurtured and exposed to pharmacovigilance best practices and training to build confidence and competence. The term pharmacovigilantes was coined to describe individuals who advocated for pharmacovigilance. How they courted and nurtured the pharmacovigilantes is exemplified in the following quote:

“In Kenya in particular, one of the key people we identified very early on in Pharmacovigilantes Sans Frontiers. We courted him and nurtured him… we provided exposure to best practices outside and in Kenya starting from way back in 2004 and started sowing the seeds. So through our direct efforts there is a pharmacovigilance centre and [it]
became affiliated with the WHO program. And now they’re one of the leading countries in Africa.” (INGO/NGO 02)

The relationship between pharmacovigilance and patterns of engagement between state and exogenous actors is shown in Figure 7.

**Figure 7. Patterns of interactions between Domestic and Exogenous Actors Affecting Pharmacovigilance**
The patterns of engagement between exogenous and domestic actors and their effect on the pharmacogovernance domains are shown in Figure 8.

Figure 8. Patterns of interactions Between Domestic and Exogenous Actors Affecting Pharmacogovernance
Exogenous actors’ engagement with the PPB was largely consultative regarding setting pharmacovigilance priorities. Input was gathered from actors at the policy level (government), implementation level (health facilities), oversight level and the private sector “to determine what our focus areas really should be and once determined, support aspects of quality assurance of medicines issues and aspects of ensuring that patient safety is optimal” (IGO/NGO-1). As a consequence of the consultations, “agreed milestones and timelines of giving this support” were established (IGO/NGO-1). One key informant stated that when meeting with the County Health Executive, “we were looking out for all of these things together, the commitment they are making, and listening to the plans that they have and telling them what we are looking out for and what we plan to do in the future.” (IGO/NGO-1)

Kenya PPB, IGO and INGO key informants’ policy preferences for pharmacovigilance are compared in Table 10.

**Table 10. Comparison of Pharmacovigilance Priorities between State and Exogenous actors**

<table>
<thead>
<tr>
<th>PPB</th>
<th>County</th>
<th>Generic Pharma</th>
<th>Multinational Corporation</th>
<th>INGO (non-state)</th>
<th>IGO (external actors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug safety in addition to availability</td>
<td>• Drug safety in addition to access</td>
<td>• Substandard, fake, and counterfeit drugs</td>
<td>• Harmonization of reporting requirements</td>
<td>• Drug safety in addition to access</td>
<td>• Increase policy makers and donors awareness of the connection between access and PV Health systems strengthening</td>
</tr>
<tr>
<td>• Increase ADR reporting (public &amp; health workers)</td>
<td>• Detect and report ADRs</td>
<td>• Detect and report poor quality medicines</td>
<td>• Training for all employees to increase awareness of PV</td>
<td>• PV Systems strengthening</td>
<td>• Active surveillance</td>
</tr>
<tr>
<td>• Poor quality medicines reporting</td>
<td>• Monitoring quality of medicines</td>
<td>• PV as a clearly defined role</td>
<td>• Capacity building to improve the quantity and quality of ADR reports</td>
<td>• PV Legislation (e.g., qualified PV personnel in each drug company)</td>
<td>• Ensure quality of products procured</td>
</tr>
<tr>
<td>• Active surveillance</td>
<td>• Strengthen PV systems</td>
<td>• Maintain compliance with national PV requirements</td>
<td>• Synchronize priority areas with PPB and other IGO/INGOs</td>
<td>• Synchronize priority areas with PPB and other IGO/INGOs</td>
<td>• Harmonization of PV systems and reporting tools, nationally</td>
</tr>
<tr>
<td>• Ensure quality of products in the market</td>
<td>• Pharmaco-surveillance of drugs targeted by</td>
<td>• Spontaneous reporting only-no mandatory reporting</td>
<td>• Systems surveillance</td>
<td>• Synchronize priority areas with PPB and other IGO/INGOs</td>
<td>• Capacity building to improve the</td>
</tr>
</tbody>
</table>
surveillance of drugs used in public programs (e.g., TB, and malaria) & commonly used
• Increase awareness of PV
• Capacity building
• PV Legislation (No explicit PV laws)
• Kenya as a leader in patient safety—a Centre of Excellence
• Facilitate ease of reporting
• Take action on ADR reports
• Introduce industry reporting

public programs (TB, family planning, and malaria; high morbidity, commonly used)
• Quality testing of drugs entering through ports
• Health facilities know proper storage conditions for medicines

approach to PV
• Establish PV systems
• Adoption of a National Pharmacovigilance Policy
quantity and quality of information that supports decision making.
• Negotiate with government to achieve an appropriate legal framework for PV
• Support for pharmaceutical policies and laws
• All countries have PV systems.
• Global populations are covered by PV activities.
• Participation in UMC is expanded to increase the chance of finding rare adverse reactions
• Redefine the focus of PV to include old issues with older drugs (Evergreening)

In the next section, the analysis of Kenya’s pharmacogovernance is presented. The findings are organized within the nine pharmacogovernance domains: Policy, Law and Regulation; Participation and Representation; Information and Intelligence; Equity and Inclusiveness; Effectiveness and Efficiency; Transparency and Accountability; Responsiveness; Ethics and Stakeholder coordination.

4b.5.3.1 Policy, Law and Regulation

The pharmacogovernance domain ‘Policy, Law and Regulation’ is defined as the laws, bills, and resolutions intended to support the national mandate for safe and efficacious medicines. Kenya’s National Drug Policy, Pharmacy and Poisons Act [Rev. 2012], Food, Drug and Chemical
Substance Act [Rev. 2012] (FDCSA), and Public Health Act are the key policy and enabling legislation regulating pharmaceuticals in Kenya.

“Drug” is defined in the FDCSA which sets standards for establishing drug quality which are relevant to regulating poor quality medicines. The Pharmacy and Poisons Board, NGOs, IGOs, County Executives and county chief pharmacists in Kenya have purposely adopted the terminology 'poor quality medicine' and have chosen to avoid the terms counterfeit, substandard and falsified as a political decision. A poor quality medicine is defined as “any medicinal product that does not meet the required quality standards. The medicine may lack efficacy, lack sufficient active ingredients or be mislabeled” (IGO/INGO Interview_01, 2014). The term counterfeit drug infers a patent issue that has implications for generic manufacturers and intellectual property rights (Attaran et al., 2012; IGO/INGO Interview_01, 2014).

The FDCSA also created a Public Health (Standards) Board that was responsible for enforcement of provisions of the FDCSA. The Pharmacy and Poisons Act, Chapter 244 defined a drug as a ‘medicinal substance’. The Act created the Pharmacy and Poisons Board (PPB) and conferred upon the Board the authority to regulate medicinal substances including the authority to issue (and revoke) licenses, certificates and registrations to engage in the practice of pharmacy, manufacture medicinal substances, test for drug quality, warehouse and distribute medicines ("Pharmacy and Poisons Act, Chapter 244," Revised Edition 2012 [1989]). The Public Health Act established specific conditions under which municipalities could requisition and distribute drugs. None of the Acts specifically addressed pharmacovigilance.
WHO, Pharmacy and Poisons Board (PPB) and the Ministry of Medical Services concluded, in separate assessments, that an overhaul of Kenya’s legal framework for regulating the pharmaceutical sector was needed to address current inadequacies, mitigate drug safety issues and match access to medicines with safety (Mbíndyo et al., 2010; nd; Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). Subsequently, lawmakers proposed amendments to the Pharmacy and Poisons Act ("The Pharmacy and Poisons (Amendment) Act, 2014," 2014). Parliament debated restructuring PPB into a Pharmacy and Poisons Authority ("House Team’s Dilemma Over Proposed Parastatal", 2013; Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). The Pharmacy and Poisons (Amendment) Bill, 2014, which underwent first reading in March 2014, would grant new powers to PPB to review and approve dossiers for market approval of medicines. The Bill would make it a crime to create, sell or distribute expired or counterfeit drugs although neither the Pharmacy and Poisons Act of 1956, nor the Pharmacy and Poisons (Amendment) Bill of 2014 define ‘counterfeit drug’. The bill would also require the publication of a list of registered medicines at least once every 3 months ("The Pharmacy and Poisons (Amendment) Act, 2014," 2014). The absence of a published list has disenabled pharmacovigilance and challenged enforcement of pharmaceutical regulations because only known medicines can be regulated. Surveillance of the quality of medicines and confiscation of unregistered drugs has been impeded by the absence of an up-to-date list of registered drugs (Mbíndyo et al., 2010).\(^29\)

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\(^{29}\) In 2006 a WHO-supported survey of antimalarials in Kenya found that 42% of the products were unregistered. The status of the drugs (no longer recommended for treatment, safety profile, etc.) could not be verified due to inadequate information (Mbíndyo et al., 2010).
Exogenous actors have both catalyzed and strengthened some of the proposed changes to pharmaceutical policies, laws and regulations in Kenya. Analysis of their participation in government and Pharmacy and Poisons Board stakeholders’ meetings found their engagement was based on advocacy “to really support that law and have pharmacovigilance in that law…because when you develop policies and laws it’s not a one organization thing…there are different experts” (IGO/INGO Interview_05, 2014) shaped PPB and Ministry of Health policy preferences regarding the Pharmacy and Poisons Act Amendment and adoption of a National Pharmacovigilance System (Mbindyo et al., 2010).

Exogenous actors and state actors engaged in consultative interactions for the purpose of sharing information about pending legislation and changes in existing legislation.

“[W]e liaise with government to get to know what needs to be done, what legislation, what laws need to be put in place, what reviews need to be made, what needs to be taken to Parliament just to get the legislation in law, and all that. You know, negotiating at the government level to make sure the right laws get passed.” - (IGO/INGO Interview_01, 2014)

Despite Kenya’s adoption of global actors’ norms for pharmacovigilance (Appendix N), key informants that were interviewed asserted that the basis for engagement between state and exogenous actors in Kenya was autonomy. As such, the exogenous actors interviewed claimed that although they ‘suggested’ policy, laws, regulations and norms for adoption, they respected that “they [LMICs] know where they are going” (IGO/INGO Interview_05, 2014).
“We are aware that individual countries or regions need to develop, like European Commission did back when the European Union did not have an EU-legislation on pharmacovigilance. We also are aware that this has to evolve. Countries have to have buy-in. There have been a lot of mistakes made over the past 40 years in Europe and America. And Africa needs to learn from it and jump beyond that.” - (IGO/INGO Interview_03, 2014)

Rather than drive a specific agenda, key informants claimed that they responded to requests for support by local/national governments when they had overlapping interests. For example, IGOs that were engaged in commodities management had overlapping priorities for strengthening pharmacogovernance and pharmacovigilance in order to mitigate risks for adverse drug reactions.

4b.5.3.2 Accountability and Transparency

Accountability is defined as taking responsibility for individual or organizational activities. This would include activities to advance postmarket drug safety. Transparency is defined as sharing information and operating in a manner that makes it easy for others to see what actions have occurred. Kenya’s constitution incorporates principles of governance that include integrity, transparency and accountability (Article 10) (Republic of Kenya, 2010). However, exogenous actors, PPB, county representatives and the pharmaceutical company representatives that were interviewed reported that improvements were needed.
PPB’s actions regarding accountability and transparency were reported to both enable and hinder pharmacovigilance. PPB reportedly engaged in transparent practices which were perceived as enabling pharmacovigilance, “because whenever these centres collect [ADR reports] we will manage that data under the leadership of PPB and disseminate that information in a transparent way [to] whomever asks for it, whether it is the Ministry [or others]” (IGO/INGO Interview_05, 2014). On the other hand, PPB’s transparency was questioned related to its failure to regularly publish a list of the medicines registered in Kenya. It was suggested that PPB take greater responsibility for increasing industry’s accountability for pharmacovigilance rather than delegate their role to industry.

“I would like to see a situation where PPB is able to tell the pharm industry, ‘You know what? Get interested in the safety of the patient.’ I don’t think we are there yet.”

(IGO/INGO Interview_01, 2014)

The IGO/INGOs interviewed advocated for greater accountability by pharmaceutical manufacturers because, “industry is manufacturing medicines and releasing them out to the market and thinks once it is sold…to them it is done” (IGO/INGO Interview_01, 2014). The need for greater industry accountability was echoed by a pharmaceutical industry key informant who reported that companies that invested in pharmacovigilance were competing against companies that did not; suggesting that self-regulation was ineffective.

4b.5.3.3 Participation and Representation

The pharmacogovernance domain ‘Participation and Representation’ is defined as public involvement in regulatory authority and government meetings for setting the regulatory agenda and rules for drug safety. Although public participation in health-related decision making is
described as a guiding principle in Kenya’s health policy (Ministry of Health, nd, p. 34; *Sessional Paper No 6 of 2012 on the Kenya Health Policy 2012–2030 (DRAFT) National Development and Vision 2030*), none of the key informants interviewed for this study outlined mechanisms for civil society participation (e.g., public forums) or proportional representation. Therefore, medicines users in Kenya do not have a voice in the spaces where policy decisions are made that affect them. The absence of public representation hinders pharmacogovernance and it leaves consumers vulnerable to the interests of groups with representation that may have cross purpose interests.

In contrast, global donors enjoyed a high level of representation and participation in policy decisions because of Kenya’s dependence on them to provide support to the health care system. Their policy preferences were represented in stakeholders consultations for the National Pharmacovigilance System (Kenya PPB, 2009). Public sector representation in the consultation for the National Pharmacovigilance System (NPS) included the Ministry of Health, University of Nairobi, the Pharmaceutical Society and others. The Faith based sector was represented by the Mission for Essential Drugs, a Kenyan registered NGO (Kenya PPB, 2009). Exogenous actors collaborating with PPB in the writing of the National Pharmacovigilance Guidelines included: Management Sciences for Health (MSH), the United States Pharmacopoeia (USP), the World Health Organization (WHO), Health Action International (HAI)-Africa, and Uppsala Monitoring Centre-Sweden.  

30 The final adoption of the NPS has been delayed [key informant interview] by the 2010 election which brought in a new government, new constitution and devolved governance to Kenya’s counties.
IGO/INGO interests were also represented at county-level public health stakeholder meetings where health priorities were set.

“They usually contribute during stakeholders meetings. So for them, apart from other interests, they usually also push for issues about reporting about pharmacovigilance and sometimes they sponsor some health workers”. - (Kenya Interview_County 02, 2015)

One key informant reported that they were part of a pharmacovigilance working team comprised of the PPB and public health program representatives. The pharmacovigilance team held meetings to synchronize work plans to assure resources were available to support activities (IGO/INGO Interview_05, 2014). These examples of exogenous actors’ engagement have enabled pharmacovigilance.

The representatives of the multinational corporations interviewed reported that they also enjoyed relatively easy access to the Pharmacy and Poisons Board. One key informant reported that the PPB sought industry input regarding policy changes and was responsive to industry requests. Industry input was sought on the 2014 draft legislation to require each pharmaceutical company to employ a qualified person for pharmacovigilance (QPPV). Another informant reported that PPB “obviously wants to engage with industry, wants collaboration, and wants our input” (Kenya Interview_Pharma 01, 2014). The key informant reported that PPB had been responsive to previous requests including a request to modify the schedule for completing the Periodic Safety Update Report (PSUR) to harmonize with the reporting schedule for regulatory authorities in the European Union.
“So I wrote to Kenya and asked would you mind following the PSUR schedule as per the European Union? And there wasn’t a problem at all. That’s why I said there’s a good working relationship. They’re very willing to assist us, be flexible, as long as they receive the information that is required they are happy, I think. They are willing to bend a little bit and that makes the procedure that much easier.” - (Kenya Interview_Pharma 01, 2014)

The industry representatives that were interviewed suggested that industry participation enabled pharmacovigilance because when they are included in decision-making, “they have buy-in from the pharmaceutical companies and the compliance is going to be that much better” (Kenya Interview_Pharma 01, 2014). In contrast, this study found that industry participation hindered pharmacovigilance with respect to its rejection of QPPV legislation and requests to relax reporting timelines.

4b.5.3.4 Equity and Inclusiveness

‘Equity and Inclusiveness’ are defined as parity in public participation for pharmacovigilance policy-setting with ease of access to decision making spaces by all segments of the population (inclusiveness). In this study, equity includes allocation of economic and social resources to ensure that all regions within the country have access to safe medicines and the resources to detect and act on drug safety signals.

Gaps were found in both equity and inclusiveness in Kenya. The study did not find evidence of public participation in policy decisions regarding pharmacovigilance thus the process was not inclusive. Neither has Kenyan’s right to health been operationalized in regards to the
distribution of health resources. All of the county representatives interviewed reported that there was no budget allocated for pharmacovigilance in their region. Health resources have remained inequitable despite the amendment to Article 204 of the Constitution of Kenya (2013) that transferred disbursement of the Equalization Fund, money ear marked to assist ‘marginalized areas to achieve the same level of development as the rest of the country’, from the national government to constituencies in which the marginalized areas exist (Ministry of Health, nd).

One county representative interviewed commented that, “we know is it is always good to set up pharmacovigilance because we want to know about adverse drug reactions, we don’t know about adverse events, about safety of medicines or many other aspects so we need to have a pharmacovigilance system” (Kenya Interview_County 03, 2014). The only pharmacovigilance available in some rural, historically under-resourced counties however, “is identifying substandard drugs…and this is basically looking at the physical characteristics of the drugs, tablets and syrups” (Kenya Interview_County 02, 2015). ADR reporting was beginning, “it’s just, at least up to now, [its] just for antiretrovirals because it has not been introduced to other stakeholders... most of the HIV clinics operate independently”(Kenya Interview_County 02, 2015).

Many exogenous actors in Kenya have demanded access and availability to medicines and medicinal products but that’s only a minimum, suggested one key informant (IGO/INGO Interview_05, 2014). Global actors involved in health commodities should actively advocate for pharmacovigilance within the vertical programs that they manage because “…you can see basically that’s commodities management. Pharmacovigilance is just one [part] of it. I talk passionately when I advocate for pharmacovigilance. I say that we have to match ACCESS with
“SAFETY” (IGO/INGO Interview_05, 2014). Some exogenous actors have engaged in collaborative interactions with the counties to provide resources to support greater ADR reporting and to facilitate dissemination of ADR reports submitted.

“We normally support that because health care workers report and the reports are laying in the facilities because they don’t necessarily have a system of how they are getting to the Pharmacy and Poisons Board. So that is both for ADRs and reports for the whole country not just in certain counties.” - (IGO/INGO Interview_05, 2014)

The implementation of the PPB’s online reporting system, developed with support from USAID, is anticipated to further enable pharmacovigilance by increasing the number of reports and improving the quality of reports thus reducing inequities in ADR reporting (PPB 02).

4b.5.3.5 Ethics

In this research, ethics pertains to respect for justice, autonomy, non-maleficence and beneficence to safeguard patients’ interests in the right to safe medicines and health. This study found a lack of beneficence and justice on the part of multinational corporations, the Kenyan government and PPB regarding the collection and dissemination of information needed to inform decision making.

The government’s inability to enact legislation that requires drug companies to report ADRs can be interpreted as being a failure of pharmacogovernance. The absence of full information leaves the PPB with less information to make decisions about marketed medicines than countries with greater reporting standards. One drug company interviewee reported that they disclosed
information that was officially requested by PPB however “there is nothing specifically that Kenya is requesting from us. If they ask for anything we’ll do it on an ad hoc basis but there is no specific annual report or risk management plan or anything going on there” (Kenya Interview_Pharma 02, 2014).

Pharmaceutical companies’ advocacy against Kenya’s draft legislation requiring a qualified person for pharmacovigilance (QPPV) also negatively impacted pharmacogovernance and pharmacovigilance. Corporate claims that pharmacovigilance is a priority cannot be reconciled with their actions to advocate against QPPV legislation.

“It’s impossible for a pharmaceutical company to have a pharmacovigilance person, totally responsible for pharmacovigilance in each country. So, they [PPB] have [proposed] a stricter guideline which I have written back and said we can’t do that.”- (Kenya Interview_Pharma 01, 2014)

In the absence of QPPV legislation, the MNCs interviewed had assigned a single individual to oversee more than 25 countries. One key informant was responsible for overseeing 26 African countries. Another had responsibility for overseeing 42 African countries. Corporate decisions to appoint a regional head for pharmacovigilance rather than a country head and to oppose QPPV legislation impedes patient safety and therefore contradicts beneficence.

PPB’s ethics has also been questioned. One non-state actor suggested that PPB had conflicts of interests related to revenue generation that hindered pharmacovigilance. As a semi-independent regulatory body, PPB may generate revenue to support its operation. The revenue collected by PPB from industry was perceived as a disincentive to adopting stronger industry guidelines/regulation. In a news story about a donation to PPB by Pfizer Pharmaceuticals, The
Daily Nation reported that ‘regulators should steer clear of those they are meant to regulate as this might lead to a perception that the regulator is in the deep pockets of the companies they are meant to police’ ("Policing the Drug Business", 2012). A key informant commented that, “the policies and laws, the current governance structure has delayed the finalization of key policies” because “PPB is not leading them because it against their stakeholders.” (IGO/NGO-5)

4b.5.3.6 Effectiveness & Efficiency

The pharmacogovernance domain ‘Effectiveness’ is defined as pharmacovigilance policies, laws, regulations, and practices that benefit patient safety. This includes pharmaceutical industry compliance with policy, laws and regulations. Actions to improve pharmacovigilance that are undertaken in a timely manner are a measure of ‘Efficiency’. Kenya has limited policies, laws and regulations to guide pharmacovigilance (Bill & Melinda Gates Foundation, 2013; Strengthening Pharmaceutical Systems, 2011). This study found that enforcement of existing laws was also lacking.

County representatives and INGOs interviewed reported that national pharmacovigilance would be enabled by a more effective, comprehensive system. At present, postmarket surveillance is typically only undertaken for public health products (e.g., ARVs, anti-malarials and anti-tuberculosis (TB) drugs).

“Our priority area is strengthening pharmacovigilance systems because as we have right now, we don’t have a comprehensive system. The system that we have is mostly for the HIV program.” - (Kenya Interview_County 02, 2015)
“What about the rest of the system? Yeah. And then, even when it’s funded, the other challenge with it, which I would like you to flag, is that it’s ad hoc.” - (IGO/INGO Interview_05, 2014)

Fragmentation has impeded both effectiveness and efficiency of existing pharmacovigilance practices in Kenya. We found a lack of integration between parallel public, private NGO and faith-based sectors in regards to pharmacovigilance. Fragmented engagement between domestic and exogenous actors contradicts systems-strengthening. What some IGO/INGOs “are trying to do is integrate so we don’t have parallel organs taking place at different times we integrate and have one”(IGO/INGO Interview_05, 2014).

Kenya’s proposed National Pharmacovigilance System (NPS) would integrate communication between the Ministry of Health and public health programs; reducing fragmentation (Kenya PPB, 2009) however the NPS, as proposed, would not close the communication gap among the faith-based sector, counties and districts regarding the dissemination of information about ADRs because an integrated communication network is not proposed. As proposed, the faith-based sector would continue to submit ADR reports to PPB rather than communicate safety issues directly to the county/district team (Kenya PPB, 2009). This practice hinders effective and efficient pharmacovigilance because there is a delay between the time PPB processes reports and when the information is communicated to the Ministry of Health in the originating county.

“It took time because at the beginning they’re not getting any information. It took months. But assuming it was in the county we could easily detect it, make a phone call and stop it; say OK don’t use that medicine.” - (Kenya Interview_County 03, 2014)
In contrast to the county key informants’ perception of the effectiveness of pharmacovigilance in Kenya, an IGO/INGO key informant reported that, “Kenya, I would say is comparatively successful” (IGO/INGO Interview_02, 2015).

4b.5.3.7 Responsiveness

The pharmacogovernance domain ‘Responsiveness’ is defined as acting to address drug safety issues and enact pharmacovigilance policies/regulations within a reasonable timeframe. This study found that Kenya is increasingly responsive to drug safety issues related to poor quality medicines however it lags behind in enacting policies/regulation that would strengthen pharmacovigilance and reduce ADRs. Pharmacovigilance is relatively new in Kenya and it took a long time before a national department of pharmacovigilance was established in the Pharmacy and Poisons Board (Kenya Interview_County 04, 2014).

In response to an interview question about policies for identification and reporting of ADRs and falsified or substandard medicines, county key informants described responsiveness in regards to substandard medicines but not ADRs. The presence of substandard, spurious, falsely labelled, falsified, counterfeit and poor quality medicines, in the supply chain has been a concern in Kenya. The issue has been debated in Parliament and was raised as a major concern in Mombasa where the drugs have been imported through its ports. Removing poor quality medicines from the supply chain was cited as a key priority by nearly all sector representatives interviewed (Table 10).
Key informants from each county described their policies pertaining to actions taken upon receipt of a report of a substandard drug. In all cases the drug was removed from the supply chain. The counties diverged in how rapidly they made their decision to withdraw the drug. The speed of withdrawal ranged from “the same date discovered” (Kenya Interview_County 02, 2015; Kenya Interview_County 03, 2014) to “upon receipt of several reports” (Kenya Interview_County 04, 2014). At least one county key informant considered responsiveness in addressing substandard medicines as an issue of accountability to consumers (Kenya Interview_County 02, 2015).

The hierarchy of reporting in Kenya reduces the counties' responsiveness to ADRs and poor quality medicines. Spontaneous reports of ADRs and poor quality medicines are submitted online directly to PPB (federal); then the county waits for the PPB to evaluate the safety signal and report back to the county. Communication of potential risks is not sent to the County Director of Pharmaceutical Service for dissemination across the county until after the signal is assessed. This process assures that the ADR is evaluated at a level that has expertise to assess safety signals however PPB lacks capacity to efficiently respond to reports. The chief pharmacist in one region may be unaware of an emerging drug safety signal in one of the counties in their region until receiving a delayed notification from PPB. The delay in risk communication may place the population at risk for continued exposure to preventable adverse events.

Exogenous actors have acted as a catalyst to foster responsiveness to pharmacovigilance issues and advocate for resources to support of pharmacovigilance. “Even though the department of pharmacovigilance is there, funding has not been adequate. It has not been given priority until
recently when WHO, [the] World Health Organization, started involving members from Kenya in their seminars and they started giving some grants for pharmacovigilance…but as a country, it has not been adequate” (Kenya Interview_County 04, 2014). County responsiveness in addressing drug safety issues was complemented by their engagement with IGO and INGO. Their engagement with IGO/INGO actors was characterized as consultative. One INGO key informant reported that they consulted with the County Directors of Health during routine visit to the counties, “so you can get more information from them and share with them what you are seeing in other counties because they will only see what is available in their county” (IGO/INGO Interview_01, 2014).

Although unanticipated, one pharmaceutical company key informant commented that they supported corporate governance that enabled prompt response to reports of ADRs. Their opinion regarding corporate pharmacogovernance may be a benefit derived from the key informants’ past experience with the Pharmacy and Poisons Board. The MNC representative suggested that their policy to train and empower all employees to report ADRs was a strategy for enhancing the company’s responsiveness in addressing drug safety issues.

“We have a policy, an internal policy that every staff person in this office has to be sensitized on pharmacovigilance…So, from the watchman to the receptionist, to our staff-our gardeners, our office personnel- everyone would get to be trained on pharmacovigilance.”- (Kenya Interview_Pharma 02, 2014)
4b.5.3.8  Intelligence and Information

The pharmacogovernance domain ‘Intelligence and Information’ is defined as databases and mechanisms of communication among the national regulatory authority, the state pharmacovigilance centres, patients, healthcare professionals, policymakers and the general public for the purpose of sharing information to support pharmacovigilance, the safe use of medicines and patient safety.

PPB lacks sufficient data to inform its decision making about marketed drugs. The information gap could be improved by increasing the data received from the pharmaceutical industry, spontaneous reporting and active surveillance (Ministry of Health, 2015). We found that the Pharmacy and Poisons Board, County health and pharmaceutical company key informants priorities for pharmacosurveillance overlapped (Table 10). The Pharmacy and Poisons Board’s newly introduced online reporting system and mobile phone application (2014), designed to capture reports of ADRs and poor quality medicine, has made Kenya a regional leader in pharmacosurveillance technology. The development of the e-reporting system was a collaborative initiative between the PPB and USAID. Hospitals, health care workers and patients are now able to submit reports of ADRs and poor quality medicines using the online system (Kenya PPB, 2015).

Key informants reported that the online system was anticipated to increase the number of ADRs reported, however expanding the scope of health care workers reporting was still needed.

“Up to now, most of our reports are from pharmacists and pharmaceutical technologists because the other health workers don’t know much about pharmacovigilance and the
Communication of the safety signals to the counties remains inadequate. Some remote counties have only recently obtained computers and “the internet is slow” even in some urban centres (Kenya Interview_County 04, 2014). Despite being the regional pharmacy contact, one key informant had no idea how many [spontaneous] reports came from her region because, “when they report using this software it just goes to Pharmacy and Poisons Board. The Pharmacy and Poisons Board communicates [with KEMSA] without us receiving the report. If they find it has failed the test, they have to quarantine it. After they quarantine it, they instruct KEMSA to come and collect all the drugs in the health facilities. But at that point I am [still] not informed. After action has been taken, they say we got this number of reports from [your] region and we took action” (Kenya Interview_County 04, 2014).

This study found that PPB and exogenous actors’ priorities overlapped regarding their interests in improving data collection, data analysis and sharing ADR reports. Their interests in harmonization of databases and ADR submission formats also converged, although their rationale differed. For IGOs interviewed, “harmonization is absolutely necessary for us to make sense of data from all around the globe” (IGO/INGO Interview_02, 2015). The multinational drug companies interviewed expressed a priority for harmonization of timelines for reporting ADRs because, “when you are registering a lot of products in various countries and various countries require the PSUR, it’s very hard to keep on top of that submission deadline all the time” (Kenya Interview_Pharma 01, 2014). PPB’s prioritization of standardized drug registration and postmarket requirements is reflected in the quote, “We want to look at ONE guideline for
pharmacovigilance in the whole of the East African Community” (Kenya Interview_PPB 01, 2014). It is posited that PPB’s position on harmonization has been influenced by its membership in the EAC and AMRH. The mandate of both organizations is to promote trade. If the amendment to the Pharmacy and Poisons Act is adopted as proposed a legal basis for harmonization will be created. The prioritization of improving intelligence and information about ADRs in Kenya was perceived as enabling pharmacovigilance.

4b.5.3.9 Stakeholder Coordination

The pharmacogovernance domain ‘Stakeholder Coordination’ pertains to the coordination of domestic and global actors’ activities that benefit pharmacovigilance (e.g., strengthening the national regulatory authority and developing human resource capacity for drug surveillance). In this research, key informants described the need for a system-wide approach to drug safety. Systems-strengthening was associated with a reduction in fragmentation related to pharmacovigilance. Most key informants interviewed identified systems-strengthening as a responsibility of the Pharmacy and Poisons Board with global actors’ participation. The pharmaceutical industry key informants interviewed did not perceive systems-strengthening was their responsibility.

Advocacy, collaboration and stakeholder coordination were the modes of engagement that characterized the interactions among the PPB and exogenous actors for the purpose of systems-strengthening (Figure 7). Non-state and external actors used the power of their existing networks to advocate for the creation of new networks for the purpose of mobilizing resources to strengthen pharmacovigilance and active pharmacosurveillance. The European Commission, WHO and UMC have worked with PPB to implement Cohort Event Monitoring and, “they
provided seed money and they supported us to develop the clinical trials registry in collaboration with the Kenya Medical Institute” (Kenya Interview_PPB 02, 2014).

“We’ll pool [resources]. Like that Cohort Event Monitoring program, the HIV and us... We work together. They have put in some support or even technical assistance for that. During the implementation of that program we draw on that money to support it. We also use the money from there to train the sites”. - (IGO/INGO Interview_05, 2014)

Stakeholder coordination reportedly resulted in redistribution of targeted resources to pharmacovigilance through matching funds. For example, funding that was targeted to support commodities for family planning, vaccines for children, AIDS, TB, and malaria was ‘stretched’ to cover pharmacovigilance.

“[b]ecause we are systems-strengthening we receive money from the HIV, malaria, [and] PMI, we make sure if we are doing it that we a stretching [it] and bring in other things. When we build the capacity of health care workers, although we are using these monies that are disease focused, you train them to look out for ADRs for all medicines and medicinal products. So the skills are for everything.” - (IGO/INGO Interview_05, 2014)

This study found that state and exogenous actors’ engagement that was characterized as ‘fragmentation’ hindered stakeholder coordination and pharmacovigilance due to impaired communication between parallel systems.

The Ministry doesn’t [want separate systems] ...they want everything to become like one system...which helps, but of course there is some resistance to reports that are coming
direct. But the main government is trying to have one system...to fit into what is existing.” - (Kenya Interview_PPB 01, 2014)

Several key informants reported that IGO/INGOs’ advocacy for stakeholder coordination in Kenya was part of a broader agenda, to strengthen pharmacovigilance regionally. A network of pharmacovigilantes that have been trained in Kenya have been delegated the responsibility to educate Kenya’s neighbours, build local capacity for pharmacovigilance and advocate for regional strengthening of pharmacovigilance systems. PPB will be able to implement this agenda in their capacity as a pharmacovigilance RCORE.

“Officers from PPB are part of our outreach strategy, part of Pharmacovigilantes Sans Frontiers... and it’s working. The more you can influence big countries the more you use them to influence those around them.” - (IGO/INGO Interview_03, 2014)

4b.6 Discussion

The research findings provide insight into the Pharmacy and Poisons Board’s pattern of regulatory governance, national preferences for pharmacovigilance in Kenya and how transnational policy preferences have been integrated into Kenya’s pharmacogovernance.

Brass (2012) found that NGOs in general, were well integrated into Kenya’s governance and the line between government policy makers and NGO implementing partners was blurred. This study similarly found exogenous actors had influenced pharmacogovernance in Kenya. The research suggests that Kenya’s governance, that permits delegation of authority to non-state implementing partners to build infrastructure and implement domestic programs, creates space
for exogenous actors to influence normative policy, policy instruments and practices that affect pharmacovigilance.

All of the key informants interviewed perceived that engagement among state, non-state or external actors had a positive influence on pharmacovigilance likely because the study found that exogenous actors’ priorities for pharmacovigilance were adopted in tandem with domestic interests. Moreover, the Pharmacy and Poisons Board exercised autonomy over its choice to adapt or adopt suggested policy norms. As an example, in designing its e-reporting system, PPB adapted WHO norms for pharmacosurveillance and enabled reporting of suspected poor quality medicine. PPB signaled its priority to expand the definition of pharmacovigilance beyond ADRs.

Exogenous actors’ greatest influence was found in the domain of policy, law and regulation through engagement characterized as advocacy. To strengthen pharmacogovernance, non-state and external actors advocated for expansion of PPB’s regulatory authority as well as amendments to the Food, Drug and Chemical Substance Act and Pharmacy and Poisons Act. Neither of the Acts included language on pharmacovigilance when first passed.

The state-exogenous actors’ relationship regarding the pharmacogovernance domain ‘Policy, Law, and Regulation’ was mostly positive, however this study found that efforts by some exogenous actors to limit regulatory reforms hindered pharmacovigilance. The MNC consultations with PPB, that aimed to discourage adoption of requirements for a QPPV on the grounds that the policy was unnecessary and too costly, impeded pharmacovilance. Olsson, Pal, & Dodoo (2015) similarly suggested that International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
pharmacovigilance guidelines for market authorization holders are too expensive and would disadvantage domestic generic companies in LMICs. The argument is refuted by evidence that the generic industry has not been disadvantaged by similar regulation in other countries, suggesting this concern is unsubstantiated.

We argue that pharmacovigilance may also be hindered by exogenous actors’ policy preferences for the harmonization of regulatory requirements for drug registration because the aim of policies promoted by the AMRH and the EAC is to reduce trade barriers rather than pharmacovigilance. The WHO has also called for regulatory harmonization in Kenya to address cross-border pharmaceutical issues (Mbinyo et al., 2010). Although this study found convergence in key informants’ perceptions of regulatory harmonization, regardless of the sector they represented, the benefits of regulatory harmonization have been contested in the literature due to the trend to harmonize to the lowest standard rather than raise regulatory requirements, even in high income countries (Abraham, 2007; Lexchin, 2012).

Despite their advocacy for changes to pharmacogovernance aimed at strengthening regulation of pharmaceuticals in Kenya, by creating more comprehensive, harmonized regulatory functions ("House Team's Dilemma Over Proposed Parastatal ", 2013; Ministry of Health, nd), this study did not find evidence that exogenous actors influenced legislation to address the lack of resources for pharmacovigilance. Neither the legislation proposed to create the Pharmacy and Poisons Authority (PPA) nor amendments to the Pharmacy and Poisons Act, require a percentage of revenues collected by the PPA be allocated to pharmacovigilance. Additionally, the Pharmacy and Poisons Act (Amendment) 2014, explicitly states that enactment will not require the expenditure of additional public funding ("The Pharmacy and Poisons (Amendment) Act,

In regards to the pharmacogovernance domain ‘Stakeholder Coordination’, we found strong engagement among exogenous actors. This is because a sector-wide approach to development has been widely promoted by the neoliberal agenda (OECD, 2003). Patterns of engagement between state and exogenous actors that fostered stakeholder coordination had a positive effect on pharmacogovernance and pharmacovigilance. Patterns of engagement that were based on advocacy, collaboration and cooperation all fostered stakeholder coordination and led to resource allocation for active pharmacosurveillance (e.g., CEM and TSR) as well as innovations in data collection and risk communication (e.g., e-reporting and mobile phone apps). Donor support for pharmacovigilance was cited as important by key informants in this study and in the literature because resources available for pharmacovigilance are limited in Kenya and other LMICs (Bill & Melinda Gates Foundation, 2013; Moscou et al., 2013; Strengthening Pharmaceutical Systems, 2011). Exogenous actors including USAID, MSH, WHO, Global Fund, and the Bill and Melinda Gates Foundation have recommended multi-sectoral engagement as a mechanism to expand resources for pharmacovigilance in resource-limited settings.

Deficits that were found in the other pharmacogovernance domains were not overcome by state-exogenous actor engagement. PPB’s current delegation of its limited authority to industry in the form of self-regulation represented a gap in ‘Ethics’ that hindered pharmacovigilance by conflicts of interest inherent in asking industry to police itself. Industry is accountable to shareholders that are motivated by profits over surveillance (Forman & Kohler, 2012; Moscou et al., 2013), except when the company fears their reputational risk is at stake. The gap in
pharmacogovernance related to ‘Intelligence and Information’ posed an overlapping ethical issue by leaving the decision regarding how much information to disclose about ADRs to drug companies; a conflict of interest. Industry preference for compliance with local reporting requests creates information inequities between countries with stringent requirements and countries with lax requirements, and is further evidence that self-regulation is unrealistic in Kenya. Self-regulation is unrealistic globally because pharmacovigilance is not integrated into the corporate governance of most pharmaceutical companies (Maennl, 2008; Moscou et al., 2013).

Key findings also suggest a deficit in the pharmacogovernance domain ‘Participation and representation’ in regards to civil society engagement. Even though Kenya’s Health Policy Framework (KHPF) 2012-2030 claims to support social accountability and participation (i.e., participatory governance) a mechanism is not outlined for civil society participation in the framework. The literature suggests that when civil society involvement in decision making is limited, societal interests are not well represented (Kohler & Martinez, 2015). Social participation could assure regional equity in pharmacovigilance by holding state and exogenous actors to account for their action or inaction regarding pharmacovigilance in Kenya however, to be effective, training and education about deliberative governance is required (Kohler & Martinez, 2015).

4b.7 Conclusions

This research contributes to the literature on exogenous actors’ influence on pharmacogovernance in Kenya by analyzing the relationship between patterns of engagement between exogenous and domestic actors and their effect on pharmacovigilance. The research
advances our understanding of the factors that enable and hinder pharmacovigilance which is important because in the coming decade dozens of new drugs are anticipated to be introduced exclusively in LMICs.\footnote{LMICs where new products are anticipated to be launched in 2016-2022 include: Burundi, Malawi, Kenya, Gambia, Zambia, Ethiopia, Benin, Democratic Republic of Congo, Bangladesh, Pakistan, Cambodia, Nepal and India (Bill & Melinda Gates Foundation, 2013).} New treatments for malaria (e.g., tafenoquine) and new product formulations for pediatric HIV (e.g., lopinavir/ritonavir [LPV/r] oral mini-melt pellets) are in the pipeline. The LPV/r study was conducted in Kenya. Five or more higher-risk drugs\footnote{A higher-risk drug is defined as a drug with identified or important potential risks.} are anticipated to be launched in Kenya between 2012-2015 and four or more drugs are planned for 2016-2018 (2013). Data collected about ADRs in Kenya and other LMICs will increase the chance of finding rare adverse reactions that will benefit patients globally.

The literature on risk governance has promoted shared responsibility for managing risk between state and non-state actors (Renn et al., 2011; Renn & Schweizer, 2009). Key findings suggest that in Kenya, pharmacogovernance and pharmacovigilance were strengthened by fostering interdependent engagement among county, national and exogenous actors. Specifically, the research found that engagement based on collaboration and advocacy among the Pharmacy and Poisons Board, Ministry of Health and exogenous actors favoured resource allocation by exogenous actors to support pharmacovigilance and reduce drug safety risk.

Global pharmacogovernance would further benefit LMICs with limited resources by establishing a funding stream for pharmacovigilance to enable equity in global pharmacovigilance. The
international funding model proposed by the BMGF Safety Surveillance Working Group, based on collaboration among governments, donors and industry, would create a trust fund to provide short-term funding to resource-limited countries seeking to establish pharmacosurveillance and establish industry fees to ensure sustainability (Bill & Melinda Gates Foundation, 2013). Any global funding model should support a national pharmacovigilance system that covers all medicines rather than only newly released molecules. Funding should support ‘Equity’ and ‘Intelligence and Information’ through the development of a nationwide risk communication network for rapid dissemination of drug safety information. However, the research cautions against sole funding for pharmacovigilance by global donors.

To be sure, exogenous actors will continue to advocate for pharmacovigilance in Kenya while interests align. This paper argues that the sole use of exogenous actors to fill a deficit in capacity for pharmacovigilance in Kenya leaves the country vulnerable to: 1) conflicts of interest and cross purpose interests; 2) a fragmented pharmacovigilance system; 3) ad hoc, drug specific pharmacosurveillance; and/or 4) exogenous actors’ shifting priorities. Kenya is already experiencing the effect of shifting priorities that have reduced donor funding while, at the same time, increasing support to previously underfunded countries in the region (IGO/INGO Interview_05, 2014). Kenya last received a Global Fund grant in 2009 (although the country still has 8 active grants). Other donor funding has also been reduced (IGO/INGO Interview_01, 2014). While key informants interviewed recognized Kenya’s autonomy to adopt global actors’ norms, less consideration was given to donors’ autonomy to determine to whom to provide their resources and support.

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33 See http://portfolio.theglobalfund.org/en/Country/Index/KEN
Pharmacogovernance in Kenya must be strengthened and the government must hasten to adopt a national pharmacovigilance system and funding model to support it. Systems-strengthening, in which local capacity for pharmacovigilance at the national and county level is developed, is needed to achieve a sustainable pharmacovigilance system. PPB must continue to build the capacity to determine the safety profile of the drugs and vaccines introduced in Kenya. The research finding, that past experience is an indicator of future preferences for pharmacogovernance, supports continued development of a network of pharmacovigilantes in Kenya.

This study suggests that Kenya’s 2010 constitution and Kenya’s Health Policy Framework (KHPF) 2012-2030 already embody the guiding principles to support the creation of governing structures, policy instruments and institutional authority to promote societal benefits from patient safety and protection from adverse drug events. Several of the KHPF guiding principles overlap the pharmacogovernance domains in this study. Overlapping domains include Equity, Participation and Representation (Social accountability, Participation), Effectiveness and Efficiency (Efficiency), and Stakeholder coordination (Multi-sectoral) (Sessional Paper No 6 of 2012 on the Kenya Health Policy 2012–2030 (DRAFT) National Development and Vision 2030, p. 17). This suggests that improvements in pharmacogovernance are achievable with political will to address existing gaps.

**Competing interests:** None of the authors have any competing interests.
Chapter Five

Chapter Five: Conclusions

5.1 Preamble

The purpose of this research was to examine the relationship between pharmacogovernance and pharmacovigilance in Brazil and Kenya in order to identify the factors that enable pharmacovigilance. Given the presence of the global actors in Kenya and Brazil, the research also aimed to analyze the complex interplay between global and state factors (and actors) that affected pharmacogovernance institutions and pharmacovigilance.

The 3-paper thesis investigated: how pharmacogovernance influences pharmacovigilance; how and why the State (at all levels), global actors (non-state) and the pharmaceutical industry interact to affect pharmacogovernance and ultimately postmarket drug safety in a low and upper-middle income country; and how patterns of governance (e.g., devolved and decentralized) affect pharmacovigilance.

The final chapter of this thesis is organized as follows. The first section of Chapter 5 discusses the key findings from each of the three papers that comprise this thesis (Chapter 3, 4a and 4b). The key findings related to the impact of pharmacogovernance on enabling or hindering pharmacovigilance are discussed. Next, Network Governance Theory and Ideation Theory- the

34 Pharmacogovernance is defined as the manner in which governing structures; policy instruments; and the institutional authority to act, implement and enforce norms, policies and processes are managed to promote societal interests for patient safety and protection from adverse drug events.
theories underpinning the research conducted, are critically examined for their relevance in explaining how and why global actors and state actors engaged in interactions pertaining to pharmacogovernance and pharmacovigilance. A new theoretical framework emerging from the research is presented that describes the nature of relationship between pharmacogovernance institutions, structures and governing networks within a domestic and global policy forum. Chapter 5 concludes with a discussion of the policy alternatives and implications for improving pharmacogovernance, thereby enhancing pharmacovigilance and taking a step toward achieving the goal of global equity in drug safety. The strengths and limitations of the research are described and suggestions for future research are presented.

5.2 Summary of key findings

This thesis consists of three papers. In Chapter 3: “Fulfilling the constitutional right to health: pharmacogovernance and postmarket drug safety” the pharmacogovernance framework is described. The analytic framework provides a novel approach to analyzing the effectiveness of the national regulatory systems in advancing pharmacovigilance and for understanding the relationship between governance and pharmacovigilance. The research objective investigated in Chapter 3 pertained to how pharmacogovernance shapes postmarket drug safety policy, law, regulations and accountability at the national and subnational level. The research also investigated how national governance shapes pharmacogovernance.

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35 Network Governance Theory is an explanatory theory for understanding how and why governance networks, comprised of state, civil society and exogenous actors form and interact. Ideation Theory is an explanatory theory for understanding policy uptake by domestic and exogenous actors.
Key findings suggest that even when policy, laws, and regulations support the national regulatory authority mandate to ensure access to safe medicines and health products, gaps in pharmacogovernance may hinder postmarket drug safety. The research suggests that strengthening pharmacogovernance to increase accountability and social participation may enhance pharmacovigilance. The application of policy instruments such as regulatory impact analysis (RIA) to analyze the impact of decentralization/devolvement on pharmacogovernance may also advance pharmacovigilance.

**Chapter 4a** “Governance and Pharmacovigilance in Brazil: A scoping review”, investigated the relationship between governance, pharmacovigilance, and Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil. The research investigated pharmacogovernance institutions and their impact on pharmacovigilance. In Chapter 4a, the research also investigated how and why state and non-state actors interacted to influence pharmacogovernance. The literature pertaining to global institutions was analyzed in order to identify how transnational policy ideas for regulatory governance have been integrated and translated into pharmacogovernance in Brazil.

The research found that Brazil's policy, laws, and regulations supported ANVISA's authority to ensure access to safe medicines and health products, however ANVISA’s broad mandate and gaps in other pharmacogovernance domains such as ‘Equity and Inclusiveness’ accounted for regional disparities in monitoring and assessing drug safety.

In **Chapter 4b** the impact of exogenous actors on pharmacogovernance and pharmacovigilance in Kenya was investigated. The study investigated how and why state and non-state actors’ interactions influenced pharmacogovernance. The relationship between specific modes of
engagement (e.g., autonomy, collaborative) among exogenous and domestic actors at the national and subnational level was examined for its effect on enabling or hindering pharmacogovernance or pharmacovigilance.

A key finding from this research is that state and exogenous actor engagement primarily enabled both pharmacogovernance and pharmacovigilance. Specifically, the research found that when engagement among PPB, Ministry of Health and exogenous actors was based on interdependency (e.g., collaborative, cooperative, consultative) or dependency (advocacy, empowerment, delegated) pharmacogovernance and pharmacovigilance was enhanced. Dependent and interdependent engagement was associated with capacity building; strengthening legislation and stakeholder coordination.

The research found examples where exogenous actors hindered pharmacovigilance such as the action by one MNC to lobby against enactment of the policy requiring Qualified Pharmacovigilance Persons within the company. Fragmentation (independent engagement) among public, private, and INGO-run health programs was found to impede risk communication between thereby hindering pharmacovigilance.

The research suggests that pharmacovigilance depends on (a) an internal policy framework, (b) external partnerships and (c) the active cultivation of organizational capabilities to analyze policy effectiveness and ensure compliance.
5.3 Emerging theoretical framework

The theoretical framework emerging from this research is an interconnected tripartite model comprised of pharmacogovernance structure, institutions and governance networks. The intersection of these three pillars is a relationship based on interdependence (i.e., mutual reliance between two or more entities or groups). Although pharmacovigilance in Brazil and Kenya benefitted by the strengths of each pillar independent of the others, pharmacogovernance and pharmacovigilance was advanced by interdependent interaction among all three pillars (Fig. 9).

Figure 9. Tripartite Model for Pharmacogovernance
Pharmacogovernance structure, institutions and networks are filtered through the domestic and
global policy communities. This emergent model suggests that global policy community can
modulate domestic factors that contribute to pharmacogovernance. For example, global norms for
accountability within the national regulatory authority may have a modulating effect on
pharmacovigilance by increasing transparency in drug procurement. The global policy
community may also support domestic policy actors’ efforts to strengthen pharmacovigilance
through participation in governance networks. On the other hand, the domestic policy
community may exercise its voice through constitutional channels established for social
participation. Chapter 1, 3 and 4 provide the foundation for the discussion of the tripartite pillars
of pharmacogovernance that follows.

5.3.1 Pharmacogovernance structure

Pharmacogovernance structure, manifested within the national governance of Brazil and Kenya,
included the division of powers between levels of government that were responsible for
pharmacovigilance, rules and authority for resource allocation and the enabling framework for
enforcement of pharmacovigilance. The differences and similarities that were found assisted in
explaining variations in postmarket drug safety.

Brazil and Kenya are Federal republics with decentralized (Brazil) or devolved (Kenya)
governance. The Brazilian republic is comprised of 26 states; each with its own governance
structure. Kenya’s federal republic is comprised of 47 counties; each with their own governance
structure. The research suggests that the similarity in the country’s governance structure may
contribute to the similar characteristics in their pharmacogovernance. The authority for
postmarket drug safety policy-setting occurs at the federal level with implementation of national
pharmacovigilance policy delegated to subnational government in both countries. States, county and municipalities also have limited authority to determine their pharmacovigilance priorities. Subnational level engagement in pharmacovigilance priority-setting, activities and policy implementation was found to be conditioned on resources, pharmacovigilance capacity and the state or county’s past experience with pharmacovigilance priority-setting.

Fundamental differences were found in how the responsibility for pharmacovigilance was shared between national and subnational levels in Brazil and Kenya. States and municipalities in Brazil were found to have greater involvement in pharmacovigilance than Kenya. This was largely attributed to the newness of devolved governance in Kenya. Devolved governance was ushered in with the adoption of the Kenyan 2010 constitution transferring authority over pharmacogovernance to the subnational level of government. County governments lacked administrative experience to implement and enforce national or county level policies, including pharmacovigilance (Otieno et al., 2014). Historically under-resourced counties also lacked the financial and human resources to detect and monitor drug safety risks. As such, devolved governance was found to hinder pharmacogovernance and pharmacovigilance.

Centralized pharmacogovernance whereby PPB retained control over postmarket drug safety was preferred by several key informants in Kenyan counties with limited resources because centralization shifted responsibility for pharmacovigilance from the subnational to national level where resources and experience was greater. County representatives stating a preference to exercise the autonomy that devolved governance conferred were not interested in recentralization. Their preference was to request an expansion of federal transfer payments which they could allocate to pharmacovigilance as well as exercise county control over
procurement. A key finding from this research is that a gap in the pharmacogovernance domain ‘ethics’ could lead to corruption in procurement which has implications for postmarket drug safety (Baghdadi-Sabeti et al., 2009; Kenya Interview_County 04, 2014; Otieno et al., 2014; Torstensson & Pugatch, 2012).

State control over pharmacogovernance and pharmacovigilance was also preferred in Brazil despite the similar lack of capacity in Brazilian states (e.g., Acre). The research found however, greater subnational-level pharmacogovernance, including power and capacity to determine pharmacovigilance priorities, in Brazil than Kenya. The research suggests that adoption of pharmacovigilance by some Brazilian states, as early as the 1990s, fostered the development of state pharmacovigilance centres and other infrastructure to enable pharmacovigilance.

Individual states’ history of mobilization around pharmacovigilance also contributed to strengthening pharmacogovernance structure and institutions within a specific state. According to this research, states establishing pharmacovigilance units in the 1990s (e.g., Ceará and São Paulo) continue to have stronger pharmacovigilance today. This suggests that prior experience with policy networks and collective problem solving (i.e., participatory health councils or municipal councils) may be an important factor in pharmacogovernance (van Laerhoven, 2014). The importance of policy actors’ engagement in influencing pharmacogovernance was another key finding in the research that will be discussed further in the section about governance networks.

Although decentralization benefitted pharmacovigilance in some states, Rich and Gomez (2012) posited that decentralization actually weakens national regulatory authority. As autonomy over
service provision is strengthened, national government oversight over health policy implementation is weakened (Rich & Gomez, 2012). This is because data on subnational implementation of national policies, spending and outcomes is collected irregularly in Brazil, resulting in little information to monitor compliance and limited mechanisms for enforcing national policy guidelines (Rich & Gomez, 2012).

The question posed by this research (Question 3) was: How do patterns of governance affect pharmacovigilance? The key implication of this research is that mechanisms to address gaps in each pharmacogovernance domain must be instituted regardless of national governance structure. Decentralized or devolved governance supports pharmacovigilance if the subnational government has established pharmacogovernance institutions, resources and prior experience with pharmacovigilance. Re-centralization of governance, proposed by Rich & Gomez (2012) to reassert national regulatory capacity in Brazil and improve accountability, would be insufficient to strengthen pharmacovigilance without addressing gaps found in the other pharmacogovernance domains (e.g., Equity & Inclusiveness, Ethics) that impede pharmacovigilance. Centralization that does not take into account mechanisms for addressing equity, inclusiveness and ethics could undermine opportunities for equitable representation and participation in decision making for drug safety policies by persons most affected by the policies. This is consistent with key findings from the research of pharmacogovernance in Kenya.

5.3.2 Pharmacogovernance institutions

Pharmacogovernance institutions were found at the federal and subnational level in Brazil and Kenya. At the federal level, the pharmacogovernance institutions that were entrusted with overseeing the national medicines policy and pharmacovigilance were the Agência Nacional de
Vigilância Sanitária (Brazil) and the Pharmacy and Poisons Board (Kenya). In Brazil, pharmacogovernance institutions also comprised state pharmacovigilance units (CVS) and the Ministry of Health. In Kenya, county pharmacogovernance was under the direction of the Ministry of Health.

The analysis of Brazil and Kenya’s pharmacogovernance institutions, using the pharmacogovernance framework, found that each of the pharmacogovernance domains were important for strengthening pharmacovigilance. On the other hand, the pharmacogovernance domains that had the greatest impact on pharmacovigilance in both Brazil and Kenya were 1) Policy, Law and Regulation, 2) Participation and Representation, 3) Stakeholder Coordination, 4) Equity and 5) Ethics. Policy, Law and Regulation had a direct impact on pharmacovigilance practice standards and an indirect effect on other pharmacogovernance domains including Participation and Representation; Equity and Inclusiveness; and Effectiveness and Efficiency in both countries. Stakeholder Coordination had also indirect effects on Participation and Representation. Normative policy rather than enabling legislation accounted for its effect on representation in Kenya. In contrast legislation, in addition to normative policy, influenced social participation in Brazil. A further look at the domains is now presented.

5.3.2.1 Policy, Law and Regulation

Pharmacogovernance in Brazil was strongest in the domain of policy and law. Enabling legislation provided ANVISA with the authority to create rules to register drugs, monitor adverse

36 The pharmacogovernance framework domains are: Policy, Law and Regulation; Transparency and Accountability; Ethics; Equity and Inclusiveness; Participation and Representation; Responsiveness; Information and Intelligence; Effectiveness and Efficiency; and Stakeholder Coordination.
effects and enforce compliance (Agência Nacional de Vigilância Sanitária, 2009; Moscou, Kohler, & MaGahan, 2016). In contrast, Kenya’s pharmaceutical sector infrastructure was found to be weak, laws were conflicting and PPB enforcement was lacking (Mbíndyò et al., 2010; *Sessional Paper No. 1 on the National Pharmaceutical Policy*, 2010; *Strengthening Pharmaceutical Systems*, 2011). For example, the absence of a law requiring the publication of an up-to-date list of registered drugs impeded pharmacovigilance by inhibiting pharmacosurveillance and subsequent confiscation of unregistered drugs (Mbíndyò et al., 2010).

### 5.3.2.2 Ethics

In this research, it was argued that gaps in pharmacogovernance in the domain ‘Ethics’ have a direct effect on policy, law and regulation. Lapses in ethics impede pharmacovigilance by hindering adoption of legislation (e.g., Qualified Person for Pharmacovigilance requirement in Kenya); monitoring pharmaceutical industry compliance; and enforcement of laws pertaining to pharmacovigilance. Gaps in ethics also create an opportunity to exploit a culture of corruption in Brazil and Kenya. The literature suggests that corruption is prevalent in Kenya and Brazil (de Lima, 2013; Otieno et al., 2014; Rich & Gomez, 2012). This finding is consistent with key informant interviews.

In Kenya, ethical gaps have led to service delivery that is skewed to ‘politically loyal key decision makers’ and procurement malpractice whereby tenders were awarded to “politically connected bidders” (Kenya Interview_County 04, 2014; Otieno et al., 2014). Political interests have incentivized governors and mayors to implement policy and allocate resources to “politically popular social programs” in Brazil (Brazil Interview_State 04, 2014; Rich & Gomez, 2012). ANVISA’s effectiveness, posited Ramalho (2009), has been challenged by a culture of
disregard for rules of the State. Consequently, pharmacogovernance within Kenya and Brazil is reflective of broader societal and political incentive structures that impede effective governance.

The literature suggests that when the regulatory authority has cross purpose interests the regulatory role is weakened (G. H. Silva, 2011). Miranda (2010) and Silva (2011) suggest that ANVISA has a dual mandate to support industry growth and medicines safety that must be reconciled. Key findings from this research are consistent with their finding as in the example of ANVISA permitting sibutramine (a weight loss medicine) to remain on the market in Brazil despite being withdrawn in Europe and the United States. In this research it is argued that cross purpose interests resulting from ANVISA’s dual mandate represents a gap in ethics.

5.3.2.3 Participation & Representation

Citizen participation and representation were perceived as a mechanism to improve institutional accountability and transparency in Brazil and Kenya (Otieno et al., 2014; G. H. Silva, 2011). This research found that Brazil and Kenya employed different models for civil society participation in pharmacovigilance decision making.

In Brazil, national governance has created a framework for social participation at the federal, state and municipal level and laws have been enacted to enable citizen participation (Constituição da República, 1988; "Law 8.080," 1990). Brazil also has a long history of citizen engagement in participatory health councils (Kohler & Martinez, 2015). These factors have been attributed to ANVISA’s norms for social participation in determining its regulatory agenda (ANVISA, nd-b). In contrast to Brazil, Kenyan civil society representation and participation in pharmacovigilance policy making was principally comprised of IGOs and INGOs rather than
citizen engagement. This is consistent Kenya’s history of non-state actor integration in its governance (Brass, 2012).

The literature suggests that the pharmaceutical industry and global donors are positioned as ‘experts’ and their opinions are sought by pharmacogovernance institutions (Brass, 2012; Gaetani & Albuquerque, 2009; Wiktorowicz et al., 2012). When actors with perceived ‘expertise’ are provided access to regulators, regulatory policy may be skewed toward their interests (Hochstetler, 2013). In both Kenya and Brazil the research found that industry had greater representation and access to engaging with policy makers than consumers. In Kenya, their participation in policy making was enabled by national policies supporting the integration of exogenous actors and industry in governance networks. Consistent with the literature, the research found examples of pharmaceutical industry efforts to shift pharmacovigilance policy toward their interests, employing consultative interactions described in this research. Key informants reported that drug companies in Kenya were consulted on pending regulation requiring a qualified person for a pharmacovigilance person in Kenyan drug companies (Kenya Interview_Pharma 01, 2014). Key informants reported that the pharmaceutical industry also had strong political power in Brazil (Brazil Interview_State 04, 2014).

5.3.2.4 Equity & Inclusiveness

‘Equity’ was defined in this research as economic and social resource allocation that assures all regions within the country have access to safe medicines and the resources to detect and act on drug safety signals. Distribution of resources to support pharmacovigilance was not found to be equitable in Brazil or Kenya. The asymmetry in pharmacovigilance throughout each country was found to be related to regional wealth and density of pharmaceutical industry.
The research found that wealthy Brazilian states and Kenyan counties had a greater number of sentinel sites for pharmacosurveillance (IBGE, nd). The pharmacovigilance units with the greatest resources and autonomy to set state pharmacovigilance priorities were located in states with a large pharmaceutical industry (e.g., Sao Paulo). Moreover, the prevalence of sentinel hospitals and other institutions conducting pharmacosurveillance was greatest in highly resourced regions (IBGE, nd).

These findings are consistent with the literature and suggest that the medicines users’ experience with postmarket drug safety is dependent on where they live.

5.3.2.5 Stakeholder Coordination

The responsibility for managing risks, particularly risks not confined within specific borders, should be shared between multiple state and non-state actors (Renn, Klinke, and van Asselt 2011). This research found that national, subnational and exogenous actors came together to collaborate, cooperate and advocate for strengthened pharmacovigilance in Kenya and Brazil. Exogenous actors coordinated with other non-state actors, PPB and several Kenyan universities to fund active and passive pharmacosurveillance initiatives. A collaboration between the state pharmacovigilance centre in Sao Paulo and the University of Sao Paulo strengthened pharmacovigilance by expanding capacity to address ADR reports while training students.

In the next section, key findings related to interactions among policy actors in Brazil and Kenya that shape pharmacogovernance and regulatory governance are presented.
5.3.3 Pharmacogovernance networks

The research relating to pharmacogovernance networks was conducted on the basis of the theoretical proposition that state (endogenous) and non-state (exogenous) actors jointly contributed to pharmacogovernance in Kenya and Brazil. How and why they interacted to shape pharmacogovernance: including administrative authority, drug safety policy and resource allocation was the focus of this research.

*Network Governance Theory* posits that governance networks and policy networks form to address issues that network members perceive require interdependence. The literature on risk governance suggests managing risks (e.g., drug safety and the environment) that extend beyond national boundaries is a shared responsibility (Renn et al., 2011; Renn & Schweizer, 2009). Global pharmacogovernance favours state and exogenous actors’ engagement to reduce drug safety risks by strengthening pharmacovigilance.

Governance networks in Brazil consisted of ANVISA, state pharmacovigilance units, CEATOX, MoH, pharmaceutical companies (domestic and MNC) and IGOs (e.g., WHO). Governance networks in Kenya comprised the PPB, MoH, county health executives and health departments, pharmaceutical companies (domestic and MNC), IGO and INGOs. The exogenous actors played a “critical role” in the network shaping regulatory governance, pharmacogovernance and pharmacovigilance (Brass, 2012; Cruz, 2009; Moscou et al., 2016; Rich & Gomez, 2012; Suku et al., 2015). Their interactions with other network actors at the national and subnational level influenced the articulation and implementation of pharmacovigilance policies affecting the quality of pharmacovigilance nationally and regionally in Kenya and Brazil. State and exogenous actors cooperated by sharing risk-communications pertaining to adverse drug
reactions and drug safety signals because global interdependence was perceived to be needed to expand the pool of data mined for signals of potential drug safety threats. Exogenous actors reported that they formed governance networks to address global drug safety issues (e.g., identification of adverse reactions and poor quality medicines) while at the same time advocating for strengthening regulatory governance and building pharmacovigilance capacity in Brazil and Kenya.

It has been suggested that a key feature of governance networks is that over time, as the network becomes institutionalized, there becomes increased normalization and acceptance of the legitimacy of network norms, rules and institutional practices (Torfing, 2012). The evolution in adoption of policy norms found through in this research is consistent with predictions of Network Governance Theory and Ideation Theory. Norms and policy preferences were transferred and reinforced between network participants through peer learning (Gaetani & Albuquerque, 2009; Stone, 2004). In this research, peer learning was asymmetrical and policy transfer was mono-directional. This finding is consistent with both Ideation Theory and Network Governance Theory in which it has been suggested that policy uptake occurs with technical and financial support from transnational policy actors moreover, network actors shape problem definition and solutions (Béland & Orenstein, 2010; Blanco et al., 2011; Torfing, 2012).

The participation of exogenous actors in governance networks was more prominent in Kenya than in Brazil. Their participation was perceived positively by all of the key informants interviewed in Kenya, likely because the study found that exogenous actors’ priorities for pharmacovigilance were in tandem with domestic interests which is consistent with Network Governance Theory. IGOs and INGOs were active in fostering pharmacovigilance and
pharmacogovernance by providing resources for pharmacosurveillance and advocacy for legislation. When priorities differed, the regulatory authority exercised autonomy over its choice to adapt or adopt suggested policy norms. Such was the case with PPB’s decision to expand the definition of pharmacovigilance beyond ADRs to include poor quality medicines.

Interactions between national and subnational-level network actors had a greater impact on pharmacogovernance and pharmacovigilance in Brazil than interactions between exogenous actors. The difference between Kenya and Brazil may be explained by cultural traditions such as ‘jabuticaba’. Jabuticaba is a pejorative expression used to explain the culture of creating Brazil-specific standards rather than adopt international norms because Brazil is unique. An alternate explanation may be provided by Brazil’s negative prior experience with exogenous actors around policy setting such as its confrontation with the World Trade Organization over the TRIPS Agreement. In 1994, the World Trade Organization passed the Trade Related Intellectual Property Rights (TRIPS) Agreements to enforce patent protection through potential trade sanctions. The more than 300 proceedings and complaints filed against Brazil before the WTO tribunal in an effort to get the country to comply with conditions TRIPS, influenced the Brazilian pharmaceutical regulatory framework (McCabe, 2007).

5.4 Conclusion and Policy recommendations

This research contributes to the identification and measurement of variables that represent a new theoretical concept “pharmacogovernance”. The pharmacogovernance framework is the metric for measuring pharmacogovernance. The research contributes to the understanding of variables that are important to pharmacogovernance and illuminates the complex interplay between global and state factors (and actors) in the addressing pharmacovigilance. Their interchange is filtered
through pharmacogovernance structure, institutions and networks. The research contributes to theories of integrated governance by examining the impact of governance that is shared by domestic and exogenous actors and pharmacovigilance in LMI countries. It further contributes to theory of network interactions by exploring the modes of engagement between network actors that enable and hinder pharmacovigilance. The major findings are as follows:

- Pharmacovigilance is advanced through (a) an internal policy framework, (b) external partnerships and (c) the active cultivation of organizational capabilities to analyze policy effectiveness and ensure compliance.

- The authority that pharmacogovernance institutions have over pharmacovigilance is enabled by legislation, regulation and policy however implementation is filtered through interdependency with pharmacogovernance structure and governance networks.

- Stakeholder coordination may positively contribute to pharmacogovernance and pharmacovigilance through mechanisms such as mobilizing networks within the domestic and global policy communities for the purpose of advocating for pharmacovigilance resources and norms.

- Interdependent (collaborative, cooperative, consultative) engagement among national, subnational and supranational actors is mostly associated with positive outcomes (e.g., capacity building; strengthening legislation and stakeholder coordination).

- Policy instruments (e.g. Regulatory Impact Analysis) adopted to improve regulatory policy effectiveness have not yet been applied to policies that related to pharmacovigilance. As such, gaps persists in the pharmacogovernance domains ‘Accountability and Transparency’, ‘Ethics’ and ‘Effectiveness and Efficiency’.

- Decentralized/devolved governance may augment the impact of the gaps in pharmacogovernance, particularly in under-resourced states (Brazil) and counties.
This research on pharmacogovernance establishes that, in Brazil and Kenya, investments in pharmacogovernance processes, institutions and network engagement may further improve pharmacovigilance.

5.4.1 Sustainable funding model for pharmacovigilance

Resource allocation and resource alignment has vital implications for pharmacovigilance because it influences capacity to conduct pharmacosurveillance, risk communication, postmarket safety studies and initiatives to mitigate risks inherent in the use of medicines.

This research suggests the current funding model for pharmacogovernance institutions is potentially susceptible to fluctuations in resources for pharmacovigilance because neither Brazil nor Kenya has a dedicated budget for pharmacovigilance. Gaps that were found in the pharmacogovernance domain ‘Ethics’ in Brazil and Kenya, may exploit the culture of corruption and permit conflicts of interests. Politically motivated decision making was reported to affect funding levels, funding alignment and procurement decisions. All of which were reported by key informants and the literature as a risk to drug safety related to insufficient pharmacovigilance, poor quality medicines in the supply chain, substandard therapies and increased ADRs.

The research suggests sustainable funding for pharmacovigilance would narrow the gap in the pharmacogovernance domains ‘Ethics’ and ‘Equity’. Innovative solutions are needed to address
resource deficits in Brazil and Kenya. Governance networks act as a bridge for knowledge and norms exchange between the global policy community and the domestic policy community. The tripartite model of pharmacogovernance suggests the interdependency between pharmacogovernance networks and pharmacogovernance institutions might be articulated through the establishment of a funding pool for pharmacovigilance. Existing mechanisms utilized by governance networks such as mobilizing their internal networks within the domestic and global policy communities may be employed. The global funding model that supports a national pharmacovigilance system would advance pharmacovigilance in LMI countries. It is consistent with Risk Governance and Network Governance Theories that suggest participation by actors across multiple jurisdictions to address high risk, complex issues involving uncertainty. Domestic and global funding targeting the development of a nationwide risk communication network for rapid dissemination of drug safety information would increase equity in pharmacovigilance in Brazil and Kenya.

At the domestic policy level, targeted funding for pharmacovigilance, that is modeled after the Kenya local authorities’ transfer-fund (LATF) and Brazil’s participatory health councils (PHCs), could serve a model for targeting funding to historically under-resourced states to achieve regional equity in distribution of resources for pharmacovigilance.\textsuperscript{37}

\textsuperscript{37} The Local Authorities Transfer Fund was established to supplement ‘to supplement the financing of services and facilities they are required to provide under the Local Government Act’ (Otieno et al., 2014, p. 59)
5.4.2 Strengthening social participation, representation and inclusion

Key findings suggest that pharmacogovernance is influenced by who is represented in the policy making process, their legal rights to participate, and institutional mechanisms through which groups are able to articulate their interests/preferences related to the drug policy agenda and norms for pharmacovigilance. A key finding of this research is that the pharmaceutical industry and global donors have a greater voice in decision making forums than Brazilian and Kenyan citizens. The absence of citizen participation in decision making spaces has implications for medicine users because their interests are under-represented. This is particularly important when there are gaps in other pharmacogovernance domains (e.g., ethics, equity and inclusiveness) that affect capacity and distributions of pharmacovigilance nationally.

Pharmacogovernance that endorses social participation through adoption of legislation and norms is important for creating a climate in which social participation is valued. The literature suggests that the creation of formal institutions and legal obligation do not automatically lead to local participatory governance (van Laerhoven, 2014). This is because participation is conditioned on a number of factors that cannot be addressed solely by legislation.

The reasons for citizen under-representation in policy settings in Brazil and Kenya ranged from lack of awareness of decision making spaces to lack of an explicit framework for participation. Each must be addressed in order to expand citizen participation in decision making. Such efforts must include outreach to inform citizens about when, where and how to provide input into the regulatory agenda. Notices of public forums must be provided in accordance with the literacy and technology of the population if participation is to be inclusive.
The literature suggests that even when citizens participate in decision making forums, such as participatory health councils in Brazil, the impact of their participation may be marginalized by their lack of education, training and technical knowledge of many health system issues (de Lima, 2013; Kohler & Martinez, 2015; Otieno et al., 2014). Politics may also affect citizen participation in Brazil and Kenya - a point echoed by key informants (de Lima, 2013; Otieno et al., 2014). In Kenya, citizens have been expected to “rubber stamp” proposals presented by their leaders (Otieno et al., 2014). In Brazil, political patronage to entrench a politician’s power base is endemic and influences policy decisions, especially during elections (de Lima, 2013). Education regarding pharmacovigilance policy issues and training in participatory governance would mitigate these barriers to participation.

5.4.3 Strengthening Regulatory Authorities

The research suggests that strengthening regulatory authorities, referred to as ‘systems-strengthening’ by key informants in Kenya, would benefit pharmacovigilance in low and middle income countries in the long term. It would assure that national capacity for pharmacovigilance is developed in order to 1) conduct pharmacosurveillance, 2) assess safety signals, 3) communicate information about risk across all regions and 4) evaluate the effectiveness and responsiveness of postmarket drug safety strategies. The research highlights the benefit of establishing a pharmacogovernance framework for analyzing areas for systems strengthening. Systems-strengthening that includes the adoption of policy tools to assess the impact of regulatory authority pharmacovigilance policies nationally and at the state and municipal level is recommended. Policy instruments should not only be adopted but annual assessments should be imposed by the national and subnational governments of Brazil and Kenya. Regulatory authority strengthening should include the adoption and enforcement of ethical guidelines that eliminate
cross purpose interests. Cross purpose interests could be eliminated by limiting ANVISA’s regulatory authority to pharmaceuticals and the health sector. Regulation of Brazil’s and Kenya’s pharmaceutical industry and other commercial sector activities should be delegated to another regulatory authority however interdependent interactions should be maintained with the national regulatory authority to assure adherence to the pharmacovigilance mandate.

5.4.4 Interdependent engagement between pharmacogovernance structure, institutions, and networks

The pharmacovigilance system framework developed as part of this research shows interdependence between state and exogenous actors is integral to national pharmacovigilance in Kenya and could benefit Brazil. Exogenous actors may have a role in de-legitimizing societal and political patronage incentives that hinder pharmacovigilance, while acknowledging strong national identity within Kenya and Brazil who may perceive external pressure as meddling. Interdependent engagement involving consultative, collaborative and cooperative engagement that fosters pharmacovigilance in tandem with national priorities would mitigate negative perceptions, as was found in the study of exogenous actors’ engagement in Kenya.

Policy actors engaged in governance networks could also advocate for national level policies that reduce fragmentation and enhance coordination to strengthen pharmacovigilance. This research suggests that fostering interdependent engagement among pharmacogovernance institutions, structure and networks at the county, national and supranational level would enable pharmacovigilance in Brazil and Kenya. Interactions that are collaborative, cooperative and involve advocacy, coupled with technical and financial support, contribute to the uptake of
pharmacovigilance, pharmacogovernance and regulatory governance norms. Findings suggest that incentives to strengthen collaboration and cooperation between the national and subnational level for the purpose of pharmacovigilance is preferred to reduce dependency on exogenous actors’ resources. While engagement with exogenous actors benefitted national pharmacogovernance and pharmacovigilance in Brazil and Kenya, over-dependency on was shown to create ad-hoc pharmacovigilance and risk for shifting donor priorities.

Interdependent, collaborative engagement between regulatory and academic institutions could contribute to building a culture of pharmacovigilance and domestic capacity for pharmacosurveillance and risk assessment. Findings show that academic institutions have played a key role in fostering pharmacovigilance that could be expanded.

5.4.5 Networking between pharmacogovernance structures and institutions

In Kenya, where services and commodities are supplied by parallel public private and faith-based systems, the fragmentation was found to hinder risk communication (Sessional Paper No. 1 on the National Pharmaceutical Policy, 2010). Similarly, parallel systems for collecting data about adverse drug reactions and adverse vaccine reactions coupled with poor data exchange and communication has created unnecessary fragmentation, hindering comprehensive pharmacovigilance (Olsson et al., 2015). Fragmented interactions among state actors (national and subnational level) and state-exogenous actors were a threat to pharmacovigilance.

Greater networking between pharmacogovernance structures and institutions would strengthen pharmacovigilance. For example, policy and norms that require public, private and donor-run programs to share information about drug safety issues might be implemented to reduce delays in communicating risks. Public, private and donor programs could also collaborate in active
pharmacosurveillance activities. These recommendations are consistent with the tripartite model for pharmacogovernance.

5.5 Implications for governance in newly evolving arenas

This research on pharmacogovernance may have implications for other newly evolving areas that are highly specialized, involve high risk, embody multiple complexities and uncertainty, such as artificial intelligence. The research questions whether societal norms are playing ‘catch up’ in newly evolving areas in addition to who should be involved in establishing ‘norms’. The research suggests that frameworks will be needed to proactively assess the relationship between governance structure, institutions and networks and the over-arching global policy community and domestic policy community.

5.6 Limitations

The key informants interviewed for this research represented a convenience sample. However, the interviewees were representative of the key sectors important to understanding pharmacogovernance in low and middle income countries. The sectors that were represented (e.g., regulatory authorities, government, global donors, industry, urban and rural regions) were consistent with the quota sample that was calculated. Interviews were conducted until saturation was reached and the study findings were triangulated by employing secondary data sources such as peer reviewed literature and government documents.

5.7 Future research

This research suggests that pharmacogovernance is important to postmarket drug safety. Mitigating gaps in the pharmacogovernance domains can strengthen pharmacovigilance.
Addressing the gaps that were identified by this research will likely be a stepped process, given resource constraints. Policymakers would benefit by research that aims to identify key domains to invest in first. This represents an area of future research.

Another area for future research is a study based on *Network Governance Theory* and *Ideation Theory* that investigates Brazil and Kenya’s impact on regional policy agendas and pharmacovigilance priorities. Both Brazil and Kenya are in the process of transitioning from recipients of global actors’ influence and resources to regional actors with capacity to influence neighboring countries. Kenya has been designated a Regional Centres of Regulatory Excellence to address pharmacovigilance and Brazil is recognized by PAHO as one of 5 regional reference authorities for pharmacovigilance.

Lastly, an analysis of pharmacogovernance in highly resourced countries such as Canada, the United States and Europe would identify areas for bi-directional learning that would strengthen pharmacovigilance in under-resourced regions such as First Nations reserves.
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Appendix A. Paper: Corporate governance and medicines safety
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. The ADR reporting rate in India is 1%, despite the recent establishment of 40 ADR monitoring centers and 140 medical college reporting centers.

Compliance with pharmacovigilance regulations has been low in some developing countries. Endemic corruption, as one example, in emerging economies may de-incentivize regulatory compliance. 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. 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.

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.

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. 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>Corp.</th>
<th>Pharmaco-vigilance described as corporate value</th>
<th>Pharmaco-vigilance flow chart published</th>
<th>Pharmacovigilance 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 regulator reporting requirements described as a ‘threat’</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>Pharmaco-vigilance or drug safety not described in 2010 Annual Report</th>
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<tr>
<td>Eli Lilly</td>
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<td>X</td>
<td>X</td>
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<tr>
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</tbody>
</table>

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 than 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

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
<th>Tier 4</th>
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</thead>
<tbody>
<tr>
<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</td>
<td>≤ 3 corporate values that are characteristic of pharmacovigilance governance and</td>
<td>≤ 2 corporate values that are characteristic of pharmacovigilance governance or ≥ 3 corporate values not characteristic of pharmacovigilance governance and &gt; 15% PMR requirements pending or uninitiated</td>
</tr>
<tr>
<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>&gt; 50% PMR requirements pending or uninitiated</td>
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</tbody>
</table>

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 publicly 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 through 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. 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.\(^{45}\) MRL safety teams evaluate the safety of medicines and vaccines.\(^{46}\) Merck’s Global Compliance Organization periodically audits global pharmacovigilance practices for compliance with regulations and guidelines.\(^ {47}\) 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’.\(^ {48}\)

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.\(^ {49}\) 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.”\(^ {50}\) 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,\(^ {51}\) 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.\(^ {52}\) 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.\(^ {53,54}\)

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.\(^ {55}\) 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.\(^ {56}\) 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.\(^ {57}\)
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. 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. The completion date for one of the delayed studies was originally set for 2009. 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. 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. 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.

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. 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.

GPCS AND POSTMARKET DRUG SAFETY IN INDIA

India’s population increasingly has access to new and older pharmaceuticals. 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.” 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. All three drugs, produced by GPCs (Sanofi, Sanofi India and Lundbeck Italy), including generic pioglitazone, had been banned in other countries years earlier. 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. Without a fulltime drug controller general since 2012, the DCGI’s capacity to monitor pharmacovigilance compliance has been limited. 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.

**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.

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. 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. 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. 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.

Kathy Moscou is a PhD candidate in Pharmaceutical Sciences Collaborative Program in Global Health at the University of Toronto Leslie Dan Faculty of Pharmacy and Dalla Lana Faculty of Global Health.
**Jillian C. Kohler, PhD** is Associate Professor and Director of Global Health at the Leslie Dan Faculty of Pharmacy and the Munk School of Global Affairs at the University of Toronto.

**Joel Lexchin, MD** is a Professor in the School of Health Policy and Management at York University and University Health Network emergency department doctor in Toronto Canada.

**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>
<tr>
<td><strong>The quality process is fully integrated into each and every stage of drug development: the design phase, the delivery phase and the monitoring phase</strong> - Eli Lilly Corporate Responsibility Report update 2012</td>
<td></td>
</tr>
<tr>
<td><strong>The safety governance framework states that staff is ‘required to report immediately any issues relating to the safety or quality of our medicines’</strong> - GSK Global Public Policy Issues-Position on Pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td><strong>Recognizing that all health care products and procedures entail some degree of risk, we are committed to working with a broad range of stakeholders to minimize these potential risks while optimizing opportunities for improved health and well-being’</strong> - Abbott 2010 Global Citizenship Report</td>
<td></td>
</tr>
<tr>
<td><strong>It is important that research is undertaken to establish the most effective ways to minimise the risks of medicines including effective ways of communicating the risks and benefits</strong> - The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium</td>
<td></td>
</tr>
</tbody>
</table>
(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.

<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>[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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-market drug safety described as a threat</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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
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 - GSK 2012

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 2010-2013

<table>
<thead>
<tr>
<th>Number of PMR</th>
<th>Drugs with PMRs</th>
<th>Drug Name(s)</th>
<th>Studies not initiated, pending or delayed</th>
<th>Studies Submitted or fulfilled</th>
<th>Final report past milestone</th>
<th>Ongoing Studies</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>1</td>
<td>1</td>
<td>Depakote</td>
<td>0</td>
<td>1</td>
<td></td>
<td>Drug interaction between Depakote + olanzapine</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>22</td>
<td>6</td>
<td>Prozac, Effient, Zyprexa, Forteo, Cymbalta, Symblyax</td>
<td>3</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>70c</td>
<td>14</td>
<td>Arzerra, Horizant, Altabax, Votrient, Advair diskus, Zofran, Zyban, Potiga, Arixtra, Veramyst, Alli, Promacta,</td>
<td>34</td>
<td>18</td>
<td>14</td>
<td>Flonase and Nicorette studies were released</td>
</tr>
<tr>
<td>Company</td>
<td>PMR Study Terminated</td>
<td>PMR Study Terminated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>---------</td>
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<td>----------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Merck</strong></td>
<td>69 (^d)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Janumet, Janumet XR, Januvia, Gardasil, Victrelis, Zolinsta, Cancidas, Vioxx, Juvisync, Emend, Isentress, Dulera, (+17 vaccines)</td>
<td>28</td>
<td>27</td>
<td>3</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Novartis</strong></td>
<td>118 (^e)</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TOBI Podhaler, iLaris, Signifor, Reclast, Neoral, Tyzeka, Foradil, Fanapt, Coartem, Lioresal, Gleevec, Afinitor, Gilenya, Exjade, Tasigna, Voltaren gel, Nexcede (+20 vaccines)</td>
<td>61</td>
<td>29</td>
<td>25</td>
<td>\textit{Zelnorm study terminated. Drug withdrawn from market.}</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pfizer</strong></td>
<td>52 (^f)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Advil Allergy &amp; Congestion Relief, Advil, Zithromax, Vfend, Revatio, Chantix/Champix, Geodeon</td>
<td>24</td>
<td>5</td>
<td>2</td>
<td>15</td>
<td></td>
<td></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).
8 The AMI ranking is based upon 101 indicators across seven key areas.
9 Ibid., p.67.


27 Ibid.

28 Ibid., p.25.

29 Ibid.

30 Eli Lilly-India, "Our Values," Available at: https://www.lillyindia.co.in/values.cfm.

31 Ibid.


33 Ibid.


39 Abbott, "Results Disclosure For Abbott Study Information Formerly On ClinicalStudyResults.org (Through August 2011)" Available at: http://www.abbott.com/citizenship/disclosures/clinical-study-results.htm.

40 Ibid.


42 Ibid.


46 Ibid.


48 Ibid., p.2.


50 Ibid., p.22.

51 Merck & Co. Inc, "Patient Safety".

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).


56 Kiran Kabtta Somvanshi, "Drugs banned abroad may still be of use in some cases," The Economic Times January 8, 2013.

57 The list of drugs banned in India is available at: http://cdsco.nic.in/writereaddata/drugs%20banned%20in%20the%20country.pdf
The GSK statement on pharmacovigilance is available online at: http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-pharmacovigilance.pdf


Ibid., p.3.


Ibid.

Ibid.


Ibid.


Novartis International AG, "Novartis Group Annual Report." 2010

Ibid., 5.


Ibid., 178-9.


Ibid.


Ibid.


Ibid., 22.

Eli Lilly-India, "Patient Safety," Available at: https://www.lillyindia.co.in/patient_safety.cfm.

Ibid.

Eli Lilly-India, "About Us," Available at: https://www.lillyindia.co.in/index.cfm.

Ibid.


Ibid.


GlaxoSmithKline, "Global Public Policy Issues- GlaxoSmithKline's Position on Pharmacovigilance".

Ibid.


Abbott statement on Drug Safety and Global Citizenship

http://www.abbot.com/citizenship/priorities/support/quality.htm

Merck & Co, Inc, "Patient Safety".


List of iSAEC members http://www.imi-protect.eu/index.html

GlaxoSmithKline, "Clinical Trials in the Developing World".
100 Merck & Co. Inc, "Patient Safety".
101 Vijay Thawani, S. Sharma, and K. Gharpure, "Pharmacovigilance: Is it possible if bannable medicines are available over the counter?," Indian Journal of Pharmacology 37, no. 3 (2005): 191.
102 AbbVie, "Code of Business Conduct."
104 FDA, "Inspections, Compliance, Enforcement, and Criminal Investigations- Merck, Sharpe, and Dohme Warning Letter."
105 FDA, "Inspections, Compliance, Enforcement, and Criminal Investigations- Pfizer, Inc. Warning Letter NYK 2010-19."
107 Ibid.
110 Central Drugs Standard Control Organization, "Drugs Banned in the Country".
112 Pfizer, "Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 Form 10-K."
113 Pfizer India, "Annual Report 2011-2012."
114 Ibid.
117 Ibid.
118 Ibid.
119 Abbott, "2012 Annual Report on Form 10-K."
121 Fagin v. Scolnick et. al In re Merck & Co., Inc. Consolidated Derivative Litig., No. 08-3158, CASE No. 619, (February 1, 2010).
123 FDA, "Inspections, Compliance, Enforcement, and Criminal Investigations- Pfizer, Inc. Warning Letter NYK 2010-19." 124 Ibid.
125 Ibid.
127 Ibid.
128 Ibid.
129 Ibid.
130 Ibid.
131 Ibid.
132 Ibid.
133 Ibid.
134 Ibid.
135 Forman and Kohler, Access to Medicines as a Human Right: Implications for Pharmaceutical Industry Responsibility
137 Ibid.
139 Olsson, Pal, Stergachis, and Couper, “Pharmacovigilance Activities in 55 Low- and Middle-Income Countries A Questionnaire-Based Analysis.”
141 Mukherjee, "House panel: Government clearing harmful drugs".
143 Soma Das, "Health ministry bans two drugs Analgin and Pioglitazone; industry protests," The Economic Times June 27, 2013.
144 Mukherjee, "House panel: Government clearing harmful drugs."
145 Soma Das, "Health ministry bans two drugs Analgin and Pioglitazone; industry protests."
147 "India’s drug regulation system in a total shambles."
148 Amrita and Roomi, "Scenario of Pharmacovigilance and ADR Reporting Among Pharmacists in Delhi."
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
Appendix B1. Ethics Approval - University of Toronto
PROTOCOL REFERENCE # 29254

October 26, 2015

Dr. Jillian Kohler  
Ms. Kathy Moscou  
FACULTY OF PHARMACY  
FACULTY OF PHARMACY

Dear Dr. Kohler and Ms. Kathy Moscou,

Re: Your research protocol entitled, "Safety and equity: Transnational actors' influence of pharmacovigilance-A case study of pharmacovigilance policy in Brazil and Kenya"

<table>
<thead>
<tr>
<th>ETHICS APPROVAL</th>
<th>Original Approval Date: November 4, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expiry Date: November 3, 2016</td>
</tr>
<tr>
<td></td>
<td>Continuing Review Level: 1</td>
</tr>
<tr>
<td></td>
<td>Renewal: Data Analysis Only</td>
</tr>
</tbody>
</table>

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your protocol. Note that annual renewals for protocols cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Elizabeth Peter, Ph.D.  
REB Chair

Daniel Gyewu  
REB Manager

OFFICE OF RESEARCH ETHICS
McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1S8 Canada
Tel: +1 416 946-3273  Fax: +1 416 946-5763  ethics.review@utoronto.ca  http://www.research.utoronto.ca/for-researchers-administrators/ethics/
PROTOCOL REFERENCE # 28320

October 14, 2014

Dr. Jillian Kohler
FACULTY OF PHARMACY

Dear Dr. Kohler,

Re: Your research protocol entitled, "Evaluating accountability, transparency and governance in Brazil's pharmaceutical system"

We are writing to advise you that a member of the Health Sciences Research Ethics Board (REB) has granted approval to an amendment (Received September 29, 2014) to the above-referenced research protocol under the REB's delegated review process. This amendment approval letter only applies to what was outlined in the request form under section 5.a) or otherwise marked in the revised protocol.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible.

Best wishes for the successful completion of your research.

Yours sincerely,

Elizabeth Peter, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
Appendix B2. Ethics Approval - Kenya
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3
Reference: IREC/2013/186
Approval Number: 0001151

Kathy Moscou,
322 14th St Brandon,
Manitoba,
CANADA, R7A 4T6.

Dear Ms. Moscou,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:

“Safety and Equity: Transnational Actors’ Influence on Pharmacovigilance in Low and Middle-Income Countries – A Case Study of Pharmacovigilance Policy in Brazil and Kenya.”

Your proposal has been granted a Formal Approval Number: FAN: IREC 1151 on 13th March, 2014. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 12th March, 2015. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

[Signature]

DR. W. ARUASA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc  Director - MTRH
     Principal - CHS
     Dean - SOM
     Dean - SOP
     Dean - SON
     Dean - SOD
Appendix B3. Ethics Approval - Brazil
PARECER CONSUSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** Avaliação da Governança, Responsabilidade e Transparência no Sistema Farmacêutico Brasileiro

**Pesquisador:** Sueli Gandolfi Dallari

**Área Temática:** Pesquisas com coordenação e/ou patrocínio originados fora do Brasil, excetuadas aquelas com copatrocínio do Governo Brasileiro;

**Versão:** 5

**CAAE:** 18428213.0.0000.5421

**Instituição Proponente:** Faculdade de Saúde Pública da Universidade de São Paulo - FSP/USP

**Patrocinador Principal:** Leslie Dan Faculty of Pharmacy

DADOS DO PARECER

**Número do Parecer:** 686.734

**Data da Relatoria:** 27/06/2014

**Apresentação do Projeto:** Inalterado

**Objetivo da Pesquisa:** Inalterados

**Avaliação dos Riscos e Benefícios:** Adequados

**Comentários e Considerações sobre a Pesquisa:**
A lista de comentários e adequações oriunda da CONEP e acatada por este CEP foi atendida pela pesquisadora

**Considerações sobre os Termos de apresentação obrigatória:**
Termos adequados nesta versão do projeto

**Recomendações:**
Nada a acrescentar

**Conclusões ou Pendências e Lista de Inadequações:**
Pendências atendidas

Endereço: Av. Doutor Arnaldo, 715
Bairro: Cerqueira Cesar
UF: SP
**Município:** SAO PAULO
**Telefone:** (11)3061-7779
**Fax:** (11)3061-7779
**E-mail:** coepfspusp.br
Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:
Acatado parecer do Relator quanto à aprovação, após a pesquisadora ter atendido às recomendações do CONEP.

SAO PAULO, 13 de Junho de 2014

__________________________
Assinado por:
Sandra Roberta Gouvea Ferreira Vivolo
(Coordenador)
Appendix C. Invitation to participate in the study

Dear

I am a PhD candidate in the Pharmaceutical Sciences Collaborative Program Global Health at the University of Toronto, Leslie Dan Faculty of Pharmacy and Dalla Lana Faculty of Public Health, Toronto. I am conducting research that examines the relationship between policy makers and global actors (e.g., global institutions, non-governmental organizations, and the pharmaceutical industry) on postmarket drug safety policy choices. The title of the study is: Safety and Equity: Transnational Actors’ Influence on Pharmacovigilance in Low and Middle Income Countries- A Case Study of Pharmacovigilance Policy in Brazil and Kenya.

The research investigates global actors’ influence on national and state policy preferences for postmarket drug safety (pharmacovigilance), governance and resources. I am interested in gathering information about pharmacovigilance in __________. The information will be an invaluable contribution to my research which is approved under University of Toronto ethics protocol #29254 and Moi University FAN:IREC #1151

I would like to invite you to participate in a one-on-one interview between October 6 and October 31, 2014. The interview will take approximately 60-90 minutes of your time. You may suggest a date that is convenient for your schedule.
A copy of the interview questions will be provided in advance of the scheduled interview. With your permission, the interview session will be audiotaped and transcribed at a later date. You may end the interview session at any time and request that the data provided not be used. I would also like to request your assistance in identifying other persons knowledgeable about the pharmacovigilance systems in Kenya.

The results of the interview will be used in my doctoral thesis, future presentations at conferences, and publications. The identity of participants will not be disclosed. You may contact me directly at kathy.moscou@utoronto.ca should you have questions.

Thank you for your consideration of my request.

Kathy Moscou, RPh, MPH, PhD candidate, PPRC Fellow
Pharmaceutical Sciences Collaborative Program Global Health
Leslie Dan Faculty of Pharmacy and Dalla Lana Faculty of Public Health
University of Toronto

kathy.moscou@utoronto.ca
Appendix D1. Letter of consent - English

Dear,

I am writing to request an interview with you that will inform my PhD research. My research investigates the relationship between policy makers in Kenya and transnational actors (e.g., intergovernmental, non-governmental organizations, and the pharmaceutical industry) on pharmacovigilance policy choices. The research also examines how adopted policies are implemented under devolution. Your knowledge of pharmacovigilance in [County/State] will be an invaluable contribution to this research. Information about the study and your participation are outlined below, if you choose to participate.

Title of Study: Safety and Equity: Transnational Actors’ Influence on Pharmacovigilance in Low and Middle Income Countries- A Case Study of Pharmacovigilance Policy in Kenya and Brazil

Principal Investigator: Kathy Moscou, RPh, MPH, PhD candidate

Leslie Dan Faculty of Pharmacy

University of Toronto

kathy.moscou@utoronto.ca

Research Supervisor: Dr. Jillian Clare Kohler, PhD
Background and Purpose of the Research

There is growing recognition that pharmacovigilance matters for health outcomes. Pharmacovigilance, defined as activities to detect, assess, understand and prevent adverse effects and drug-related problems, has not kept pace with increasing access to medicines in developing countries. Knowledge about the use of antiretrovirals (ARVs) in patients that also have tuberculosis (TB) or tropical diseases (e.g., malaria) not common in the countries where drug clinical trials have been conducted is limited. Additionally, knowledge of the real-world effectiveness and safety of fixed dose combination (FDC) therapies is incomplete. The overburdened and under-resourced healthcare system in low and middle income countries has focused limited resources on public health areas perceived to be a higher priority. Global actors influence postmarket drug safety policy, governance and resources in low and middle income.

A case study of Kenya and Brazil (a low income and middle-income country) will be conducted examines their influence and cross-purpose policy ideas on policy and accountability for postmarket drug safety. This research addresses a gap in the literature by investigating the relationship between pharmacovigilance policy choices, accountability, and global actors in Kenya and Brazil.

Study Procedures

The interview will take approximately 60-90 minutes of your time. The researcher will ask you to comment on issues pertaining to postmarket drug safety (pharmacovigilance) in Kenya.
The researcher will also ask you to comment on actions taken by various national and transnational actors pertaining to pharmacovigilance policies. The researcher may contact you after the interview to obtain additional information or clarification that is relevant to the study. With your permission, the interview session will be audiotaped and transcribed. If you chose not to be audio-taped, this researcher will take notes instead. You have the option to review the transcripts of your interview. The results of your interview will be used in my doctoral thesis and in future presentations at conferences, and publications. You may request a copy of my dissertation by contacting me directly at kathy.moscou@utoronto.ca.

**Funding**

This research is funded by the Global Health Student Research Award.

**Benefits and Risks**

While you will not receive personal benefit from participation in this research, the information you provide will contribute to our understanding of governance and accountability for postmarket drug safety in low LMI countries. The research will assist policymakers in decisions pertaining to pharmacovigilance policies and resources to prevent adverse drug reactions and improve drug safety.

The potential of this study to have a negative impact on you or your employment is minimal however there is a potential social risk of loss of status or reputation if your responses to questions become public. Measures will be taken to protect your confidentiality. Your interview will be conducted in a non-threatening environment (e.g., away from your place of employment) approved by you. The data you provide will be coded. Your name or other identifying information will not be included in my doctoral thesis or any manuscripts that contain information you have provided is included. The principal investigator has been conducting research on the topic of pharmacovigilance since 2006 and has previous experience conducting
key informant interviews, analyzing key informant transcripts and reporting on research findings while maintaining confidentiality.

**Privacy and Confidentiality**

Your decision to participate will be kept confidential. Should you choose to participate in this research, information you provide will be included in my dissertation and may be published. Your identity will not be disclosed without your permission to reduce risks of any repercussions from your interview. Interviewees will be identified by country and role (e.g., Kenya medicines regulator), however there still exists the potential for you to be identified by others if your quotations are published. To minimize this risk, when the number of people who can provide information-rich descriptions is small, and it is anticipated that coding is insufficient to protect your identity, you will not be quoted.

Audiotapes, transcriptions, and consent forms will be confidential and filed in a locked cabinet at the University of Toronto. Your name and other identifying information will be removed and substituted with a scrambled identification code. Only the study investigator and research supervisor will have access to the study data. Audiotaped interviews will be transcribed and then destroyed.

**Conditions for Participating**

Your participation in this doctoral research is voluntary. You may decline to answer any question asked and end the interview session at any time. You may also request that any information that you provided not be used in my doctoral thesis.

You waive no legal rights by participating in this study. You may contact the University of Toronto, Office of Research Ethics at: ethics.review@utoronto.ca or 416-946-3273, if you have questions about your rights as a participant or require more information.

**Obtaining Additional Study Information**
This research is conducted by Kathy Moscou, PhD candidate at the Leslie Dan Faculty of Pharmacy, University of Toronto. The research is supervised by Dr. Jillian Clare Kohler, Associate Professor at the Leslie Dan Faculty of Pharmacy, University of Toronto. If you have questions about the study please email Kathy Moscou at kathy.moscou@utoronto.ca.

If you agree to the conditions set forth in this informed consent as well as audiotaping this interview session, please sign the consent form below.

I hereby consent to participate in this research study entitled, “Safety and Equity: Transnational Actors’ Influence on Pharmacovigilance in Low and Middle Income Countries- A Case Study of Pharmacovigilance Policy in Kenya and Brazil”. I give my consent to be interviewed in-person by SKYPE or by phone. I understand that the interview will be audiotaped however I can request to have the researcher take notes instead. I may review the transcript of the interview that I participated in upon request.

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Appendix D2. Letter of consent - Portuguese

Termo de Consentimento Livre e Esclarecido

[Date]

Prezada __________________________.

Eu estou lhe escrevendo para solicitar uma entrevista com você ou resposta por escrito às perguntas da entrevista que informarão minha pesquisa de PhD. A minha pesquisa investiga a relação entre os formuladores de políticas no Brasil e atores transnacionais (por exemplo organizações não-governamentais, intergovernamentais, e a indústria farmacêutica) nas escolhas políticas de Farmacovigilância. O estudo também examina como as políticas adotadas são implementadas em estados descentralizados. O seu conhecimento em Farmacovigilância será de contribuição imensurável para esta pesquisa. As informações sobre o estudo e sua participação estão descritas abaixo, caso você queira participar.

Título do Estudo: Segurança e Igualdade: A influência dos atores transnacionais na Farmacovigilância em países de baixa e média renda- Um estudo
de caso das políticas de Farmacovigilância no Brasil e Quênia.

**Investigador Principal:**
Kathy Moscou, Farmacêutica
Mestre em Saúde Pública, Candidata a PhD
Faculdade de Farmácia Leslie Dan
Universidade de Toronto, Canada
kathy.moscou@utoronto.ca

**Supervisor de Pesquisa:**
Dra. Jillian Kohler, PhD
Professora Associada
Faculdade de Farmácia Leslie Dan
Universidade de Toronto, Canada
+1 (416) 946-8708

Antecedentes e Propósito da Pesquisa

Existe um reconhecimento crescente de que a Farmacovigilância é importante no êxito da Saúde. A Farmacovigilância, definida como as atividades de detectar, avaliar, entender e prevenir reações adversas e problemas relacionados à fármacos, não tem acompanhado o aumento no acesso a medicamentos nos países em desenvolvimento. O conhecimento sobre o uso de antirretrovirais em pacientes que também têm Tuberculose ou doenças tropicais, como a Malária, ainda é escasso. Além disso, o conhecimento em escala mundial da eficácia e segurança de terapias de combinações fixas de doses é incompleto. Os Sistemas de Saúde sobrecarregados e subfinanciados dos países de baixa e média renda têm focado seus limitados orçamentos em áreas de Saúde Pública percebidos como sendo de alta prioridade. Atores globais influenciam nas
políticas de segurança de pós-comercialização de medicamentos, bem como nos governos e orçamentos dos países de baixa e média renda.

Um estudo de caso sobre o Quênia e o Brasil (países de baixa e média renda, respectivamente) será conduzido para examinar a sua influência e propostas-cruzadas de ideias políticas na responsabilidade e políticas sobre a segurança de medicamentos pós-marketing. Esta pesquisa chama a atenção para a falta de literatura específica sobre o assunto. Assim, será investigada a relação entre as escolhas políticas de Farmacovigilância, a responsabilidade e a influência de atores globais no Quênia e no Brasil.

Procedimentos de estudo

Conclusão da sua resposta escrita às questões de estudo levará aproximadamente 60-90 minutos de seu tempo. O pesquisador lhe pedirá para comentar sobre questões pertinentes à segurança de medicamentos na pós-comercialização (Farmacovigilância) no Brasil. Também lhe será pedido para que você comente sobre as ações tomadas por vários atores nacionais e transnacionais pertinentes às políticas de Farmacovigilância. O pesquisador pode entrar em contato com você depois de receber a sua resposta por escrito para obter informações adicionais ou esclarecimentos que forem relevantes ao estudo. Você tem a opção de rever as transcrições da sua entrevista. Os resultados das informações que você dá será usado em minha tese de PhD (Doutorado) e em apresentações futuras em conferências e publicações. Você pode solicitar-me uma cópia da minha dissertação final, contatando-me através de kathy.moscou@utoronto.ca.

Financiamento

Esta pesquisa é financiada pelo Global Health Student Research Award.
Benefícios e Riscos

Apesar de você não ser beneficiado diretamente pela participação na pesquisa, as informações que você fornecer contribuirão para um maior entendimento sobre a governança e a responsabilidade na segurança de medicamentos pós-comercialização em países de baixa e média renda. Este estudo auxiliará os formuladores de políticas nas decisões pertinentes às políticas e investimentos em Farmacovigilância para prevenir reações adversas a medicamentos e a melhorar a segurança dos mesmos.

O potencial deste estudo em ter um impacto negativo para você ou seu emprego é mínimo. Entretanto, há um potencial risco social de perda de status ou reputação caso as suas respostas se tornem públicas. Medidas serão tomadas para proteger a sua confidencialidade. Os dados que você fornecer serão codificados. Seu nome ou qualquer outra informação que possa identificá-lo não serão incluídos em minha tese de doutorado ou em nenhum outro manuscrito que contenha informações que você tenha fornecido. O investigador principal tem conduzido estudos em Farmacovigilância desde 2006 e tem experiência prévia em conduzir entrevistas com informantes-chaves, analisar transcrições de entrevistas e reportar os achados em pesquisa, ao mesmo tempo mantendo a confidencialidade dos entrevistados.

Privacidade e Confidencialidade

A sua decisão de participar será mantida confidencial. Caso você escolha participar deste estudo, as escolhas que você fornecer serão incluídas em minha dissertação e poderão ser publicadas. A sua identidade não será revelada sem a sua permissão, a fim de reduzir riscos de qualquer repercussão da sua participação. Os participantes do estudo serão identificados por país e função (p. ex. Reguladores de Medicamentos no Brasil). Porém, há ainda certo risco de você ser
identificado por outros caso suas citações forem publicadas. Para minimizar este risco, caso o
número de pessoas que participarem for pequeno e for verificado que o processo de codificação
não será suficiente para proteger a sua identidade, suas citações não serão incluídas.

As gravações de áudio, transcrições e termos de consentimento serão mantidos confidenciais e
serão armazenados em um gabinete fechado da Universidade de Toronto. O seu nome e
quaisquer outras informações de identificação serão removidas e substituídas por um código de
identificação randomizado. Apenas o investigador do estudo e o supervisor de pesquisa terão
acesso aos dados do estudo. As entrevistas áudio-gravadas serão transcritas e, posteriormente,
destruídas.

Condição de Participação

A sua participação nesta pesquisa de PhD é voluntária. Você pode se recusar a responder
quaisquer perguntas. Você também pode pedir que algumas das informações fornecidas não
sejam utilizadas em minha tese de doutorado. Você renuncia quaisquer direitos legais ao
participar deste estudo. Você pode entrar em contato com a Universidade de Toronto-
Departamento de Ética em Pesquisa pelo ethics.review@utoronto.ca ou +1 416-946-3273, se
você tiver qualquer dúvida sobre seus direitos como participante ou requerer maiores
informações.

Obter Informações Adicionais do Estudo

Esta pesquisa é conduzida por Kathy Moscou, candidata a PhD na Leslie Dan Faculdade de
Jillian Clare Kohler, Professora Associada à Leslie Dan Faculdade de Farmácia, Universidade de
Toronto. Se você tiver qualquer questão sobre o estudo, por favor, queira entrar em contato comigo pelo endereço eletrônico kathy.moscou@utoronto.ca.

Se você aceitar as condições descritas acima bem como permitir a gravação de áudio da entrevista, queira, por gentileza, assinar o termo de consentimento abaixo.

Eu autorizo a minha participação na pesquisa intitulada “Segurança e Igualdade: A influência dos atores transnacionais na Farmacovigilância em países de baixa e média renda- Um estudo de caso das políticas de Farmacovigilância no Brasil e Quênia”. Eu dou o meu consentimento para ser entrevistado pessoalmente via Skype ou por telefone. Eu entendo que a entrevista será áudio-gravada. Entretanto, eu posso solicitar que o entrevistador tome notas apenas. Eu posso rever os transcritos da entrevista que eu participei por solicitação prévia.

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Appendix E1. Interview Guide: National Regulatory Authority - ANVISA

1. Por favor, você poderia se introduzir e dizer qual é o seu papel na ANVISA? Há quanto tempo você está nesta posição?

2. Por favor, descreva eventos específicos que levaram à adoção de políticas e legislação de Farmacovigilância no Brasil.

3. Quais são as áreas prioritárias da ANVISA para a Farmacovigilância no Brasil? Como as prioridades para a Farmacovigilância são determinadas?

4. Quais são as partes interessadas que participam das decisões políticas da ANVISA com relação à Farmacovigilância e quais são suas respectivas funções? Como a contribuição de cada grupo é medida? (p. ex. Pesquisadores, profissionais de saúde, consumidores, meio acadêmico, indústria farmacêutica).

5. Por que o processo de definição da agenda regulatória evoluiu para incluir a participação social? Como a inclusão de vozes externas impactou a Farmacovigilância?

6. Como a ANVISA tem aplicado a Análise de Impacto Regulatório na Farmacovigilância?

7. Por favor, descreva como a Farmacovigilância é descentralizada no Brasil. Existem diferenças entre as prioridades dos níveis federal e estaduais no que se refere à segurança de medicamentos na pós-comercialização? Como estas diferenças são gerenciadas?

8. Por favor, descreva a relação entre a ANVISA e os Centros de Farmacovigilância Estaduais, Centros de Vigilância Sanitária (CVS), Unidades de Farmacovigilância, Centros Toxicológicos Brasileiros (CEATOX), e farmácias sentinela.

9. Quais são as responsabilidades Federal e Estaduais para integrar o Sistema de Farmacovigilância? sco?

10. Por favor, descreva as barreiras para uma Farmacovigilância efetiva no Brasil.

11. Por favor, descreva qualquer apoio direto ou indireto que a ANVISA recebe de organizações intergovernamentais, ONGs, agências de desenvolvimento, etc, para o reforço dos sistemas de Farmacovigilância ou Farmacêutico (por exemplo, infraestrutura do centro/unidade de Farmacovigilância, orçamento para atividades de Farmacovigilância, capacitação de RH, recomendações sobre POPs e quadros reguladores, relatórios sobre RAM, formulários de notificação, análise de RAMs). Descreva o impacto.

13. Quais normas, instrumentos e diretrizes propostas por atores globais para o apoio à Farmacovigilância e ao Sistemas Farmacêuticos o Brasil adotou / rejeitou / ou adaptou? Por quê?

14. A ANVISA tem uma ampla atuação em diferentes setores com interesses diversos (por exemplo, a vigilância da saúde e a indústria farmacêutica). Como os conflitos de interesse são gerenciados?

15. Por favor, descreva como é a política de alerta de riscos da ANVISA. Você poderia descrever as estratégias que são utilizadas para divulgar os alertas de risco nas diferentes regiões (como nas regiões rurais) para profissionais de saúde e pacientes?

16. Como a Farmacovigilância é cumprida/executada Nacionalmente e em cada Estado?

17. Como a Farmacovigilância na ANVISA é financiada (por exemplo, parcerias público-privada, indústria farmacêutica, público)? Qual a percentagem do orçamento total é dirigida à Farmacovigilância?

18. Por favor, descreva a estrutura de governança da ANVISA e explique como a Farmacovigilância está integrada na governança?

19. Por favor, descreva o tipo de informação que está disponível ao público (por exemplo, dados/estudos que dão suporte à aprovação regulatória de medicamentos, decisões de retirada de medicamento do mercado, Membros de Comitês, etc).

20. Por favor, descreva a participação da ANVISA na Rede Pan-Americana para a Harmonização da Regulamentação Farmacêutica (PANDRH)? Como a PANDRH tem influenciado as políticas de Farmacovigilância no Brasil?

21. Que fatores influenciam a ANVISA para solicitar:
   a. Estudos de Fase IV / estudos de segurança pós-autorização (PASS- post authorization safety studies);
   b. Iniciar um recall de medicamentos;
   c. Emitir um alerta de risco.
   d. O que você consideraria como sendo as melhores práticas para a vigilância pós-comercialização de produtos farmacêuticos?
   e. Existem outras informações adicionais que você gostaria de fornecer que são relevantes à pesquisa sobre a Farmacovigilância no Brasil?
Para a sua conveniência, incluímos a seguir o questionário na versão em INGLÊS. As perguntas são as mesmas apresentadas em Português e podem auxiliar-lo (a) a melhor entender as questões caso a tradução em Língua Portuguesa não tenha sido clara.

**Interview Guide: ANVISA**

1. Please introduce yourself and provide background on your position in ANVISA. How long have you been in your present position?

2. Please describe specific events that have prompted the adoption of policy and legislation for pharmacovigilance in Brazil.

3. What are ANVISA’s priority areas for pharmacovigilance? How are priorities for pharmacovigilance determined?

4. Which stakeholders participate in ANVISA policy decisions concerning pharmacovigilance and what is their role? How is the input of each weighted? (Ex. researchers, health professionals, consumers, academia, pharmaceutical industry)?

5. Why has the process for setting the regulatory agenda evolved to include social participation? How has the addition of external voices impacted pharmacovigilance?

6. How has ANVISA applied Regulatory Impact Analysis to pharmacovigilance?

7. Please describe how pharmacovigilance is decentralized in Brazil? Are there differences between Federal and State in priorities for postmarket drug safety? How are differences managed?

8. Please describe the relationship between ANVISA and the state pharmacovigilance centers, Health Surveillance Center (CVS), pharmacovigilance units, Brazil’s toxicological centers (CEATOX), and sentinel pharmacies?

9. How are Federal and State responsibilities for pharmacovigilance integrated?

10. Please describe barriers to effective pharmacovigilance in Brazil.
11. Please describe any direct or indirect support ANVISA receives from IGOs, NGOs, development agencies etc., for pharmacovigilance or strengthening pharmaceutical systems (e.g., pharmacovigilance center/unit infrastructure, budget for pharmacovigilance activities, HR capacity building, recommendations re: SOPs and regulatory framework, ADR reports, reporting forms, pharmacosurveillance, ADR analysis). Describe the impact.

12. How would you rate the influence of global guidelines on the development or modification of existing norms for pharmacovigilance in Brazil (ex. WHO/UNAIDS technical guidance for pharmacovigilance for Global Fund proposals, WHO pharmacovigilance toolkits for antiretrovirals, antimalarials and TB medicines, PAHO/PANDRH Best Practices in Pharmacovigilance for the Americas, ICH standards)?

13. Which of the global actors’ norms, tools and guidelines to support for pharmacovigilance and strengthening pharmaceutical systems has Brazil adopted/rejected/or adapted? Why?

14. ANVISA has a broad mandate over varied sectors with diverse interests (e.g. health surveillance and the pharmaceutical industry. How are conflicts of interest managed?

15. Please describe ANVISA’s risk communication policies? Can you describe any regional variation (e.g., outreach to rural communities) in risk communication strategies to health professionals & patients?

16. How is pharmacovigilance enforced nationally and in each state?

17. How is the ANVISA pharmacovigilance budget funded (e.g., public, industry, Public-private partnership)? What percentage of the overall budget is directed to pharmacovigilance?

18. Please describe the ANVISA governance structure and explain how is pharmacovigilance is integrated into the governance?

19. Please describe the type of information that is publically available (e.g., data/studies that support drug regulatory approval, withdrawal decisions, committee membership etc.)
20. Please describe ANVISA’s participation in the Pan American Network for Drug Regulatory Harmonization (PANDRH)? How has PANDRH influenced pharmacovigilance policies in Brazil?

21. What factors influence/inform regulatory decisions pertaining to whether to: a)
   a. Requiring Phase IV studies/post authorization safety studies (PASS)
   b. Initiating a drug recall
   c. Issuing a risk communication
   d. What do you consider to be best practices for post-market surveillance of pharmaceutical products?
   e. Is there additional information that you would like to add that is relevant to pharmacovigilance in Brazil?
Appendix E2. Interview Guide: National Regulatory Authority - Kenya Pharmacy and Poisons Board

1. Please introduce yourself and provide background on your position and involvement in the Kenya PPB

2. How long have you been involved with the Kenya PPB?

3. What are Kenya PPB priority areas for pharmacovigilance (e.g., strengthening pharmacovigilance systems, improving ADR reporting, establishing active surveillance, reducing county variation in pharmacovigilance capacity, identify falsified or substandard drugs, other?)

4. How are priorities for pharmacovigilance (postmarket drug safety) determined?

5. What effect has devolution had on Kenya PPB priorities for national pharmacovigilance?

6. How are differences in priorities between Kenya PPB and counties managed?

7. Please describe the governance structure of the Kenya PPB and county medicines authorities.
   What is authority and responsibility of each? How are they integrated to advance pharmacovigilance?

8. How is pharmacovigilance in the public and faith-based health systems integrated in Kenya?

9. Describe specific legal provisions for pharmacovigilance in the national medicines legislation. To whom do the laws apply (e.g., pharma, healthcare providers, health facilities, other?)

10. How is pharmacovigilance enforced nationally and at the county level?

11. How is Kenya PPB and each county medicines authority funded i.e., sources (public, industry, Public-private partnership)? What percentage of the overall budget is directed to pharmacovigilance?
12. Which stakeholders participate in policy decisions concerning pharmacovigilance in Kenya? Please describe any expert advisory committees to the PPB involved in contributing to pharmacovigilance policies and describe committee representation: researchers, health professionals, consumers, government, pharmaceutical industry? How is the input of each weighted?

13. Are Kenya PPB meetings open to the public?

14. Please describe the type of information that is publically available (e.g., minutes for PPB meetings, data/studies that support drug regulatory approval/decisions, committee membership etc.)

15. Are there written guidelines pertaining to conflict of interest? Are the guidelines publically available?

16. Please describe any direct or indirect support the medicines regulatory authority receives from IGOs, NGOs, development agencies etc., for pharmacovigilance or strengthening pharmaceutical systems (e.g., pharmacovigilance centre/unit infrastructure, budget for pharmacovigilance activities, HR capacity building, recommendations re: SOP and regulatory framework, ADR reports, reporting forms, pharmacosurveillance, ADR analysis). Which standards/guidelines of pharmacovigilance have you adopted/rejected in the last 5 years? Why?

17. Please rank the following according to importance to Kenya PPB and pharmacovigilance (Likert scale): WHO, Global Fund, MSH, USAID, PEPFAR, GFATM, World Bank, UMC-Africa, ICH, AMRH, others (List).

18. How would you rate the influence of guidelines on the development or modification of existing pharmacovigilance in Kenya (e.g., WHO/UNAIDS technical guidance for pharmacovigilance for Global Fund proposals, WHO pharmacovigilance toolkits for
antiretrovirals, antimalarials and TB medicines, MSH toolkit (IPAT) for assessing pharmacovigilance, WHO Good Governance in Medicines Framework, ICH standards)?

19. Describe intended/unintended impact of transnational actor influence on pharmacovigilance/ pharmacovigilance policies in Kenya

20. Does Kenya PPB participate in the African Medicines Regulatory Harmonization (AMRH)?
   Please describe the role

21. Describe policies pertaining to identification of ADRs and falsified or substandard medicines (e.g., spontaneous reporting, cohort event monitoring, targeted spontaneous reporting, clinical trials, post authorization safety studies, summary reports from Uppsala Monitoring Centre, other).

22. Please describe Kenya PPB risk communication policies? Can you describe any regional variation (e.g., outreach to rural communities) in risk communication strategies to health professionals & patients?

Conclusion

23. What do you consider to be best practices for pharmacovigilance in Kenya? Improvements?

24. Is there additional information you would like to provide pertaining to pharmacovigilance?

25. I would like to conduct interviews in Mombasa, Turkana, Nyeri, Kisumu and Eldoret. Can you suggest people knowledgeable about pharmacovigilance that I should speak with?
Appendix F. Interview guide: State pharmacovigilance Centre - Brazil

Questionário de Entrevistas

1. Por favor, você poderia se introduzir e dizer qual é o seu papel no Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro. Há quanto tempo você está nesta posição?

2. Quais são as prioridades de Farmacovigilância determinadas em seu estado e nacionalmente?

3. Por favor, descreva como a Farmacovigilância é descentralizada no Brasil. Existem diferenças entre as prioridades dos níveis federal e estaduais no que se refere à segurança de medicamentos na pós-comercialização? Como estas diferenças são diferenças gerenciadas?

4. Por favor, descreva a relação entre a ANVISA e o Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro

5. Descreva, por gentileza, a relação entre o Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro, o Centro de Vigilância Sanitária do Estado, as unidades de Farmacovigilância, os Centros de Assistência Toxicológica (CEATOX) e as farmácias sentinelas?

6. Quais são as responsabilidades federais e estaduais para integrar a Farmacovigilância?

7. Quais são as influências diretas e/ou indiretas que atores globais têm sobre a Farmacovigilância? Por favor, classifique as seguintes instituições de acordo com a sua importância para a Farmacovigilância no Brasil (Organização Mundial da Saúde / OPAS, FDA, Agência Europeia de Medicamentos, o The Global Fund, MSH- Management Science for Health, USAID- U.S. Agency for International Development, PEPFAR- U.S. President's
Emergency Plan For AIDS Relief, a Fundação Gates, o Banco Mundial, o Uppsala Monitoring Centre, a Sociedade Internacional de Farmacovigilância, outros).

8. Por favor, descreva se existe algum apoio direto ou indireto que o Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro recebe de organizações intergovernamentais, ONGs, agências de desenvolvimento, etc., para a Farmacovigilância ou para reforçar o sistema farmacêutico (por exemplo, infraestrutura do centro/unidade de Farmacovigilância, orçamento para atividades de Farmacovigilância, capacitação de RH, recomendações sobre POPs e quadros reguladores, relatórios sobre RAM, formulários de notificação, análise de RAMs).

9. Quais normas e ferramentas internacionais têm sido adotadas no Brasil com relação à Farmacovigilância e às políticas regulatórias de medicamentos? Por quê?


11. Qual tem sido o impacto da agenda regulatória atual da ANVISA de participação social, transparência e prestação de contas na Farmacovigilância?

12. Quais normas/diretrizes globais de Farmacovigilância não foram adotadas nos últimos 5 anos (por exemplo, ferramentas de relatórios harmonizados de RAMs ex. Vigibase)? Por quê?

13. Descreva o impacto da influência dos atores transnacionais na Farmacovigilância no Brasil e nas políticas relacionadas a ela.

14. Descreva as políticas estaduais adotadas para identificação de RAMs e de medicamentos falsificados (por exemplo, notificação espontânea, monitoramento de eventos de coorte, alvo
de notificação espontânea, ensaios clínicos, estudos de segurança pós-comercialização, relatórios resumidos de Uppsala Monitoring Centre, outros).

15. Por favor, descreva a política de comunicados de risco do Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro. Quais estratégias são adotadas para alcançar outras regiões (p.ex. comunidades rurais)

16. Como a Farmacovigilância é aplicada no nível nacional e em seu estado?

17. Como o Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro é financiado (ex. via público, privado, indústria, parcerias público-privada)? Qual a percentagem do orçamento geral é destinado à Farmacovigilância?

18. Quem participa das decisões políticas relativas à Farmacovigilância em seu estado e qual é o papel de cada um? (p. e.x pesquisadores, profissionais de saúde, pacientes, meio acadêmico, indústria farmacêutica.)? Como a participação de cada grupo é mensurada?

19. Por favor, descreva o tipo de informação que está disponível ao público pelo seu Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro (por exemplo, dados/estudos que dão suporte à aprovação de medicamentos, decisões de retirada de medicamento do mercado, comissões do Centro, etc).

- Existe informação adicional que você gostaria de fornecer relacionadas à Farmacovigilância?
- Você poderia, gentilmente, sugerir contatos da Anvisa, Ministério da Saúde ou Indústria Farmacêutica que conheçam a Farmacovigilância e que seria interessante entrevistarmos?

Para a sua conveniência, incluímos a seguir o questionário na versão em INGLÊS. As perguntas são as mesmas apresentadas em Português e podem auxilia-lo (a) a melhor entender as questões caso a tradução em Língua Portuguesa não tenha sido clara.
**Interview Guide: State Pharmacovigilance Centers**

1. Please introduce yourself and provide background on your position and role at Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro. How long have you been in your present position?

2. How are priorities for pharmacovigilance determined in your state and nationally?

3. Please describe how pharmacovigilance is decentralized in Brazil? Are there differences between Federal and State in priorities for postmarket drug safety? How are differences managed?

4. Please describe the relationship between ANVISA and the Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro.

5. Please describe the relationship between Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro and the Health Surveillance Center (CVS), pharmacovigilance units, Brazil’s toxicological centers (CEATOX) and sentinel pharmacies?

6. How are Federal and State responsibilities for pharmacovigilance integrated?


8. Please describe any direct or indirect support Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro receives from IGOs, NGOs, development agencies etc., for pharmacovigilance or strengthening pharmaceutical systems (e.g., pharmacovigilance center/unit infrastructure, budget for pharmacovigilance
activities, HR capacity building, recommendations re: SOPs and regulatory framework, ADR reports, reporting forms, pharmacosurveillance, ADR analysis).

9. Which international tools and norms have been adopted in Brazil pertaining to pharmacovigilance and medicines regulatory policy? Why?

10. How would you rate the influence of global guidelines on the development or modification of existing norms for pharmacovigilance in Brazil (ex. WHO/UNAIDS technical guidance for pharmacovigilance for Global Fund proposals, WHO pharmacovigilance toolkits for antiretrovirals, antimalarials and TB medicines, PAHO/PANDRH Best Practices in Pharmacovigilance for the Americas, ICH standards)?

11. What has been the impact of ANVISA’s current regulatory agenda of social participation, transparency and accountability on pharmacovigilance?

12. Which global standards/norms and guidelines for pharmacovigilance have not been adopted in the last 5 years (e.g., harmonized ADR reporting tools ex. Vigibase)? Why?

13. Describe intended/unintended impact of transnational actor influence on pharmacovigilance/pharmacovigilance policies in Brazil

14. Describe state policies pertaining to identification of ADRs, substandard, and falsified medicines (e.g., spontaneous reporting, cohort event monitoring, targeted spontaneous reporting, clinical trials, post authorization safety studies, summary reports from Uppsala Monitoring Centre, other).

15. Please describe Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro risk communication policies? Can you describe any regional variation (e.g., outreach to rural communities) in risk communication strategies to health professionals & patients?

16. How is pharmacovigilance enforced nationally and in your state?
17. How is the Unidade de Farmacovigilância da Superintendência de Vigilância Sanitária do Estado de Rio de Janeiro funded (ex. public, industry, Public-private partnership)? What percentage of the overall budget is directed to pharmacovigilance?

18. Which stakeholders participate in policy decisions concerning pharmacovigilance in your state and what is their role? (Ex. researchers, health professionals, consumers, academia, pharmaceutical industry)? How is the input of each weighted?

19. Please describe the type of information that is publically available (e.g., data/studies that support drug regulatory approval, withdrawal decisions, committee membership etc.)

- Is there additional information you would like to provide pertaining to pharmacovigilance?
- Can you suggest people knowledgeable about pharmacovigilance that I should speak with from ANVISA, MoH, or the pharmaceutical industry?
Appendix G. Interview guide: County pharmacovigilance official - Kenya

1. Please introduce yourself and provide background on your position and involvement in the County Government. How long have you been in your current position?

2. What are priority areas for postmarket drug safety or pharmacovigilance in your County (ex. strengthening pharmacovigilance systems, improving ADR reporting, establishing active surveillance, reducing county variation in pharmacovigilance capacity, identify poor quality or falsified medicines, other?)

3. How are priorities for pharmacovigilance (postmarket drug safety) determined?

4. If there are differences in National and County priorities for pharmacovigilance, how are they managed?

5. What have you observed (or anticipate) to be the effect of devolution on pharmacovigilance (postmarket drug safety) in your County?

6. How does devolution create opportunities/risks to postmarket drug safety policy, practice and accountability in your County?

7. Please describe the governance structure for the County health authorities pertaining to medicines and pharmacovigilance?

8. What is the County authority and responsibility pertaining to pharmacovigilance? How is it integrated with the National authorities and the Kenya Pharmacy and Poisons Board?

9. How is pharmacovigilance in the public and faith-based health systems integrated in your County?

10. Please describe specific legal provisions in the national medicines legislation pertaining to pharmacovigilance in your County. To whom do the laws apply e.g., pharma, healthcare providers, health facilities, other?
11. How is pharmacovigilance enforced at the county level?

12. Which stakeholders participate in policy decisions concerning pharmacovigilance in your County? Please describe any expert advisory committees to the PPB involved in contributing to pharmacovigilance policies and describe committee representation: donors, researchers, health professionals, consumers, Kenya PPB, pharmaceutical industry? How is the input of each weighted?

13. What direct or indirect has support the County health authority received from been the role of global actors (e.g., WHO, Global Fund, USAID) pertaining to postmarket drug safety policy in your County? How has this changed since devolution? (Examples: policy setting, infrastructure support, HR capacity building, standard operating procedures, guidelines, ADR reporting, etc.)

14. Which standards/guidelines for pharmacovigilance have been adopted or rejected by the County in the last 2 years? Why?

15. Has funding been allocated for pharmacovigilance in the County budget? If so, can you describe the sources for funding (public, industry, donors)?

16. Please rank the following donors according to their importance to pharmacovigilance policies and/or implementation in your County (List the top 3): WHO, Global Fund, MSH, USAID, PEPFAR, Bill & Melinda Gates Foundation, World Bank, UMC-Africa, others (List).

17. How would you rate the influence of donor guidelines on the development or implementation of pharmacovigilance in your County (ex., WHO/UNAIDS technical guidance for pharmacovigilance for Global Fund proposals, WHO pharmacovigilance toolkits for antiretrovirals, antimalarials and TB medicines, MSH toolkit (IPAT) for assessing pharmacovigilance, WHO Good Governance in Medicines Framework,)?
18. Describe intended/unintended impact of global actors’ influence on pharmacovigilance policies in Kenya

19. Please describe risk communication policies in your County? Can you describe any regional variation (e.g., outreach to rural communities) in risk communication strategies to health professionals & patients?

20. Describe policies pertaining to identification and reporting of ADRs, falsified or poor quality medicines in your County.

21. Please describe the type of information that is publically available pertaining to pharmacovigilance policymaking in your County (meeting minutes, data/studies that support drug risk communication, committee membership etc.)

22. Are there written guidelines pertaining to conflict of interest? Are the guidelines publically available?

Conclusion

23. What improvements would you like to see in pharmacovigilace policies/implementation in your County (i.e. future goals)?

24. Is there additional information you would like to provide pertaining to pharmacovigilance?
Appendix H. Interview guide: Multinational corporation

1. Please kindly introduce yourself and provide background on your position and involvement with pharmacovigilance at [INSERT]. How long have you been involved in this position?

2. Describe methods used to by [INSERT] to identify ADRs that may indicate serious safety problems (spontaneous reporting, cohort event monitoring, targeting spontaneous reporting, clinical trial, data mining, other).

3. Describe methods used to identify falsified or poor quality drugs in the supply chain

4. What factors influence decisions to issue a risk communication?

5. How is risk communicated nationally and regionally since devolution and prior to devolution? Please describe any regional variation in risk communication strategies (e.g., outreach to rural communities)?

6. How is pharmacovigilance enforced nationally and at the county level?

7. Are there Risk Management Plans (RMPs) for any of Merck’s medicines marketed in Kenya? Which?

8. Please describe how [INSERT] engages with the Kenya PPB, County Health authorities and faith-based healthcare systems pertaining to pharmacovigilance, prior to and post devolution.

9. Please describe how pharmacovigilance is integrated into [INSERT] corporate governance (e.g., corporate social responsibility, business strategy, drug safety policy, other?)

10. Where is pharmacovigilance located within the governance structure of [INSERT] (i.e. organogram)? (Examples: Pharmacovigilance and Epidemiology (P&E) Dept. reports to the Chief Medical Officer) How does the pharmacovigilance department interact with other departments (e.g., clinical development and regulatory affairs teams and the epidemiology unit)? Is it integrated throughout?)
11. How does staffing and budget for pharmacovigilance compare to other company departments (e.g., R&D)?

12. Please describe the type of information that is publically available (e.g., Corporate Annual Reports, Postmarket requirements (PMR), advisory meetings minutes, risk communication, data/studies that support risk communication decisions, etc.)

13. How does the pharmacovigilance strategy practiced in Kenya compare to Merck parent company policy? Does the Kenya subsidiary adopt all of the Parent company policies (e.g., risk communication, reporting) or are country specific policies adopted? Which standard is followed in Kenya where differences exist?

14. What are [INSERT] priority areas for pharmacovigilance and how are priorities determined?

15. Describe any differences in how [INSERT] (industry), Kenya PPB, and County Health authorities, civil society organizations prioritize pharmacovigilance in Kenya? How have differences been managed?

16. In R&D partnerships for drug development, who is accountable for satisfying any postmarket drug safety requirements? How is accountability determined?

17. Please describe any direct or indirect support that [INSERT] has provided for pharmacosurveillance or strengthening pharmaceutical systems (e.g., pharmacovigilance centre/unit infrastructure, budget for pharmacovigilance activities, HR capacity building, ADR reports, reporting forms, pharmacosurveillance, and ADR analysis) in Kenya.

18. What are barriers to pharmacovigilance in Kenya?

19. What do you consider to be best practices for post-market surveillance of pharmaceutical products?

20. What improvements would you like to make in the way that the [INSERT] engages with national regulatory authorities pertaining to pharmacovigilance?

Please describe.

Conclusion

22. Is there additional information that you would like to add that is relevant to this research of pharmacovigilance in Kenya or corporate governance and pharmacovigilance?

23. Can you recommend others to speak to regarding the domestic or multinational pharmaceutical industry pertaining to pharmacovigilance?
Appendix I. Interview guide: Domestic pharmaceutical company

Empresas farmacêuticas

1. Por favor, você poderia se introduzir e dizer qual é o seu posição e envolvimento com pharmacovigilance em Fiocruz / Farmanguinhos. Há quanto tempo você está nesta posição?

2. Quais são as prioridades de Farmacovigilância e como essas prioridades são determinadas?

3. Por favor, descreva como o Setor de Farmacovigilância do(a) Fiocruz / Farmanguinhos interage com a Anvisa e com os Centros Estaduais de Farmacovigilância. Como esta interação pode ser melhorada/aperfeiçoada?

4. Descreva os métodos usados pelo(a) Fiocruz / Farmanguinhos para identificar RAMs que podem indicar sérios problemas de segurança (notificação espontânea, monitoramento de eventos de coorte, alvo de notificação espontânea, ensaios clínicos, etc).

5. Quais fatores influenciam nas decisões referentes ao tipo de evidencias necessárias para emitir alertas de risco?


7. Como a farmacovigilância é cumprida nacionalmente em comparação a outros estados?

8. Existe algum Plano de Gerenciamento de Risco para os medicamentos do(a) Fiocruz / Farmanguinhos comercializados no Brasil? Qual?

9. Por gentileza, descreva como a farmacovigilância é integrada na governança do(a) Fiocruz / Farmanguinhos (p. ex. responsabilidade social corporativa, estratégia de negócios, a política de segurança de medicamentos, outro).
10. Onde a farmacovigilância é alocada dentro da estrutural de governança do(a) Fiocruz / Farmanguinhos (p. ex. Departamento de Farmacovigilância e Epidemiologia)? Qual é a relação com outros departamentos (p. ex. Pesquisa e Desenvolvimento)? A farmacovigilância é integrada completamente?

11. Qual é a relação de número de empregados e de orçamento para farmacovigilância quando comparados ao setor de P&D e demais setores da companhia?

12. Por favor, descreva o tipo de informação que é disponível publicamente (p. ex. Relatórios Anuais da Companhia, Requerimentos Pós-Comercialização (Postmarket requirements), pautas de reunião de conselho, alertas de risco, dados/estudos que baseiam as decisões sobre os alertas de risco, etc).

13. Descreva o envolvimento das diferentes partes interessadas nas decisões sobre as estratégias de segurança de medicamentos pós-comercialização. Quais partes interessadas participam (p. ex. Anvisa, Ministério da Saúde, planos de saúde, profissionais de saúde, consumidores, outros)?

14. Nas parcerias de P&D para o desenvolvimento de fármacos, quem é responsável por satisfazer todas as exigências de segurança pós-comercialização de medicamentos? Como é determinada esta responsabilidade?

15. O (a) Fiocruz / Farmanguinhos participa da Conferência Pan-Americana para a Harmonização da Regulamentação Farmacêutica (PANDRH- Pan American Network for Drug Regulatory Harmonization)? Por favor, descreva.

16. Por favor, descreva algum apoio direto ou indireto que o (a) Fiocruz / Farmanguinhos tem fornecido para fortalecer o Sistema de Farmacovigilância no Brasil (p. ex. infraestrutura de centros/unidades de farmacovigilância, orçamento para atividades de farmacovigilância, capacitação de RH, relatórios de RAMs, formulários de notificação, análise de RAMs, outros).
17. Descreva o impacto intencional/não intencional do (a) Fiocruz / Farmanguinhos no envolvimento com autoridades reguladoras de medicamentos relacionadas à farmacovigilância no Brasil.

18. Descreva os métodos utilizados para identificar medicamentos falsificados ou de baixa qualidade na cadeia produtiva.

- Existem outras informações adicionais que você gostaria de fornecer que são relevantes à pesquisa sobre corporações e Farmacovigilância no Brasil?
- Você poderia, gentilmente, sugerir outros contatos para que pudéssemos conversar sobre a Farmacovigilância na indústria farmacêutica nacional e multinacional?

Para a sua conveniência, incluímos a seguir o questionário na versão em INGLÊS. As perguntas são as mesmas apresentadas em Português e podem auxiliá-lo (a) a melhor entender as questões caso a tradução em Língua Portuguesa não tenha sido clara.

**Interview Guide: Domestic Pharmaceutical Companies**

1. Please kindly introduce yourself and provide background on your position and involvement with pharmacovigilance at Fiocruz / Farmanguinhos. How long have you been involved in this position?

2. What are priority areas for pharmacovigilance and how are priorities determined?

3. Please describe how Fiocruz / Farmanguinhos interacts with the ANVISA, state *Centros de Farmacovigilância*. How can these interactions be improved?

4. Describe methods used to by Fiocruz / Farmanguinhos to identify ADRs that may indicate serious safety problems (spontaneous reporting, cohort event monitoring, targeting spontaneous reporting, clinical trial, data mining, other).
5. What factors influence decisions pertaining to the type of evidence needed to issue a risk communication?

6. How is risk communicated nationally versus regionally? Please describe any regional variation in risk communication strategies (e.g., outreach to rural communities)?

7. How is pharmacovigilance enforced nationally as compared to each state?

8. Are there risk management plans (RMPs) for any of Fiocruz / Farmanguinhos medicines marketed in Brazil? Which?

9. Please describe how pharmacovigilance is integrated into Fiocruz / Farmanguinhos governance (e.g., corporate social responsibility, business strategy, drug safety policy, other?)

10. Where is pharmacovigilance located within the governance structure of Fiocruz / Farmanguinhos? (e.g., Pharmacovigilance and Epidemiology (P&E) Dept.)? What is its relationship to other departments (e.g., R&D)? Is PV integrated throughout?

11. How does staffing and budget for pharmacovigilance compare to R&D and other company departments?

12. Please describe the type of information that is publically available (e.g., Corporate Annual Reports, Postmarket requirements (PMR), advisory meetings minutes, risk communication, data/studies that support risk communication decisions, etc.)

13. Describe stakeholder involvement in decisions concerning postmarket drug safety strategies. Which stakeholders participate (ex. ANVISA, MoH, drug benefit plan managers, health professionals, consumers, others)?

14. In R&D partnerships for drug development, who is accountable for satisfying any postmarket drug safety requirements? How is accountability determined?

15. Does Fiocruz / Farmanguinhos participate in the Pan American Network for Drug Regulatory Harmonization (PANDRH)? Please describe.
16. Please describe any direct or indirect support that Fiocruz / Farmanguinhos has provided to strengthen pharmaceutical systems in Brazil (e.g., pharmacovigilance centre/unit infrastructure, budget for pharmacovigilance activities, HR capacity building, ADR reports, reporting forms, pharmacosurveillance, and ADR analysis).

17. Describe intended/unintended impact of Fiocruz / Farmanguinhos engagement with drug regulatory authorities pertaining to pharmacovigilance in Brazil.

18. Describe methods used to identify falsified or poor quality medicines in the supply chain

• Is there additional information that you would like to add that is relevant to this research of corporations and pharmacovigilance in Brazil?

• Can you recommend others to speak to regarding the domestic or multinational pharmaceutical industry and pharmacovigilance?
Appendix J. Interview guide: IGO or INGO representative

1. Kindly introduce yourself and provide background on your position with [IGO/INGO] and experience with pharmacovigilance/pharmaceutical policies. How long have you been in your current position?

2. Please provide a brief history of [IGO/INGO] role in pharmacovigilance in Kenya [Brazil].

3. What have been [IGO/INGO] priority areas for postmarket drug safety?

4. How are priorities for pharmacovigilance (postmarket drug safety) determined?

5. Please describe the nature of [IGO/INGO] engagement with the Kenya Pharmacy and Poisons Board (PPB) [ANVISA]


7. Please describe the [IGO/INGO] experience in Kenya [Brazil] to address disease-focused systems for pharmacovigilance and pharmacosurveillance of ARVs, TB and malaria medicines.

8. Please describe the intended/unintended impact of [IGO/INGO] engagement on pharmacovigilance/pharmacovigilance policies in Kenya [Brazil]

9. How would you rate the effectiveness of the [IGO/INGO] technical guidelines and pharmacovigilance assessment tools (e.g., IPAT) on the development or modification of existing pharmacovigilance norms/practices in Kenya [Brazil]?

10. What has been the uptake and utilization of pharmacovigilance tools developed by [IGO/INGO] (e.g., the Indicator-Based Pharmacovigilance Assessment Tool) in Kenya [Brazil]? Has an assessment of Kenya [Brazil] been conducted?
11. Please describe any direct or indirect support that [IGO/INGO] provides to the medicines regulatory authority for pharmacovigilance or strengthening pharmaceutical systems (e.g., pharmacovigilance centre/unit infrastructure, budget for pharmacovigilance activities, HR capacity building, ADR reports, reporting forms, pharmacosurveillance, and ADR analysis).

12. Please describe specific legal provisions or national medicines legislation for pharmacovigilance, that [IGO/INGO] has recommended for adoption in Kenya [Brazil].

13. Please describe standard operating procedures or norms for pharmacovigilance that [IGO/INGO] has recommended for adoption in Kenya [Brazil].

14. Please provide specific examples and list in order of perceived importance/impact, [IGO/INGO] support for pharmacovigilance in Kenya [Brazil]

15. Please describe the governance structure of the [IGO/INGO] in Kenya [Brazil]?

16. To what extent are various stakeholders such as the pharmaceutical industry, national regulatory authorities, county governments, health professionals, researchers and consumers engaged in [IGO/INGO] decisions concerning pharmacovigilance? How is the input of each weighted?

17. If there are differences priorities of stakeholders, how are the differences in priorities managed?

18. Please describe the type of information that is publically available (e.g., minutes for meetings, committee membership and written guidelines pertaining to conflict of interest etc.)

19. Please describe any interactions or collaboration with other global actors pertaining to pharmacovigilance in Kenya [Brazil]

20. What improvements would you suggest in the way that [IGO/INGO] engages with national regulatory authorities pertaining to pharmacovigilance?
21. Describe methods promoted by [IGO/INGO], to identify ADRS/serious safety problems (spontaneous reporting, cohort event monitoring, targeting spontaneous reporting, clinical trial, data mining, other).

22. Describe methods promoted by [IGO/INGO] to identify falsified or substandard drugs in the supply chain

23. What do you consider to be best practices for postmarket surveillance of pharmaceutical products?

24. Is there additional information that you would like to add that is relevant to this area?
## Appendix K. Governance and pharmacovigilance codebook

<table>
<thead>
<tr>
<th>Patterns of interactions</th>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
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| **Autonomy**             |      | Self-governing or acting independently. | *So that’s the thing with devolution. You can make the decision. You don’t have to wait for somebody to tell you what you do if this or that.*  
Yeah, It’s quite complicated for faith-based organizations, at least for the Catholic church. They have their own system. |
| **Advocacy**             |      | *Motivates change in policies, priorities and/or resource allocation* to advance pharmacovigilance | *The country can identify it [pharmacovigilance] as a priority but if it had not been an important focus area from Washington, then it becomes difficult for the local region to get sufficient resources for it. For pharmacovigilance, getting the issue up in Kenya has required a lot of strong backing from USAID Washington.* |
| **Collaborative**        |      | *Formal or non-structured partnerships* for the joint development of programs, policies, and pharmacovigilance | *[The standard operating procedures and guidelines were] jointly developed by the USAID implementing partner AND government along with the PPB.* |
| Conflict of interest/cross purpose interests | Individual, institutional, or government intents that produce behavioural or regulatory impediments to pharmacovigilance. | Policies have to be passed concerning medicines and there are several people with their interests that won’t allow it to go through. |
| Consultative | Engages external advisors in pharmacovigilance decision-making. | So you want to work closely with the County Directors of Health, the County pharmacists so that you can get more information from them. And share with them what you are seeing in other counties because they will only see what is available in the county. |
| Contractual | **Contracted services** to strengthen pharmacovigilance. May comprise outsourcing a specific activity (e.g., training, active surveillance study, regulatory functions), or secondment of personnel. | And so as a contractor we have to respect what the management and the Board does. They give us a modest amount of money... and we have to account for it and report to them. |
| Cooperative | Agreement made between federal, state, county, or | \[B]ilateral cooperation is agreed among the countries. We may or may not take |
global actors to **work together or jointly support a specific issue.**

**Delegative**
Gives oversight of pharmacovigilance activities to another entity or group (e.g., national regulatory authority to county/state dept. of health; MoH to NGO; nurses to pharmacists).

*The staff in the county, they’re mostly drug inspectors; there are no pharmacovigilance case [workers]. So in case the [regulatory authority] wants to conduct pharmacovigilance they will contact me to coordinate the activities in Coast region.*

**Fragmented**
Interrelated PV responsibilities and overlapping functions with limited integration of PV activities and accountability.

*The nationwide deals essentially with policy and sometimes inspections. Here in the state I deal specially with industries. The city government does inspections. City government, not state government [deals directly with consumer issues] so it can’t go to the state directly related to consumers.*

**Hierarchical**
Organized according to a series of levels with different importance or status, each subordinate to the one above it.

*[B]ecause as a global group I don’t report here. My director is based in headquarters. I have a dotted line to the country manager but my group reports directly to headquarters.*

**Pharmacogovernance Domains**
<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accountability</td>
<td>Taking responsibility for individual or organizational activities. This would include activities to advance postmarket drug safety. Sharing information and operating in a manner that makes it easy for others to see what actions have occurred.</td>
<td><em>We would not hesitate to immediately inform the Pharmacy and Poisons Board via official letter and depending on the situation, sit down immediately with them and tell them this is what we have or come across and this is what we need to kind of work on.</em></td>
</tr>
<tr>
<td>and Transparency</td>
<td></td>
<td><em>I can say minutes of meetings, they are publicly available. Even the data that we report it is available, at least to health workers.</em></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>The capacity to evaluate the utility of pharmacovigilance policies and monitor pharmaceutical industry compliance with policy, law and regulation pertaining to postmarket drug safety.</td>
<td><em>We did a lot of new things in a very simple manner. We made sure that deliberately we cut down on all the red tape. You can imagine, in a government office, they have tons of red tape. But we made sure that we overcame this as a barrier to our benefit, alright...so we can bring that...much faster, as close to the patient as possible.</em></td>
</tr>
<tr>
<td>and Efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethics</td>
<td>The fair and impartial enforcement of national pharmacy policy and national pharmacovigilance</td>
<td><em>Basically the only pharmacovigilance available to other sectors is identifying substandard drugs...Our system has not advanced beyond that.</em></td>
</tr>
<tr>
<td>Equity and inclusiveness</td>
<td>Spaces for public participation in pharmacovigilance policy setting are accessible to all segments of the population (Inclusiveness).</td>
<td>Public participation in the field of regulation enables greater credibility to the regulatory process...</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Economic and human resource allocation to ensure that all regions within the country have access to safe medicines and resources to detect and act on drug safety signals (Equity).</td>
<td>The issue is to assure the provision of human resources to cover all the country and to assure the performance, the quality performance. And also to keep the central reporting and actively and engaging all of the actors.</td>
<td></td>
</tr>
<tr>
<td>Intelligence and Information</td>
<td>Databases and mechanisms to improve communication between national regulatory authorities, state pharmacovigilance centres, patients, healthcare professionals, policymakers and the general public with respect to supporting safe use of</td>
<td>They fill the form online and then send to the Pharmacy and Poisons Board. We have software- let me show it to you. So individual hospitals if they found poor quality medicine, they will go online and they fill in the form. One you can use your smart phone if you...</td>
</tr>
<tr>
<td>Participation and Representation</td>
<td>Involvement in decision making by the public at regulatory authority and government public meetings pertaining to setting the regulatory agenda and rules for postmarket drug safety.</td>
<td>Generally none! Social participation is defined as public consultation but there is little information.</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Policy, Law, and Regulation</td>
<td>Laws, bills, and resolutions intended to support the regulatory authority mandate to assure access to safe medicines, health products and services.</td>
<td>There’s no explicit law that will tell you that [requires] a pharmacovigilance system but we already have a law says that you have to assure quality, safety and efficacy.- Kenya</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As I said, regulation is the key IF the regulation is transparent and taking action. What I mean by taking action? There has to be some sort of discipline. And that may bring in self-regulation.—Kenya domestic drug company</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>Act to adopt pharmacovigilance policies/regulations and/or</td>
<td>So I write to [the health authority] and ask would you mind following the PSUR schedule as per the European Union?</td>
</tr>
</tbody>
</table>
| Stakeholder Coordination | address drug safety issues within a reasonable time frame. | And there wasn’t a problem at all. So they follow the EU schedule. 

We would immediately move to change our label- update our label. Inform the relevant authorities where this product is registered that this is what we are now seeing. If there is a risk management plan that needs to be put in place then we will do that. |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Domestic and global actors coordinate activities for the purpose of strengthening the national regulatory authority and human resources to benefit pharmacovigilance.</td>
<td>[T]hey send you their comments. We look at the comments, see that they make sense or not. Then after that …Cause we cannot do a guideline without the input from the stakeholders. We even require that in our constitution. Anything that is going to affect your stakeholders, it is important that you get input from them.</td>
<td>- Kenya</td>
</tr>
</tbody>
</table>
### Appendix L. Scoping review search terminology

1. Non-state actor and priorities and pharmacovigilance and Brazil  
2. Non-state actor and pharmacovigilance and governance and Brazil  
3. Non-state actor and transparency and pharmacovigilance and Brazil  
4. Transnational actor and priorities and pharmacovigilance and Brazil  
5. Transnational actors and pharmacovigilance and governance in Brazil  
6. Transnational actor and priorities and transparency and pharmacovigilance and Brazil  
7. Intergovernmental priorities and pharmacovigilance and Brazil  
8. Intergovernmental agency and pharmacovigilance and governance and Brazil  
9. Intergovernmental agency and transparency and pharmacovigilance and Brazil  
10. Global governance and pharmacovigilance in Brazil  
11. Global governance and pharmacovigilance and governance and Brazil  
12. Global governance and transparency and pharmacovigilance and Brazil  
13. International institutional influence and pharmacovigilance and Brazil  
14. International institutional influence and pharmacovigilance governance and Brazil  
15. International institutional influence and transparency and pharmacovigilance and Brazil  
16. Pharmacovigilance and Brazil  
17. Pharmacovigilance and Brazil and transparency  
18. Pharmacovigilance and Brazil and governance  
19. Pharmacovigilance and Brazil and transparency and governance  
20. Pharmacovigilance and Brazil and corruption  
21. Pharmacovigilance and Brazil and Global Fund  
22. Pharmacovigilance and Brazil and WHO  
23. Pharmacovigilance and Brazil and World Health Organization  
24. Pharmacovigilance and Brazil and Gates Foundation  
25. Pharmacovigilance and Brazil and DFID  
26. Pharmacovigilance and Brazil and international development  
27. Pharmacovigilance and Brazil and World Bank  
28. Pharmacovigilance and ANVISA  
29. ANVISA and Global Fund  
30. ANVISA and World Health Organization  
31. ANVISA and WHO  
32. ANVISA and World Health Organization and pharmacovigilance  
33. ANVISA and Gates Foundation  
34. ANVISA and ICH  
35. Pharmacovigilance and Brazil and ICH  
36. Pharmacovigilance and Brazil and Fiocruz  
37. Pharmacovigilance and Brazil and DNDi  
38. Pharmacovigilance and Brazil and USAID  
39. Pharmacovigilance and Brazil and PAHO  
40. Pharmacovigilance and Brazil and Sanofi  
41. Pharmacovigilance and Brazil and Merck  
42. Pharmacovigilance and Brazil and PEPFAR  
43. Pharmacovigilance and Brazil and UK Department for International Development  
44. ANVISA and corruption  
45. ANVISA and transparency  
46. ANVISA and governance  
47. Medicine safety and Brazil and policy  
48. Drug safety and Brazil and policy  
49. Drug safety and Brazil and governance  
50. Drug safety and Brazil and transparency  
51. Drug safety and Brazil and “pharmaceutical industry”  
52. Drug safety and Brazil and pharma  
53. Pharmacovigilance and Brazil and policy  
54. Pharmacovigilance and ANVISA and policy  
55. Pharmacovigilance and Brazil and policy and World Health Organization  
56. Pharmacovigilance and Brazil and policy and Gates Foundation  
57. Pharmacovigilance and Brazil and policy and World Bank  
58. Pharmacovigilance and Brazil and policy and Fiocruz  
59. Pharmacovigilance and Brazil and policy and Global Fund  
60. Drug safety and Brazil and policy and Global Fund  
61. Drug safety and Brazil and civil society  
62. Pharmacovigilance and Brazil and PAHO  
63. Pharmacovigilance and Brazil and Pan American Health Organization
## Appendix M. Global institutions pharmacovigilance norms adopted in Brazil

<table>
<thead>
<tr>
<th>Norm</th>
<th>BRAZIL</th>
<th>WHO</th>
<th>UNAIDS</th>
<th>PAHO/PANDRH</th>
<th>Global Fund</th>
<th>OECD</th>
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<td>Risk identification and assessment</td>
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<td>UMC member</td>
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<td>X^b</td>
<td>X^b</td>
<td>X^c</td>
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<td>(62nd member)</td>
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<td>Spontaneous reporting^i</td>
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<td>X^a</td>
<td>X^b</td>
<td>X^c</td>
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<tr>
<td>Cohort Event Monitoring^ii</td>
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<td>X^a</td>
<td>X^b</td>
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<tr>
<td>Targeted Spontaneous Reporting^iii</td>
<td>---</td>
<td>X^a</td>
<td>X^b</td>
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<td>Signal generation &amp; data management</td>
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<td>ADR reporting forms</td>
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<td>X^b</td>
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<td>X^c</td>
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<td>X^c</td>
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<td>Brazilian National Medicines Monitoring Centre (CNMM)</td>
<td>Ministerial decree No. 696, of 5/7/2001 (2001)</td>
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<td>X^b</td>
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<td>Center for Drug Surveillance (NVF)-Health Surveillance Center</td>
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<td>(CVS) of the São Paulo Dept. of Health</td>
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<td>Pharmacovigilance Unit (UFARM)</td>
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<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>(Coordinates the NPS and houses the National Drug Monitoring Centre)</td>
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<td>Sentinel reporting sites</td>
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<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Adverse events management guidelines</td>
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<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Rational use of medicines</td>
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<td>Human resources</td>
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<td>Pharmacovigilance integrated into national curricula</td>
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<td>Pharmacovigilance expertise</td>
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<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
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<td>Access to training in the country and abroad</td>
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<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>X</td>
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</tr>
<tr>
<td>Policy, law, and regulations</td>
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<td>National drug surveillance</td>
<td>Ministerial Decree No. 696/01 2001</td>
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<td><strong>Federal Constitution</strong></td>
<td>1988</td>
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<td>The Organic Law of Health and National pharmacovigilance policy</td>
<td>Law 8,080/90</td>
<td>1991</td>
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<td>Mandatory postmarket surveillance of pharmaceuticals and industry reporting</td>
<td>Law 6.360 article 79 1976</td>
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<td></td>
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<td>Law n.º 6.360/76 article 79</td>
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<td>Importer/exported reporting of ADRs required</td>
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<td></td>
<td></td>
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<td>Mandatory ADR reporting by health professionals</td>
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<td></td>
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<td>Stakeholder coordination</td>
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<td>Pharmacovigilance system strengthening (^1)</td>
<td>---</td>
<td><strong>X</strong>(^b)</td>
<td><strong>X</strong>(^b)</td>
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<td><strong>X</strong>(^c)</td>
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<td>Regulatory Governance</td>
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<td>Good Regulatory Practices Program</td>
<td>Ordinance n° 422, April 2008</td>
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<td>Regulatory policy monitoring and evaluation</td>
<td>Bill 3.337/04 2004</td>
<td></td>
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<td>(Regulatory Agenda)</td>
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</table>
| Transparency\(^e\)  
• Supply chain management (GGM) \(^1\) | Decree n° 5.482, June 2005 |  |  | **X**\(^{abd}\) |  | **X**\(^c\) |
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<th>Risk mitigation decisions</th>
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<td>Civil Society/public sector participation iv</td>
<td>Laws 8.080 Art. 7 VIII and 8.142, 1990</td>
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<td>Public forums</td>
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<td>Codes of ethics to prevent corruption</td>
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<tr>
<td>Regulatory impact analysis deployed as part of PMR</td>
<td></td>
<td>2003h</td>
</tr>
</tbody>
</table>

Source:


Endnotes

i Health professionals reporting: voluntary, Industry reporting: mandatory (Law 6360 art.79)

ii A prospective, observational, cohort study of adverse events associated with one or more medicines.

iii Healthcare professional screens for ADRs at each routine patient encounter.

iv Public consultation is pursuant to Ordinance 354/2006 art 51
Appendix N. Global institutions pharmacovigilance norms adopted in Kenya

<table>
<thead>
<tr>
<th>Norm</th>
<th>KENYA</th>
<th>WHO</th>
<th>UNAIDS</th>
<th>Global Fund</th>
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<td>Risk identification and assessment</td>
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<td>UMC member</td>
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<td>Spontaneous reporting</td>
<td>X</td>
<td>X^a</td>
<td>X^b</td>
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<td>Cohort Event Monitoring</td>
<td>X</td>
<td>X^a</td>
<td>X^b</td>
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<td></td>
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<td>Targeted Spontaneous Reporting</td>
<td>X</td>
<td>X^a</td>
<td>X^b</td>
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<td>Signal generation &amp; data management</td>
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<td>Database to receive, collate, manage, and analyze ADR reports</td>
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<td>X^b</td>
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<td>Pharmacovigilance Unit (within</td>
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<td>the Directorate of Medicines Information and Pharmacovigilance)</td>
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<td>System</td>
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<td>Mandatory postmarket surveillance of pharmaceuticals and industry reporting</td>
<td>Pharmacy and Poisons Act, Cap 244, 1957 Revised Edition 2012 [1989] (surveillance only)</td>
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<td>• Public forums • Donor/IGO/NGO</td>
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- Regulatory impact analysis deployed as part of PMR

Source:


i A prospective, observational, cohort study of adverse events associated with one or more medicines.

ii Healthcare professional screens for ADRs at each routine patient encounter.

iii ADR reports submitted to WHO-UMC for analysis
Copyright Acknowledgements