Addressing Variability in Drug Quality: Finding The Right “Quality” Framework(s)

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science.

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University of Toronto

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2012

Abstract

**Background:** In many countries, a significant proportion of medicines traded and consumed are of poor or variable quality. Meanwhile, failures in appropriately framing and responding to the problem have led to a proliferation of public health and governance challenges.

**Objective:** To examine the issues exacerbating the trade and consumption of medicines of poor or variable quality, as well as present locally relevant strategies.

**Methods:** Analytic triangulation was applied to the synthesis of publicly available documents.

**Results:** Where economic and regulatory environments are less structured, supply chain security strategies that fixate on ‘counterfeits’ often fail in limiting the prevalence of poor quality medicines. In addition to a multivariate drug quality classification chart, three quality frameworks are presented for examining appropriate policy strategies in mediating drug quality.

**Conclusion:** These tools can assist stakeholders in determining more locally relevant and context-specific strategies, while interrogating the proposition for greater transparency vis-à-vis drug quality.
Acknowledgments

"Nearly all men die of their medicines, not of their diseases."

Molière (1622-73)

The genesis of this dissertation can be traced back to 2008, where a stimulating discussion with two professors provoked a literal interpretation of the French playwright's famous épigramme in *Le malade imaginaire*. It is difficult to overstate my gratitude to those two professors, Drs. Peter Pennefather and Jillian Kohler, for sparking and subsequently agreeing to supervise what has been an immeasurably enriching intellectual and personal journey.

With your boundless cerebral breadth, animated curiosity, and inexhaustible support, a student could not have asked for a better pedagogue and mentor, Peter. Our long discussions and occasional intellectual detours with Dr. West Suhanic catalyzed pivotal moments of clarity in what sometimes felt like an interdisciplinary tug-of-war. Likewise, Jillian, your candid style, uncompromising standards and spirited guidance were central, helping me become a better researcher and focusing my ideas. I was also privileged with an enviable thesis advisory committee in Drs. Halla Thorsteinsdóttir and Manny Papadimitropoulos: your constructive feedback and revisions, as well as your constant encouragement were instrumental.

I moreover remain deeply indebted to Dr. James Orbinski, whose unyielding moral and intellectual integrity and extraordinary trust over the years have been a profound source of motivation, intellectually and personally. The opportunity to continue my doctoral studies under your tutelage in Waterloo is at once humbling and tremendously exciting. I owe sincere gratitude additionally to the many mentors I have had the pleasure of studying under over the years, including Graham Bye, Drs. Richard Lee, Paul Hamel and Janice Stein.

The entire cast of Universities Allied for Essential Medicines furthermore deserves my eternal appreciation and affection, not least for their infectious optimism, coupled with the unimaginable breadth and depth of knowledge among its intimidatingly accomplished members. For allowing me to imagine, learn and laugh over access to medicines and beyond, I think each of you, with special gratitude to Ethan, Rachel and Sunny.

My final words go to my family and friends, as in this type of work the loved ones are always mistreated. For embracing my insufferable idiosyncrasies and lavishing me with your inexhaustible love and support, Marianna, I love you. While the encouragement and support of many friends has been indispensable, I would like to particularly acknowledge Binesh, Louis and Kouros for always reminding me of the power of ideas, values and imagination, respectively. A kid honestly could not have asked for better friends.

Last but certainly not least, I remain eternally indebted to my infinitely loving and forgiving family: for the endless sacrifices you continue to make; for reminding me to always remain proud, yet maintain humility; for stimulating my curiosity and love of the abstract; and most importantly, for serving as living examples that dialogue, as Paulo Freire once said, is indeed the “essence of revolutionary action.” Thank you all from the bottom of my heart.
# Table of Contents

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract ........................................................................................................ ii</td>
</tr>
<tr>
<td>Acknowledgments .......................................................................................... iii</td>
</tr>
<tr>
<td>Table of Contents ....................................................................................... iv</td>
</tr>
<tr>
<td>List of Tables and Figures .......................................................................... vi</td>
</tr>
<tr>
<td>List of Abbreviations .................................................................................. vii</td>
</tr>
<tr>
<td><strong>Chapter One – Introduction</strong> ................................................................. 1</td>
</tr>
<tr>
<td>1.1 Research Problem .................................................................................... 1</td>
</tr>
<tr>
<td>1.2 Study Objective ...................................................................................... 5</td>
</tr>
<tr>
<td>1.3 Organization of Thesis ........................................................................... 5</td>
</tr>
<tr>
<td>1.4 References .............................................................................................. 9</td>
</tr>
<tr>
<td><strong>Chapter Two – Literature Review: Variability in Drug Quality</strong> ............... 11</td>
</tr>
<tr>
<td>2.1 Drug Regulation and Quality Control .................................................. 12</td>
</tr>
<tr>
<td>2.1.1 The Consequences of Variability in Drug Quality ............................... 15</td>
</tr>
<tr>
<td>2.2 The Scale and Scope of Poor Quality Medicines .................................... 19</td>
</tr>
<tr>
<td>2.2.1 Determining the Scale of the Problem .............................................. 24</td>
</tr>
<tr>
<td>2.2.2 Estimates in the Literature of the Scale of the Problem ...................... 27</td>
</tr>
<tr>
<td>2.3 How Have the Various Stakeholders Framed and Responded to the Problem? .... 30</td>
</tr>
<tr>
<td>2.3.1 The World Health Organization ....................................................... 32</td>
</tr>
<tr>
<td>2.3.2 The International Medical Products Anti-Counterfeiting Taskforce .......... 33</td>
</tr>
<tr>
<td>2.3.3 High-Income Countries ...................................................................... 41</td>
</tr>
<tr>
<td>2.3.4 Low- and Middle-Income Countries .................................................... 48</td>
</tr>
<tr>
<td>2.3.5 Multi-National Pharmaceutical Companies ......................................... 57</td>
</tr>
<tr>
<td>2.4 Conclusion .............................................................................................. 59</td>
</tr>
<tr>
<td>2.5 References .............................................................................................. 60</td>
</tr>
<tr>
<td><strong>Chapter Three – Research Methodology</strong> ................................................ 69</td>
</tr>
<tr>
<td>3.1 Research Limitations .............................................................................. 73</td>
</tr>
<tr>
<td>3.2 References .............................................................................................. 75</td>
</tr>
</tbody>
</table>
Chapter Four – Results: Vulnerabilities in Pharmaceutical Supply Chains .... 76

4.1 Vulnerabilities in Drug Supply Chains: High-Income Countries .............................. 77
   4.1.1 Globalization of Supply Chains for Drugs and Raw Ingredients ........................ 78
   4.1.2 Proliferation of Online Pharmacies .................................................................. 81
4.2 Vulnerabilities in Drug Supply Chains: Low- and Middle-Income Countries ...... 83
   4.2.1 Factors Exacerbating the Drug Access Gap ......................................................... 83
   4.2.2 Drug Regulatory Capacity Gaps ....................................................................... 88
   4.2.3 Informal Markets ............................................................................................. 89
4.3 Conclusion .............................................................................................................. 93
4.4 References ............................................................................................................. 94

Chapter Five – Results: Information Asymmetries & Defining Drug Quality .. 99

5.1. Asymmetries in Information Economics ................................................................. 102
   5.1.1 Informal Markets and Information Asymmetries ................................................. 104
   5.1.2 The Concept of Trust in Health Systems .......................................................... 107
5.2 Quality and Counterfeits: What Are We Measuring? ............................................... 109
   5.2.1 A New Taxonomy for Drug Quality ................................................................. 112
5.3 Deconstructing the Drug Quality Concept ............................................................ 117
   5.3.1 Systems Theory and Rational Control ............................................................. 118
5.4 Conclusion .............................................................................................................. 120
5.5 References ............................................................................................................. 121

Chapter Six – Discussion: Finding the Right Quality Framework ............... 126

6.1 Quality-by-Enforcement ......................................................................................... 126
   6.1.1 Limitations of the Quality-by-Enforcement Framework .................................... 129
6.2 Quality-by-Regulation ......................................................................................... 130
   6.2.1 Strengthening Regulatory Capacity against Poor Quality Medicines ................ 132
6.3 Quality-by-Evaluation ......................................................................................... 136
   6.3.1 Forensic Non-Destructive Drug Quality Evaluation Technology ...................... 137
6.4 References ............................................................................................................. 141

Chapter Seven – Conclusions and Future Directions ................................. 144

7.1 Policy Implications .............................................................................................. 147
7.2 Future Directions ............................................................................................... 149
# List of Tables and Figures

<table>
<thead>
<tr>
<th>Table/Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1</td>
<td>Defining Counterfeit, Substandard, Spurious and Falsely-Labeled Medicines</td>
<td>22</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Vulnerabilities of Drug Supply Chains: High-Income Countries</td>
<td>78</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Vulnerabilities of Drug Supply Chains: Low- and Middle-Income Countries</td>
<td>87</td>
</tr>
<tr>
<td>Table 5.1</td>
<td>Classification of Drug Quality Based on Material Quality and Distribution</td>
<td>112</td>
</tr>
<tr>
<td>Figure 6.1</td>
<td>Quality-by-Enforcement</td>
<td>127</td>
</tr>
<tr>
<td>Figure 6.2</td>
<td>Quality-by-Regulation</td>
<td>131</td>
</tr>
<tr>
<td>Figure 6.3</td>
<td>Quality-by-Evaluation</td>
<td>137</td>
</tr>
</tbody>
</table>
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
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<tr>
<td>CDSCO</td>
<td>Central Drugs Standard Control Organization</td>
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<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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<tr>
<td>ICE</td>
<td>Immigration and Customs Enforcement</td>
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<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturer’s Association</td>
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<tr>
<td>IMPACT</td>
<td>International Medicines Product Anti-Counterfeiting Taskforce</td>
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<tr>
<td>INTERPOL</td>
<td>International Criminal Police Organization</td>
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<tr>
<td>IPR</td>
<td>Intellectual property right</td>
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<tr>
<td>GDP</td>
<td>Good Distribution Practices</td>
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<td>GMP</td>
<td>Good Manufacturing Practices</td>
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<tr>
<td>GPP</td>
<td>Good Pharmaceutical Practices</td>
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<td>MDG</td>
<td>Millennium Development Goals</td>
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<td>MeTA</td>
<td>Medicines Transparency Alliance</td>
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<td>NAFDAC</td>
<td>Nigerian Food and Drug Administration</td>
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<td>NMRA</td>
<td>National Medicinal Regulatory Authority</td>
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<tr>
<td>PSI</td>
<td>Pharmaceutical Security Institute</td>
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<tr>
<td>RAS</td>
<td>Rapid Alert System</td>
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<tr>
<td>RCMP</td>
<td>Royal Canadian Mounted Police</td>
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<tr>
<td>RFID</td>
<td>Radio Frequency Identification</td>
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<tr>
<td>TRIPS</td>
<td>Agreement on Trade-Related Aspect of Intellectual Property Rights</td>
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<td>UN</td>
<td>United Nations</td>
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<td>US FDA</td>
<td>United States Food and Drug Administration</td>
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<td>USP</td>
<td>United States Pharmacopeia</td>
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<td>WCO</td>
<td>World Customs Organization</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WTO</td>
<td>World Trade Organization</td>
</tr>
</tbody>
</table>
CHAPTER ONE

Introduction

1.1 Research Problem

According to the World Health Organization (WHO, 2011a), more than US$5.3 trillion is spent on health services worldwide each year; pharmaceuticals are estimated to account for 25%, or $1.3 trillion, of this sum. Nonetheless, access to safe and effective medicines remains highly variable globally (WHO, 2011b; Newton et al, 2011). Based on the latest data from 2006, for example, high-income countries accounted for over 78.5% of global pharmaceutical expenditures, while representing only 46 countries, or 16% of the world’s population (WHO, 2011b).1 Low- and middle-income countries, on the other hand, representing almost 85% of the world’s population, only accounted for 21.5% of global pharmaceutical expenditures (ibid).

Even when medicine can be acquired and consumed, however, their quality and the therapeutic effects they produce can vary tremendously, disproportionately affecting low- and middle-income countries where capacity to regulate the pharmaceutical supply chain is often more limited (WHO, 2006; IMPACT, 2011; Caudron et al, 2008). One of the most significant causes of therapeutic inconsistency is variability in drug quality, which can subsequently lead to critical public health challenges. In addition to inconsistency in

---

1 WHO has adopted the country classification of the World Bank, wherein the main criterion for classifying economies is gross national income (GNI) per capita. The World Bank's (2011) analytical income categories - low-, middle-, high-income - are based on its operational lending categories. The latter were established based on the view that since poorer countries deserve better conditions from the World Bank's International Bank for Reconstruction and Development, comparative estimates of economic capacity needed to be established. For this reason, gross national income per capita, a broad measure, was considered to be the best single indicator of economic capacity and progress.
therapeutic effects, drug quality variability can exacerbate the burden of disease, promote emergence of resistance to available treatments, and moreover cause unnecessary death and suffering (WHO, 1999; Wertheimer and Norris, 2009; Newton et al, 2011). Limited health resources may moreover be wasted on poor quality products, while therapeutic failures may lead patients to experience a loss of confidence in health professionals, local health system, as well as in pharmaceutical products and brands (Guatam, Utreja and Singal, 2008).

In many higher-income countries, capital and human resource investments within extensive regulatory and quality assurance agencies have contributed to a highly regulated pharmaceutical supply chain (Wertheimer and Norris, 2009). In these markets, this has resulted in minimized exposure to medicines that may have a composition or quality outside the range specified in national pharmacopeias. According to the WHO’s International Medical Products Anti-Counterfeiting Taskforce (IMPACT, 2011), the most reliable data suggest that poor quality pharmaceuticals represent less than 1-2% of medicines within the supply chains of high-income countries.

In low- and middle-income countries, however, a large segment of the population – at least one third, and as high as one in two – lack regular access to essential medicines (WHO, 2011c). Limited access to life-saving medicines by up to two billion people has contributed to the emergence of informal supply networks for pharmaceuticals that are difficult to regulate, presenting many opportunities for misunderstanding of what is being acquired (Outterson and Smith, 2006; Pennefather et al, 2010). The WHO (2004) moreover estimates that five out of six of its member-states do not have adequate drug regulatory capacity, resulting in high levels of uncertainty in the composition and quality of medicines used within poorly regulated markets. There is increasing evidence that a large proportion of
pharmaceuticals acquired in such markets are of indeterminate and potentially poor quality, with IMPACT (2011) estimates of poor quality medicines in circulation ranging from 25% to upwards of 50% in highly vulnerable and inadequately regulated regions of low- and middle-income countries (WHO, 2006).

While the infrastructural distinctions and constraints between highly regulated and poorly regulated markets are pronounced, resulting in greater informal markets in the latter, efforts at limiting access to medicines of poor quality have, up to recently, fixated principally on the problem of drug “counterfeiting” (Mackey and Liang, 2011; Morris and Stevens, 2006; Newton et al, 2011). Advanced by trade and law enforcement perspectives in higher income countries as well as multi-national pharmaceutical companies, defining the problem as one of drug counterfeiting has prioritized “intent to deceive,” providing an opportunity for confusion between drugs that are deliberately faked, and possible failures in good manufacturing or distribution practices that may inadvertently lead to making poor quality medicines available (Gopakumar and Shashikant, 2010; Bate and Porter, 2009; Oxfam, 2011; Newton et al, 2011).

The low prevalence rates of poor quality medicines in higher income countries can seem to suggest that the “counterfeit” framework is effective where pharmaceutical supply chains are highly regulated and well-resourced law enforcement agencies can monitor the quality of medicines in the supply chain, preferably at the port-of-entry (Woo, Wolfgang and Batista, 2008a). However, the infrastructure demands of the “counterfeit” framework in addition to the human, technical and capital resource assumptions inherent to that framing remain unattainable by over 80% of member states of the WHO (2004). In these low- and middle-income countries, gaps in regulatory and law enforcement capacity exacerbate the
porous and poorly regulated markets where the quality, composition and provenance of medicines being traded and consumed are often unknown (Wertheimer and Norris, 2009; Morris and Stevens, 2010, Pennefather et al., 2010).

Most publicly available data – including those from international organizations, law enforcement agencies, regulatory bodies and local sampling – have therefore warned that prevalence rates of poor quality medicines are on the rise (IMPACT, 2011; FDA, 2011; St Jean, 2010; Newton et al, 2011). In 2006, the Center for Medicines in the Public Interest predicted revenues from “counterfeit” medicines would surpass $75 billion by 2011, while the US Food and Drug Administration (FDA) reports an almost ten-fold increase in drug investigations between 2000 and 2005 (Nelson, Vizurraga and Chang, 2006; Lutter, 2006). The US FDA warns that even the latter figure is an underrepresentation of the problem, as most cases are never reported and a single investigation can involve tens of thousands of doses, resulting in our understanding of the scale as being described as only the “tip of the iceberg” (Mukhopadhyay, 2007; Bate, 2008).

The international community, most notably through the WHO (2006; 2011d) and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT, 2011), has in recent years placed significant global attention and resources to the problem of drug quality. This is especially critical as middle-income countries particularly are developing domestic drug production capacity at a rate faster than their investment in national medicinal regulatory authorities (Bate, 2008b). As a consequence, variability in the quality of medicines is a growing challenge, particularly in low- and middle-income countries, while international efforts by public- and private-interest organizations has failed to capture the support for collective action.
1.2 Study Objective

This thesis aims to critically examine the issues that exacerbate the prevalence of the trade and consumption of poor quality medicines. In the first instance, it will draw from publicly available data to outline the problem: what is the scale and scope of variability in drug quality, who are the stakeholders that are affected, and how have they framed and responded to the challenge. The thesis will subsequently examine whether there are distinctions in the vulnerabilities between pharmaceutical supply chains of higher and lower income countries and how that has guided responses in those countries. This will be followed by an interrogation of the proposition that greater access to information vis-à-vis drug quality, provenance and composition can assist patients and health professionals and health systems make safer choices in consuming and dispensing medicines, respectively. Lastly, after challenging the existing framing of the problem by many of the stakeholders as one of counterfeit medicines, the thesis will survey the various quality frameworks that are most appropriate in addressing variability in drug quality, particularly in low- and middle-income countries.

1.3 Organization of Thesis

This thesis has been organized into a series of chapters covering the Background and Literature Review (Chapter 2), Results (Chapter 4 and 5), Discussion (Chapter 6) and Conclusion (Chapter 7) with implications of the work. Following the introduction, a literature review will be presented in Chapter 2, highlighting the importance of drug regulation in ensuring the quality of medicines in the pharmaceutical supply chains (2.1). The various consequences of variability in drug quality will subsequently be explored,
including clinical, public health and broader social and economic impacts that may not be captured by current surveillance metrics. In Section 2.2, the scale and scope of the problem will be examined. Beginning with an historic overview of the role the WHO has played in addressing variability in drug quality, the term “counterfeit” medicine will be introduced and defined as the most frequently cited classification of the problem. The section will also present other classifications forwarded to describe the problem, while arguing that insufficient and inconsistent definitions can complicate policy discussions on practical strategies for dealing with drug quality.

Two critical limitations will be presented as undermining the availability of reliable data on the scale and scope of the problem: the absence of a global consensus in defining and framing the problem, as well as the fact that most estimates are derived from sporadic “events” where poor quality medicines are seized. In addition to under-representing the problem in the literature, reliance on random drug seizures rather than comprehensive and accurate field data also associates law enforcement and customs agents as the primary source of data used to characterize a public health problem. How the problem has been conceptualized and addressed by various stakeholders is furthermore examined in Section 2.3, including by the WHO and IMPACT, national medicinal regulatory authorities in various countries, as well as by pharmaceutical companies.

Chapter 3 will then briefly provide an overview of the research methodology for the thesis. Notably, no field research was undertaken for this thesis. Therefore, data collection and analysis, as well as the theoretical framework presented are based on publicly available data only. This includes publications by international organizations, national regulatory bodies as well as publications available through the University of Toronto library. This
chapter will also outline some of the limitations of this thesis, while also providing a justification for incorporating information asymmetries, as well as the quality framework.

Chapter 4 will examine the vulnerabilities in the pharmaceutical supply chains that enable the trade and sale of poor quality medicines. In Section 4.1, the various vulnerabilities experienced by higher income countries will be outlined. In addition to the globalization of supply chains for drugs and active pharmaceutical ingredients (APIs), it will be argued that a proliferation of online pharmacies has resulted in the principal source of poor and/or inconsistent medicines in high-income countries to come from ports of entry. In many low- and middle-income countries, on the other hand a significant gap in access to essential medicines has further exacerbated limited capacity for drug regulation of the supply chain (4.2). These two factors have moreover lead to a proliferation of informal markets that are often poorly regulated, where many patients in low- and middle-income countries obtain their medicines.

In Chapter 5, vulnerabilities in pharmaceutical supply chains will be examined with respect to information asymmetries, wherein the absence of transparency vis-à-vis the provenance, composition and quality of medicines can lead to an erosion in trust, particularly in informal markets or where regulatory capacity is limited (5.1). In Section 5.2, it will be argued that the central challenge involves the classification of the problem. By focusing on “counterfeit” medicines that prioritize the “intent to deceive” while failing to capture the full range of variability with respect to material quality, the WHO will be shown to have marginalized a number of important stakeholders, and thereby limiting the opportunity, particularly through the IMPACT program, to address the problem.
This will be followed by a new taxonomy of drug quality that focuses on the very concept of quality, both as a realization of values and as a normative framework (5.3). Emphasizing the multiple dimensions of quality that are central to rational control in health systems, three particular approaches will be highlighted: quality by enforcement (5.4), quality by regulation (5.5) and quality by evaluation (5.6). The appropriateness of each, particularly in low- and middle-income countries, will be demonstrated by how it a) frames the issue of poor quality medicines, b) identifies the primary victim, and c) ascribes a particular stakeholder to respond. Lastly, Section 5.7 will present future areas of research, before concluding remarks are presented in Chapter 6.

Following, and related to, the section on future directions for this research, will be an Appendix with two publications, representing academic research outputs. The first paper, “Pill characterization data streams for reducing exposure to inadequately identified anti-malarial medication in developing countries,” was published in the Malaria Journal and represents a potential application of the quality-for-evaluation framework, envisioning material quality evaluation of anti-malarials (Pennefather et al, 2010). Meanwhile, the second paper, “Context-Specific Strategies for Addressing Variability in Drug Quality,” is a first-authored publication that has been submitted to the journal Health Affairs, pending review. In the manuscript, the authors suggest that the framing of the problem dictates the policy options, urging stakeholders to develop strategies that are relevant to the experienced challenges.
1.4 References


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WHO (2011d) "WHO’s role in the prevention and control of medical products of compromised quality, safety and efficacy such as substandard/spurious/falsely-labeled/ falsified/counterfeit medical products" A/SSFFC/WG/2/3.

~ CHAPTER TWO ~

Literature Review: Variability in Drug Quality

Medicines are unlike ordinary commodities; they have a therapeutic as well as a symbolic value in most societies for their life saving and enhancing quality (Kohler, 2007; Marks, 2009). In 1977, the World Health Organization (WHO, 2010a) introduced the concept of essential medicines, defined as medicines that “satisfy the priority health care needs of the population.”  

Over the past three decades, access to essential medicines has additionally become a key principle of the right to health discourse, as explicated in Article 12 of the International Covenant on Economic Social and Cultural Rights (ICESCR, 1976). Access to medicines has moreover been recognized as an important indicator of development, as Target 8.E. of the United Nations Millennium Development Goals (MDGs, 2010) highlights the need to “provide access to affordable drugs in developing countries,” while the WHO Model List of Essential Medicines, is currently in its 17th edition and has been endorsed by over 156 countries (WHO, 2011a). Particularly over the past decade, access to affordable medicines have increasingly becoming available, supported by sustained expression of normative values in international human rights and law vis-à-vis access to medicines, increasing globalization of commerce, and the emergence of pharmaceutical markets in low- and middle-income countries, providing the potential for dramatically reducing morbidity and mortality in resource-constrained countries (WHO, 2010b).

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2 Essential medicines are intended to be available “within the context of functioning health systems, at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford” (WHO, 2011a).
According to the WHO (1999a; 2010a), however, “access” to medicines includes multiple dimensions: in addition to the availability and affordability of medicines, their quality and composition is vital in ensuring access. Consequently, variability in drug quality remains a critical public health challenge, acknowledged in the Cotonou Declaration signed by world leaders, undermining at least three of the MDGs, stunting health systems and eroding public trust (Fernandez et al, 2010). The following chapter will therefore describe the particular challenge of trading and consumption of medicines of inconsistent and variable quality, notably in low- and middle-income countries (2.1).

After surveying available data on the prevalence of variability in drug quality, the difficulty of capturing comprehensive data of the problem will be examined, while also noting the range of terms that appear in the literature (2.2). The different classifications and conceptualizations of drug quality will then highlight its consequences on public health, health systems, as well as governance. Lastly, Section 2.3 will explore the various stakeholders affected by and responding to the problem of drug quality variability (2.3). In addition to surveying how these international, national as well as other public and private organizations have framed the problem, the section will also attempt to highlight the distinctions in the classifications and responses to the problem.

2.1 Drug Regulation and Quality Control

The pharmaceutical supply chain is a complex system that is aimed with ensuring the right drug reaches the right people at the right time and in the right condition (Kaiser Family Foundation, 2005). While the stakeholders and organizational structure vary by geography, type of medication, and other factors, a core component of any functioning
health system is an effective drug regulatory infrastructure (WHO, 1999a). Medicines regulation aims to ensure that medicines in pharmaceutical supply chains and in international markets are “safe, effective and of good quality,” are accompanied by “complete and correct product information,” and are “manufactured, stored, distributed and used” in accordance with good practices (WHO, 2003; 2010b). The WHO (2010b) therefore works with member-states to assess national regulatory systems, identifying gaps, developing strategies for improvement and supporting countries in their commitment to build national regulatory capacity.

The first World Health Assembly of the WHO in 1948 established the Expert Committee on Specifications for Pharmaceutical Preparations (“Expert Committee”) mandated to: develop global standards for pharmaceutical ingredients, update Good Manufacturing Practices (GMPs), testing of pharmaceutical products, regulatory guidelines for authorization of marketing, correct storage and distribution practices, and other quality assurance tools and systems in order to ensure that all essential medicines meet identical standards of quality, safety and efficacy (WHO, 2011b). The WHO Medicines Quality Assurance and the WHO Regulatory Support programs moreover address issues of drug quality (ibid).

Within all these programs, the WHO (2011c) has emphasized the importance of pharmacovigilence, which it defines as “the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug-related problem.” This can involve, among other steps: registration of medicines (also known as market authorization), enforcement of measures to ensure that only these registered medicines are traded, confirmation of the manufacturer's compliance with GMPs, and a dynamic system of quality assurance that is applied to the entire manufacturing process.
(Oxfam, 2011). The other components of adequate drug regulation include standards for
distribution, dispensing and the provision of information for patients, known as Good
Distribution Practices (GDP) and Good Pharmaceutical Practices (GPP).

Pharmacovigilence can also involve distributed systems of quality assessment and
detection of differences between expected and actual drug quality (WHO, 2011c). *Ensuring
the Quality of Medicines in Resource-Limited Countries: An Operational Guide* was released by US
Pharmacopeia (USP, 2007) – in collaboration with the WHO, the Program for Appropriate
Technology in Health and numerous national regulatory bodies – with particular emphasis
on the potential variability of institutional, technical and human resource capacities.

Notably, the *US Pharmacopeia Operation Guide*, as well as other international
pharmacovigilence guidelines, including those by the WHO (2002), highlight the many
challenges faced by regulatory bodies in implementing those guidelines, particularly in low-
to middle-income countries. The pharmacovigilence guidelines and policy recommendations
therefore need to take these challenges into consideration, including potential limitations in
technical, financial and/or human resources. As a result, the guidelines are suggested to be
best understood as best practices that may be context-specific, rather than fixed prescriptions
(USP, 2007). Importantly, best practices are used to maintain quality as an alternative to
mandatory legislated standards, thereby providing flexibility where resources may be limited
(Bogan and English, 1994). This enables national medicinal regulatory authorities to
incorporate best practice guidelines, and thereby strengthening local capacity for adequately
regulating drug quality, without necessitating excessive, and often unrealistic, investments in
resource limited contexts.
2.1.1 The Consequences of Variability in Drug Quality

Nonetheless, one of the central tasks of pharmacovigilence is to ensure the quality and compositions of medicines abide by defined reference standards, or pharmacopeia (WHO, 2002). Where pharmacovigilence and other regulatory best practices fail, the quality of medicines may be compromised. Pharmaceuticals with inconsistent or poor quality can consequently pose a range of challenges, to patient health, public health and the broader health system. A broad literature exists, expounding the extensive evidence that drug quality variability and therapeutic inconsistency can impact the burden of disease, lead to therapeutic failure, and even cause mortality (IMPACT, 2010; Oxfam, 2011; BBC News, 2012; Newton et al, 2011; Harris, Stevens and Morris, 2009). The US Pharmacopeia (2010) furthermore chronicle media reports from around the world, and moreover provide estimates of morbidity and mortality as a result of poor quality medicines.

Other cases are reported in the media. The US-based Center for Medicines in the Public Interest (2006) estimates that in the People’s Republic of China, at least 200,000-300,000 people die every year as a result of poor quality medicines (Schwarz and Wong, 2006). In 2008, the US Food and Drug Administration reported that at least 81 deaths and 785 cases of serious injuries were directly linked with contaminated batches of the anticoagulant, heparin, imported from China (Labadie, 2012; Harris, 2008). Pediatric formulations of paracetamol cough syrup, contaminated with antifreeze, has also been reported with hundreds of deaths, including 339 children in Bangladesh in 1990, 85 children in Haiti in 1995, over 100 children in Panama in 2007 (Harris, Stevens and Morris, 2009). In early 2012, the Federal Investigation Agency of Pakistan also reported that at least 100 people are believed to have died and at least 450 patients were being treated for serious
injuries as a result of “faulty,” poor quality cardiovascular drugs that were distributed to over 46,000 patients (Hughes, 2012).

Many regulatory bodies and independent researchers have also reported of the risk that the sale and consumption of medicines with variable or inconsistent quality could also lead to significant public health challenges associated with resistance to therapies. In one recent study by Nair et al (2011), *amodiaquine* and *amoxicillin* bacterial formulations samples in Papua New Guinea resulted in alarming findings, as none of the 14 formulations collected from registered pharmacies complied with the quality criteria (visual evaluation, quality control specifications and product authenticity). The authors moreover issued a warning that medicines that fail these quality criteria, particularly with respect to poor quality anti-bacterials, also contributed to the development of resistant bacterial strains (ibid).

In another longitudinal study by White (2004) and Newton et al (2009a), the development of drug resistance to *artesunate*-based anti-malarial medicines was measured in a number of countries in South-East Asia. The studies most notably come to the estimation that the sale and consumption of these *artesunate*-based anti-malarials with “subtherapeutic amounts” of the active ingredient, may be directly responsible for a doubling in the prevalence of drug resistance (ibid). In the case of anti-infectives, the authors suggest these subtherapeutic, or “substandard” medicines pose a greater “drug pressure” than those with no amount of the active ingredient, as resistance to available therapies can have greater public health consequences (Newton et al, 2009a).

In addition to the patient, the public health risks posed by poor quality medicines furthermore affect the formal and informal care providers, as well as pose epidemiological challenges to local, regional, as well as national and international populations, particularly in
the case of infectious diseases. When therapeutic failure or adverse events occur, patients may also experience a loss of confidence in health systems, health professionals as well as registered pharmaceutical products and brands (Gautam, Utreja and Singal 2008). Such erosion of trust can have significant implications, including patients seeking alternate treatment from unauthorized health care providers that can furthermore exacerbate the health of the individual patient as well as cascade to her immediate community (Bloom, Standing and Lloyd, 2008).

Local and national health authorities, such as the Ministry of Health, are furthermore affected by medicines of inconsistent quality, particularly when limited health resources are wasted. According to the 2011 WHO World Medicines Report, per capita spending on medicines among low-income countries is as little as US$7.61 (WHO, 2011d). Procurement of medicines of poor quality with these very limited funds, for example, can exacerbate the capacity of state authorities to fulfill its mandate of providing optimal care. The Royal Canadian Mounted Police (RCMP) have moreover suggested that the sale of “counterfeit” medicines may also bankroll terrorist groups (St Jean, 2011), while Finlay (2011) has more directly linked the problem of “counterfeit drugs as a national security threat.” In addition to regulatory authorities, donors that provide development assistance and directly procure medicines have also highlighted drug quality as a significant challenge to aid effectiveness, particularly noting the opportunities for corruption through the diversion of medicines.

The drug manufacturer emerges as another significant stakeholder. In the case of authorized multi-national or generic drug manufacturers producing quality medicines, the trade and consumption of products by unauthorized suppliers can lead to a direct loss in revenue. A 2011 study commissioned by the Business Action to Stop Counterfeiting and
Piracy (BASCAP), an International Council of Commerce initiative, estimates that by 2015, counterfeited and pirated goods will represent between US$1.2 to $1.7 trillion of goods traded (Frontier Economics, 2011). Meanwhile, the International AntiCounterfeiting Coalition (IACC, 2009) estimates the value of counterfeiting at more than US$600 billion annually.³ The Vice President of Global Brand Security at Johnson and Johnson moreover suggests health care products remain the third most counterfeited category in the world, estimated at $250 billion (Guido, 2011). A more modest figure was projected by the US Center for Medicines in the Public Interest, which estimated that revenues from counterfeits would reach $75 billion by 2011, a statistic that the WHO (2006a) has also been referencing (Nelson et al, 2006).⁴ The great variability and lack of coherence in these figures underscores the absence of a mandated organization and inadequate market surveillance methodologies.

As Newton, Green and Fernandez (2009a) have suggested, poor quality medicines can also lead to a loss of trust in the pharmaceutical brand, indirectly leading to future loss in revenue. Furthermore, a lack of clarity in defining the problem can lead to the punishment of authorized manufacturers who may produce occasional substandard batches, as is

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³ According to its website, the International AntiCounterfeiting Coalition (IACC) is the “world's largest non-profit organization devoted solely to protecting intellectual property and deterring counterfeiting.” Its membership spans across all goods (automotive, apparel, luxury goods, pharmaceuticals, software, entertainment, etc), from privately-owned to large multinationals.

⁴ The Center for Medicine in the Public Interest (CMPI) is a non-profit medical issues research group, co-founded by a former FDA Associate Commissioner for External Relations. The CMPI is controversially partially funded by the pharmaceutical industry (Herper, 2007), and according to Fang (2009), "was originally a project of the Pacific Research Institute, an older corporate front established in conjunction with Philip Morris to fabricate academic support for the tobacco industry." According to its website, its agenda includes clinical outcomes and econometric studies that analyze the value of new medicines and genomic and molecular-based medical innovation.
frequently cited with Indian generic manufacturers. In the case of Canada’s Apotex, for example, the US Food and Drug Administration has continuously issued public warning letters, not for variability in the quality of the final product, but the rigorousness of their quality assurance programs (Singer, 2010). Regardless, any uncertainty or variability can lead to a further loss of confidence in the manufacturer, and potentially leading to a loss of revenue.

Section 2.1 highlights the importance of pharmacovigilence to ensuring the quality of medicines, while also outlining the consequences of the production, trade, sale and consumption of poor quality medicines. Section 2.2 will continue by outlining the publicly available data on the scale and scope of the problem. This will include figures from local studies, national regulatory agencies, as well as estimates and projections by international organizations. The section will additionally provide an overview of the methodologies for conducting field studies on drug quality, and ultimately suggest that there remains a central challenge in how the problem is defined by the multiple stakeholders.

2.2 The Scale and Scope of Poor Quality Medicines

At a 1985 Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, the delegation called upon the WHO, other international organizations and non-governmental organizations to study the “feasibility of setting up a clearing house to collect data and inform governments of the extent of the problem” (WHO, 1999b; IMPACT, 2010). At the 41st World Health Assembly in 1988, the member-states passed Resolution WHA41.16 on the rational use of drugs, requesting governments and pharmaceutical manufacturers to cooperate “in the detection and prevention of the increasing incidence of
the export and smuggling of falsely labeled, counterfeited or substandard pharmaceutical preparations," and requested the Director General "to initiate programs for the prevention and detection of the export, import and smuggling of falsely labeled, spurious, counterfeited or substandard pharmaceutical preparations" (IMPACT, 2010). Notably, this initial mandate required the WHO to initiate programs for a broad spectrum of drug quality challenges, including “counterfeit,” “falsely labeled,” “spurious” and “substandard” drugs (Gopakumar and Shashikant, 2010).

In the following years, however, the WHO focused almost exclusively on “counterfeit” medicines, while “falsely labeled,” “spurious” and “substandard” drugs were never fully explicated, nor were they referred to in subsequent World Health Assembly Resolutions on drug quality. Gopakumar and Shashikant (2010) trace this singular fixation on “counterfeit” medicines to a 1992 meeting that was convened by the WHO, in response to Resolution WHA41.16 above, where it had gathered representatives from its member-states, the International Criminal Police Organization (INTERPOL), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the International Narcotics Control Board, the International Organization of Consumer Unions, the International Pharmaceutical Federation (FIP) and the World Customs Organization (formerly Customs Cooperation Council).

Following this meeting in 1992, a definition of “counterfeit medicines” was proposed (see Table 1 below), and at the World Health Assembly in 1994, Resolution WHA47.13 specifically requested the WHO to assist member-states in combating counterfeit drugs. As Gopakumar and Shashikant (2010) show, however, this 1992-1994 definition has notably never been formally endorsed by the WHO member-states. Nonetheless, Resolution
WHA47.13 led to the creation of the WHO Project on Counterfeit Drugs, which oversaw drafting of the WHO (1999b) Guidelines for the Development of Measures to Combat Counterfeit Drugs in 1999. Since 1994, a number of World Health Assembly Resolutions, including WHA52.19 ("Revised Drug Strategy"), have reaffirmed the WHO’s commitment.

As Gopakumar and Shashikant (2010), Newton et al (2011) and Kopp (2010) highlight, however, there is significant controversy in defining and classifying poor quality medicines. A search through international policy documents, academic journals and media stories indeed reveals a broad lexicon of classification to represent variability in drug quality, including ‘adulterated’, ‘counterfeit’, ‘fake’, ‘falsified’, ‘falsely-labeled’, ‘inauthentic’, ‘mis-branded’, ‘non-genuine’, ‘poor quality’, ‘unauthorized’, ‘substandard’, ‘spurious’, or combinations thereof. Of these terms, the four that most frequently appear in the literature are defined in Table 1.1 below, and are based on a Summon Search, which is described in the Methodology (Chapter 3). Conducting the Summon Search, the term “counterfeit medicines” returned 3,286 results, followed by “spurious medicines” (550), “substandard medicines” (265), and “falsely-labelled medicines” (5).
Table 1.1 Defining counterfeit, substandard, spurious and falsely-labeled medicines.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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| Counterfeit medicine  | According to the WHO (2006a), a counterfeit drug is:  
“...one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, wrong ingredients, without active ingredients, with insufficient quantity of active ingredient or with fake packaging.”  
According to the WHO (1999b) Guidelines for the Development of Measurers to Combat Counterfeit Drugs, the following amount to counterfeit drugs:  
a) Products, which do not contain any of the specified active ingredients despite such declarations on the labels  
b) Products, which contain active ingredients other than those specified on their labels  
c) Products, which contain the correct strength of the specified active ingredients, but whose source is different to the one declared  
d) Products, which contain the specified active ingredients but in strengths different to those declared; they may also contain different quantities of impurities. |
| Substandard medicine  | According to the WHO (2010c) Expert Committee on Specifications for Pharmaceutical Preparations:  
“Substandard medicines are pharmaceutical products that do not meet their quality standards and specifications. Each pharmaceutical product that a manufacturer produces has to comply with quality assurance standards and specifications, at release and throughout its shelf-life, according to the requirements of the territory of use. Normally, these standards and specifications are reviewed, assessed and approved by the applicable national or regional medicines regulatory authority before the product is authorized for marketing”  
Substandard medicines may be due to poor manufacturing practices, poor transportation techniques or poor storage facilities and packaging. Notably, in cases of “false-labeling” and “spurious,” there is an element of “intent to deceive” that is not necessary in the case of substandard medicines (Gopakumar and Shashikant, 2010). |
Spurious medicine

The term “spurious medicine” appears more frequently in the Indian literature. According to Gopakumar and Shashikant (2010):

“Spurious medicines are those on the contrary to the label information, which contains no active ingredient or insufficient amount of active ingredient. This applies, for instance, where a packet contains correct label information, but the actual tablet does not contain the active ingredient, or if the label states incorrect dosage. Some national laws also include drugs showing wrong information with regard to manufacturer. A spurious drug could also include a drug that contains the correct amount of active ingredients, but the label information states the name of a manufacturer other than that of the original manufacturer.”

The term is most popular in India, where the problem of poor quality medicines is conceptualized as one of ‘spurious’ medicines rather than ‘counterfeits’. This is captured in the “Report of the Expert Committee on a Comprehensive Examination of Drug Regulatory Issues, including the Problem of Spurious Medicines,” undertaken by the Indian Ministry of Health and Family Welfare (Mashelkar, 2003).

Falsely-labelled, or falsified medicine

According to a Report by the Director-General of the WHO (2011e) on Substandard/Spurious/Falsely-Labeled/Falsified/Counterfeit Medical Products:

“A falsified medical product gives a false representation of its identity and/or source and/or record keeping for traceability; pretends to have been assessed and approved by the competent regulatory authority, pretending to be a genuine quality product; has an intention to deceive by a fraudulent activity; is falsified for profit motives, disregarding public health and safety; and that disputes concerning patents or trademarks must not be confused with falsification of medical products.

In the context of medicines, false information on the label may have public health consequences, including where the manufacturer provides wrong labeling information with regard to the chemical composition, dosage, precautions while taking the medicines, information with regard to side effects, etc. (Gopakumar and Shashukant, 2010).
2.2.1 Determining the Scale of the Problem

Despite a growing body of literature, there are very few published data allowing estimation of the extent of variability in drug quality and the impact on patient and public health (WHO, 2005; Caudron et al, 2008; Newton et al, 2009b; USP, 2010). According to Sabine Kopp of the WHO Anti-Counterfeiting Program, it is difficult to measure the extent of the problem “when there are so many sources of information and different definition of counterfeit” (WHO, 2010b; Kopp, 2010). This is supported by Newton, Green and Fernandez (2009), who suggest that much of the data has been interpreted uncritically: while some data may be “inaccurate,” others don’t allow “accurate generalizations about the epidemiology” of poor-quality medicines. In the absence of a designated global body tasked with conducting drug quality monitoring and surveillance, a number of international organizations and research groups have provided estimates of global, regional and drug-specific variability in quality, based on two distinct methodologies.

The first approach, used mainly by regional offices of the WHO, national medicines regulatory authorities as well as the industry organizations, depend on formal and informal mechanisms of reporting drug quality ‘incidents’. In 2005, for example, the WHO Western Pacific Regional Office established the Rapid Alert System (RAS), a “moderated electronic communication network” that anonymously collects and alerts authorities of cases of poor quality medicines (WHO, 2011b). User-based reporting mechanisms, however, remain deeply under-utilized, with one study estimating that only between 5% to 15% of the 191 member states of the WHO report cases of “counterfeit” medicines (Newton et al, 2006).

Many of the estimates from this method of capturing ‘incidents’ come from drug seizures, typically by customs agents and regulatory agencies. INTERPOL, for example
coordinated a five-month operation in 2009, where over 20 million pills, bottles and sachets of counterfeit and illegal medicines were seized across China and seven of its South-East Asian neighbours (WHO, 2010c). The operation also resulted in the closure of 100 retail outlets and the further arrest of 33 people (ibid). In the same year, over 34 million counterfeit pills were seized by European customs officers over just two months, while a series of raids in Egypt found counterfeit medicines worth "hundreds of millions of dollars" and "exposed a criminal network feeding consumers across the Middle East" (ibid).

In many of these drug seizures, INTERPOL, the European Union (EU) and other regulatory and customs agencies are assisted by pharmaceutical industry organizations, including the Pharmaceutical Security Institute (PSI) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which is the global NGO representing the research-based pharmaceutical industry, including 25 leading multinational companies and 45 national and regional industry associations around the world. In a 2010 Statement on Counterfeit Medical Products, IFPMA (2010) estimated the reporting of at least 1,693 incidents of "counterfeit" medicines in 2009. Because this method of reporting 'incidents' and seizures depends on passive reporting along the drug supply chain, some authors have suggested the prevalence estimates to be a gross under-representation of the actual scale of the problem (Lutter, 2005).

The method is also undermined, by depending on customs officials and law enforcement, where criteria for quality have been argued to be based on intellectual property violations of intercepted shipments rather than public health (Oxfam, 2011). The second method for assessment the scale of drug quality variability, therefore, requires direct sampling of locally available medicines. Many authors have argued that this method of
actively monitoring various points along the pharmaceutical supply chain, including the point-of-dispensing, provides greater accuracy in determining the prevalence of poor quality medicines, rather than depending on data from random drug seizures (Newton et al, 2011; Caudron et al, 2008; Falagas et al; 2007).

The best evidence of direct sampling of medicines comes from the study of anti-malarial medicines, predominantly in South-East Asia, Africa and Latin America. In one study by Bate (2008), 35% of all anti-malarial medicines sampled from shops and pharmacies in six major African cities were said to have failed basic quality control tests, such as dissolution assays and colorimetric methods (Risha et al 2007). In another major study, samples of artesunate were collected in various countries in South-East Asia, including Vietnam, Cambodia, Lao and Burma (Newton et al, 2011b). Of the 391 samples, 195 (49.9%) were found to be contain no or substandard amounts of artesunate. The team of chemists, palynologists, health workers, criminal analysts, and law enforcement were able to trace the poor quality medicines to various sites in China, while subsequent studies also revealed the source of poor quality anti-malarials across Africa (Newton et al, 2011b).

In a paper proposing a standard research methodology for testing drug quality, Seear et al (2011) outline the three requirements in undertaking drug quality surveys: sampling method, analytical method and definitions of measured end-points. While a limited number of such guidelines exist, there is a paucity of literature identifying methods that have been field-tested (USP, 2007; Newton et al, 2009b). In the paper, Seear et al (2011) applied their guidelines to the city of Chennai, India, dividing the city into ten areas (along municipal lines), selecting ten stores and local “pharmacies,” and purchasing three study drugs (artesunate, ciprofloxacin and rifampicin) at each of the 100 outlets.
The 300 samples were subsequently tested by Liquid Chromatography–Mass Spectrometry, expressing the assay content as percentages of stated tablet content, and subsequently developing drug quality definitions for normal manufacturing standards, counterfeiting, decomposition, poor quality control and adulteration (ibid). Their findings were notable: out of the 300 samples, 43% fell below the widely accepted manufacturing range for generics of 90% to 110% of stated content, while also positing that poor drug quality was most likely due to decomposition during storage or poor manufacturing standards rather than criminal counterfeiting (Seear et al, 2011).

Therefore, in addition to providing more accurate data on the scale of the problem in local communities, direct sampling also allows for determination of the source of medicines traded and consumed in local markets, while also enabling a fuller appreciation of the various sources of poor quality medicines, beyond deliberate counterfeiting. This includes an understanding of the possible ways that drug quality could be compromised, such as decomposition, that would require greater investment and attention to good manufacturing practices. The US Pharmacopeia (2007) Operational Guide for “Ensuring the Quality of Medicines in Resource-Limited Countries provides specific guidelines for laboratory testing as well as rapid assessment of quality assurance for quality control of medicines that can be applied in many low- and middle-income countries.

2.2.2 Estimates in the Literature of the Scale of the Problem

The most widely cited estimate in the literature is derived from a 2006 WHO Fact Sheet that suggests 10% of the global drug supply to be "counterfeit" (WHO, 2006a). IMPACT (2006) and the WHO (2011e; 2011f) have since warned against using this figure,
both for its basis on anecdotal evidence and extrapolations from a limited number of studies. Another limitation of a single universal figure to capture the scale and complexity of the problem of poor quality medicines is due to variability between and within countries: while the WHO (2011c) estimates that under 1-2% of sampled medicines in high-income countries failed quality tests, the figure is upwards of 50% in some low-income countries, with some studies suggesting “counterfeit” rates as high as 80% in some regions in South-East Asia and sub-Saharan Africa (ibid). Another highly cited estimate comes from the US-based Center for Disease Control and Prevention, suggesting prevalence of “counterfeits” varies from approximately 1% to 10% in developed countries, and could be as high as 30% in countries in Africa, Asia, and Latin America (Green, 2009).

Cockburn et al. (2005) propose two reasons for gaps in empirical, reliable and transparent statistics. The first challenge in many countries is the lack of mandatory public reporting of inconsistencies in drug quality. This would include, for example mechanisms whereby health professionals, customs and other law enforcement officials, pharmaceutical companies as well as the general public could inform national or regional regulatory authorities when they come across spurious, or potentially poor quality, medicines. Moreover, independent market surveillance requires the deployment of substantial human and capital resources for conducting independent market surveillance. Here, it must be noted that the lack of global consensus in defining the problem has complicated policy discussions on how stakeholders frame the issue, but also more locally limiting coherence in

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5 While the South-East Asian Regional Office of the WHO established the Rapid Alert System for global and regional monitoring and reporting on potential cases, ranging from individual pills to batches, of poor or variable quality medicines, the mechanism has been heavily underutilized, as explained in Section 2.1.1 (WHO, 2011b).
quality evaluation strategies that could assist in more accurately assessing prevalence and other data that could lead to better interventions.

Even where public figures are reported, Outterson (2009) suggests inconsistency and conflation of the different dimensions of drug quality, often without defining or distinguishing between them. So while Newton et al. (2011a) report that the most frequently cited estimates are for ‘counterfeit’ medicines, some reports also conflate substandard, adulterated, as well as medicines that are parallel traded, generic or deliberate violations of trademark law (Outterson, 2009).

While emphasis has traditionally been on the low-end of the quality scale, the growth of the generic drug market – in terms of scale and sales – as well as rising global demand and purchasing power for essential medicines will moreover lead to proliferation of the problem. Member-states at the 2010 World Health Assembly therefore urged the WHO to establish coherence around defining the challenges with drug quality. The WHO (2011e) Working Group of Member States on Substandard/Spurious/Falsely-Labeled/Falsified/Counterfeit Medical Products, illustrates with the name the complexity of the problem.

In the following Section (2.3), the various stakeholders to the problem will be introduced. In addition to highlighting the centrality of the patient who consumes poor quality medicines, the section will introduce its impact on the broader community, local health system, national health ministries as well as international public and private organizations. By highlighting the responses by these stakeholders based on the literature, it will moreover be suggested that the perceived experiences by health professionals, regulatory authorities and the WHO, elucidate potential divergences in the framing of the problem, as well as perceived mandates and responses.
2.3 How Have the Various Stakeholders Framed and Responded to the Problem?

As was described in Section 2.1, the problem of poor quality medicines has multiple consequences, affecting a number of stakeholders at various levels. The most important and immediate victim, of course, is the patient that consumes medicines of inconsistent or poor quality. This person may both purchase the medicine that may be of poor quality, but furthermore experience clinical manifestations that can lead to morbidity and mortality, as described in Section 2.1.1. With respect to drug quality, two questions arise for the patient: (a) is this product what I thought it to be (i.e. drug identity) and (b) does it do what I expect it to do (i.e. drug effectiveness). Without the ability to verify the identity and quality of the medicine, the patient may ascribe treatment failure to severity of morbidity rather than drug quality, as will be described in 5.1.1. In addition to the patient, the local community can be an important stakeholder that must be acknowledged. The community can include the patient’s household, immediate and extended family and friends, as well as a defined geographical and social network within which interaction occurs. Not surprisingly, the public health effects of treatment failure due to drug quality variability are amplified within the patient’s local community (Mackey and Liang, 2011).

In addition to including the immediate support network for the patient, the consumption and trade of poor quality medicines can also have broader public health consequences that affect a wider population. For example, limitations in e.g. technical, financial and human resources in low- and middle-income countries result in reduced penetration and public access to medicines from regulated sources, such as state-run hospitals and pharmacies. These markets can be classified as “formal” for two reasons: (a) local, national and international regulatory bodies are aware of the scale and scope of their
drug dispensing, and can therefore impose quality regulations, and (b) that by virtue of regular regulation, ideally, compliance with established regulatory standards would induce greater confidence in the medical products acquired by the public (Shah, 2004).

In many low- and middle-income countries, however, patients often obtain their medicines from local markets, which may not be funded nor even recognized by regulatory authorities, limiting the capacity for imposing and monitoring quality standards. While data does not exist as to the scale of local markets, many authors that have engaged in field-testing of drug quality, have noted their extensive penetration as well as the lack of regulatory oversight in most cases (Newton et al, 2009b; Seear et al, 2011; IMPACT, 2010). In these “informal” markets, the vendor – often operating without permits and/or a pedigree of where drugs are procured and sold - in local markets that sells the drug that may be of poor quality is also an important stakeholder.

At the regional and state level, treatment failures, morbidity and mortality as a result of poor quality medicines can lead to more costly future health care costs, while furthermore posing the risk of eroding public trust in health practitioners. At the regional and national level as well, failures in ensuring access to quality medicines would further undermine the legitimacy of health systems, while necessitating legislative and enforcement mechanisms. At the international level, the WHO and other international health and governance organizations, along with multi-national pharmaceutical companies have also been active. In the following section, these various stakeholders will be introduced, along with their mandates and activities around poor quality medicines.
2.3.1 The World Health Organization

Since its inception in 1946, the WHO has acknowledged drug quality to be a global problem. Article 2 of the WHO Constitution establishes its obligation “to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products” (WHO, 2011b). Section 2.2 chronicled the evolution in the classification of the problem of poor quality medicines, highlighting the 1992 definition of “counterfeit medicines” that was subsequently ratified in 1994. For almost fifty years, however, the WHO Executive Board has mandated the Expert Committee on Specifications for Pharmaceutical Preparations, to develop quality assurance tools and systems to ensure that all essential medicines meet identical standards of quality, safety and efficacy (WHO, 2010c; 2011b). In addition to national medicines regulatory authorities and pharmaceutical manufacturers, a number of international bodies depend on the Expert Committee’s international guidelines, specifications and nomenclature. These include procurement agencies, the Global Fund to Fight, AIDS, Tuberculosis and Malaria, as well as the UN Prequalification Program, the Medicines for Malaria Venture, and Stop TB (WHO, 2011b).

At the 1994 World Health Assembly, Resolution WHA47.13 expanded the role of the Executive Committee, while furthermore launching programs to assist member-states in ensuring the quality of medicines. Over the next five years, this led to initial, albeit limited, efforts at assessing the scale and scope of the problem, the formulation of national guidelines, as well as the education and training of drug inspectors and analysts. Further recommendations were made to develop simple tests to determine drug quality where needed, while the WHO also continued to fulfill its constitutional mandate of supporting member-states in implementing regulatory mechanisms to international norms and
standards, as described above (Article 2) (Gopakumar and Shashukant, 2010). While these efforts placed the problem of drug quality on the international agenda, a comprehensive global strategy was absent.

Notably during this time, in addition to the WHO, the problem of drug quality was also on the agenda of the biennial International Conference of Drug Regulatory Authorities (ICDRA) since 1992 (IMPACT, 2010). In conjunction with the 11th ICDRA in 2004, an international meeting on counterfeit medicines was organized. At the meeting, the ICDRA requested the WHO, in collaboration with other stakeholders, draft an international convention on counterfeit drugs and to convene a meeting of drug regulatory authorities and other stakeholders, prior to the 12th ICDRA in 2006 (ibid).

While consensus was not reached among member-states on the appropriateness of, or need for, an international convention, a series of concurrent regional consultations by the WHO ultimately demonstrated the need for an international taskforce to address the problem of poor quality medicines. This conclusion was justified by the WHO (2006a) for three reasons: (a) existing national measures to meet all the challenges of poor quality medicines were insufficient, (b) there are global dimensions to the trade of pharmaceuticals beyond national capacities, and (c) political will and consensus of WHO member-states is important in making significant change.

2.3.2. The International Medical Products Anti-Counterfeiting Taskforce

In 2006, the WHO therefore organized an international conference in Rome, called “Combating Counterfeit Drugs: Building Effective International Collaboration,” that was attended by representatives of 57 national medical regulatory authorities, seven international
organizations, and 12 international associations of patients, health professionals, pharmaceutical manufacturers and wholesalers (IMPACT, 2010). The subsequent Declaration of Rome ("Declaration") was adopted by all 160 participants and stated that the WHO should take the lead in establishing a taskforce, the purpose of which would be to "lead international collaboration on combating counterfeit medicines." The Declaration also contained a set of principles and a conceptual framework for the task force’s work aimed at ensuring that it takes account of public health interests.

The resulting International Medical Products Anti-Counterfeiting Taskforce, or IMPACT (2006), was intended as a voluntary coalition of stakeholders that coordinates international activities aimed at combating counterfeit medical products for the purpose of protecting public health. The collaborating partners of IMPACT currently include, among others, representatives from the WHO, the ASEAN Secretariat, the Commonwealth Secretariat, the Council of Europe, the European Commission, the IFPMA, INTERPOL, the World Customs Organization, the World Trade Organization, the World Intellectual Property Organization, national medicinal regulatory authorities, private business associations, including the global lobbying arm of multi-national pharmaceutical companies (the International Federation of Pharmaceutical Manufacturers and Associations), as well as various inter-governmental organizations and representatives of the health-care sector (WHO, 2009; IMPACT, 2010). According to IMPACT (2010), this broad spectrum of

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6 The seven international organizations included the International Criminal Police Organization (INTERPOL), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the International Narcotics Control Board, the International Organization of Consumer Unions (now called Consumers International), the International Pharmaceutical Federation (FIP) the World Customs Organization (WCO, formerly Customs Cooperation Council), as well as the Organization for Economic Co-operation and Development (OECD) (IMPACT, 2010).
stakeholders' mandates, roles, interests and experience reflect the recognition that “combating the counterfeiting of medical products cannot be successfully achieved by the health sector alone.” While achieving multi-sectoral participation can promote buy-in from a multitude of stakeholders, it can also lead to crowding and therefore inaction.

In *The Logic of Collective Action*, Olsen (1965) offered a cogent articulation of when inaction can result due to crowding of stakeholders. When more than one individual is required to contribute to an effort to achieve a collective good, e.g. promoting access to quality medicines, Olsen suggests a collective action problem may occur, if the following two conditions are met: (a) the collective good is non-excludable, i.e. it becomes difficult to exclude non-participants from benefiting from the collective action of others, and (b) individuals can seek out short-term benefits for themselves alone, thereby benefiting without paying the costs (ibid).

In promoting access to quality medicines, for example, it can be argued that by investing human, technical and financial resources by all stakeholders, a collective good can be achieved, namely access to quality medicines, which will benefit all stakeholders, with the exception of criminals seeking to benefit from deliberately fake medicines. At the same time, some stakeholders can benefit (i.e. gain access to quality medicines) without having to participate in investing time and resources. This can therefore give rise to a collective action problem, where a crowding of stakeholders not only diffuses responsibility, but can lead to inaction, especially since the benefits can be shared even if they do not participate. Therefore, Olsen (1965) proposes effective collective action can only be achieved without selective incentives to each stakeholder, as well as mechanisms for accountability.
Although relying on voluntary international cooperation and national legislation harmonization, the stated aim of IMPACT (2010) is to harmonize and coordinate networks across and between countries in order to halt the global production and trade of ‘counterfeit’ medicines. The IMPACT has furthermore expressed its dependence on the coordinated efforts of and effective collaboration among a number of sectors, including the health sector, enforcement, border control, justice (at all administrative levels) as well as the private sector.

While the terms of reference of the IMPACT have never been endorsed by the World Health Assembly, the 12th ICDRA in 2006 welcomed the establishment of the IMPACT, while expressing their expectation that the IMPACT would “develop concrete and pragmatic proposals on how to improve national, regional and international strategies to combat counterfeit medicines” (WHO, 2011f). The IMPACT subsequently outlined five key objectives for its activities, which include:

a) “Creating awareness about the severity of the problem among stakeholders, and provide information to the health system and the public;
b) Promoting intersectoral coordination based on written procedures, defined roles, adequate resources, and effective administrative and operational tools;
c) Developing technical competence and skills in required areas;
d) Developing appropriate mechanisms for ensuring vigilance and input from patients’ groups, health-care professionals, the medical product supply chain, other stakeholders and concerned parties, and the public; and
e) Securing political will and commitment, adequate legal frameworks, implementation commensurate with the impact of counterfeiting on public health, and provide the necessary tools for coordinated and effective law enforcement.”

Following a multi-sectoral consultation process in preparation for the Rome Declaration, the IMPACT moreover identified five key areas where action was needed: legislative and regulatory infrastructure; regulatory implementation; enforcement; technology; and communication. The legislative working group was charged with reviewing national legislations
on “counterfeit” medical products, and developing a model text for national legislation. This was to be based on practical experiences from a number of member states, intended for national adaptation (WHO, 2011f). While the detailed overview of present national legislation, or in most cases the lack thereof, was highly relevant, there have been noted controversies in the legislative policy recommendations that the IMPACT has made to member states, as will be outlined below.

The regulatory support group, in addition to offering guidance on drug distribution to prevent “counterfeit” medicines from entering the supply chain, is also developing a standard sampling methodology for national medicinal regulatory authorities in order to assist them in measuring the size of the problem in such a way that survey results will be reliable and comparable between countries and over time. Here, the work has been much more limited, as substantially strengthening the capacity for regulatory monitoring demands significant resource commitments that the mandate of the IMPACT does not provide (Bate and Porter, 2009). The enforcement working group is developing a practical guide on the investigation of “counterfeit” medical products, while also aiming to training officers from national police, customs and medicines regulatory agencies. Achieving this goal requires assistance not only from existing national medicinal regulatory authorities of multiple countries but also local research teams that are undertaking local field testing of drug quality and identifying potential methodologies for scaling up (FDA, 2006; Newton et al, 2009b; USP, 2007).

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7 It should be noted that the objective of all five working groups of the IMPACT is towards addressing the problem of “counterfeit” medicines, based on the WHO definition presented in Table 1.1. The term is put in quotations, as Chapter 4 will argue the singular focus on “counterfeit” medicines has been a significant limitation of the work of the IMPACT.
The technology working group has organized two workshops, bringing together regulators and technology developers, in highlighting emerging overt, covert and forensic technologies for the detection of poor quality medicines. The stated aim of the technology working group is to disseminate information and recommendations on the merits and limitations of technologies, whereby it assesses (including piloting when feasible and necessary) technologies to prevent, deter, or help to detect counterfeit products, while taking into account the following factors: cost, scalability, specific country needs, feasibility, regulatory implications (IMPACT, 2010). While the two workshops highlighted a range of technologies, penetration at the regional, national and local level has been very limited, as each technology has its limitation, the most notable being cost, ease of implementation as well as ease of circumventing the technology (Wertheimer and Norris, 2009). Potential material quality evaluation technologies will be discussed in detail in Section 5.6.1.

Lastly, the communication working group has worked with the International Pharmaceutical Federation (FIP) in developing model information materials for health professionals as well as the general public. This includes public service announcements, booklets and fact sheets for pharmacies, drug dispensing sites as well as the general public in multiple languages, as well as a global campaign to generally raise awareness about the issue of drug quality. National medicinal regulatory authorizes as well as public health agencies, particularly in South-East Asia and sub-Saharan Africa, have noted the importance of communicating the risk, particularly where buyers acquire medicines from unregulated, or informal markets (IMPACT, 2010). A full list of the outputs of the five working groups of the IMPACT are available in the Annex of “WHO’s relationship with the International Medical Products Anti-Counterfeiting Taskforce” (WHO, 2011e; 2011f).
Despite all these significant advances by the IMPACT, the Taskforce has not been without controversy over the past six years. In 2008, for example, it was revealed that IMPACT promoted itself as a WHO project involving all 193 member-states, despite its terms of reference never having been approved by any governing body of the WHO, such as the World Health Assembly (Bate, 2008). Member-states have moreover expressed alarm at IMPACT’s “Model Elements for National Legislation,” a norm setting project that through non-tariff barriers to generic medicines, has strengthened intellectual property beyond the terms of the Agreement on the Trade Related Aspects of Intellectual Property Rights (TRIPS) (TWN, 2008).

While the WHO maintains IMPACT’s mandate to be public health with no link to intellectual property, it has framed the problem around "counterfeit" medicines, which Gopakumar and Shushikant (2010), among others, have pointed out includes elements from both civil and criminal trademark law. This is problematic, as a public health challenge such as drug quality variability, they argue, should not be pursued principally through criminal trademark law, which focuses on trademark violations, i.e. using a private company trademark such as a name, word, phrase, logo, symbol, design, image, or a combination of these elements, without the right’s holders permission (ibid). IMPACT has also proposed an expansion of that definition that could arguably cover legitimate generic medicines, as well as anti-counterfeiting measures through its *Principles and Element for National Legislation Against Counterfeit Medical Products*, the drafting of which had significant involvement from the private sector, and little input from member states (TWN, 2008).

At the 2010 World Health Assembly, a coalition of WHO member-states questioned the legitimacy of IMPACT following these controversies over guideline intentions and
alleged conflicts of interest, and succeeded in passing Resolution WHA63.23, indefinitely blocking the activities of IMPACT, pending an investigation by an intergovernmental commission regarding its mandate and affiliation with the WHO (2011e) (this is further discussed in Chapter 5). This subsequent commission was tasked with: (a) evaluating the relationship between IMPACT and the WHO, including whether this partnership should continue, b) defining the WHO's role in promoting access to medicines, and c) defining the WHO's role in promoting medicine quality, safety and efficacy (WHO, 2010e). The resolution urged all these issues to be examined, "excluding trade and intellectual property issues."

Some health and intellectual property rights scholars have warned that these unpopular decisions among WHO member states (particularly Brazil, Russia, India, and China) risk fragmenting global consensus and response to the problem of poor medicines. In order to reach consensus with these member-states, there is a need to harmonize the definition of what constitutes a poor quality medicine, while actions should also focus on identifying and removing poor quality, with drug regulatory authorities leading the efforts, using targeted measures that do not undermine access to legitimate generic medicines.

At the 2011 World Health Assembly, the Working Group of Member States on Substandard/Spurious/Falsely-Labeled/Falsified/Counterfeit Medical Products provided two comprehensive reports to the WHO Director-General, Margaret Chan, outlining “WHO’s role in the prevention and control of medical products of compromised quality, safety and efficacy” as well as examining WHO’s relationship with the IMPACT (WHO, 2011e). With respect to the WHO’s relationship with the IMPACT, the Working Group recommended an extension of the suspension, until the 2012 World Health Assembly. Regarding the
“WHO’s role in the prevention and control of medical products of compromised quality, safety and efficacy such as substandard/spurious/falsely-labeled/falsified/counterfeit medical products” (2011e; 2011f), it proposed the following four approaches to be presented to the 65th World Health Assembly in May 2012, for deliberation:

1) “The aforementioned WHO Expert Committee is suggested to form a subcommittee to give technical advice on spurious/falsely-labeled/falsified/counterfeit medical products. Such a subcommittee would enable a transparent advisory function and would rely on existing processes and structures.

2) The creation of a new international cooperation mechanism would allow coverage of the various aspects within the respective mandates of each UN organization, wherein the WHO would represent the public health perspective.

3) Creation of a new intergovernmental mechanism in collaboration with all relevant stakeholders to discuss the issue with a view to sharing best practices and reaching agreement on policy issues.

4) Set up an intergovernmental negotiating body to draw up a legally binding instrument at the international level designed to: prevent the manufacture, export, import or trade of spurious/falsely-labeled/falsified/counterfeit medical products in international markets and in international trade; and to regulate and oversee supply and distribution networks.”

In addition to the legitimacy of, and the WHO’s relationship with, the IMPACT, the member-states will deliberate on these proposals by the Working Group in order to establish the role the WHO should play in the future. In addition to multi-national fora, such as the WHO, member-states have also been establishing national strategies that will be explored in the following two sections, divided into those by higher as well as lower income countries.

2.3.3. Higher-Income Countries

According to the WHO Commission on Intellectual Property Rights, Innovation and Public Health, North America, Europe and Japan represent the top three markets for medicines representing 85% of the market, at 44%, 30% and 11% share of global pharmaceutical
sales, respectively (WHO, 2006b). To examine how higher income countries have framed and responded to the challenge of drug quality variability, this Section will outline two distinct strategies, notably employed by the United States (US) and the European Union (EU). In addition to the fact that the US and the EU comprise the two greatest pharmaceutical markets, the regions were also selected because they have made substantial institutional and resource commitments to the problem of drug quality, while their approach furthermore guides actions taken by other countries. By the latter, it is meant that many other countries around the world look to the US and to Europe, both due to the robustness of the pharmaceutical supply chain, as examples but also due to the lucrative market and opportunities for sources of funding that principally come from these two regions.

In the first instance, the US Food and Drug Administration (FDA) represents the world’s most well-resourced and extensive regulatory body (FDA, 2011a). The 2010 US Food and Drug Administration Budget Report reveals that out of an overall budget of US$2.8 billion, drug regulation costs upwards of US$1 billion alone (FDA, 2010). In this section, it will become clear why this figure is so substantial, including significant

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8 While the US and the EU have been selected for the interests of this study, it should be noted that Japan constitutes the world’s second biggest pharmaceutical market by country (WHO, 2006). In Japan, the Pharmaceutical Affairs Law (2005) regulates the manufacturing, importation, and sale of drugs and medical devices. Article 20 also outlines the following criteria for “counterfeit drugs”: (1) The drug is manufactured without prior approval; (2) The active ingredients of the drugs are inconsistent with the ingredients thereof previously approved; (3) The drugs are packed or alternated with the products of others; or (4) The duration of validity marking or label of the drugs has been altered or replaced. In Article 21, it differentiates this class of medicines from “misbranded drugs,” which directly focuses on drug quality and composition. With respect to prevalence, like many other higher income countries, Japan has only thus reported discovering “counterfeit lifestyle drugs” in the supply chain (Kimura, 2007). Anticipating the prevalence of counterfeit medicines to “be more rampant” in the future, Japan responded in 2007 by enacting more stringent customs regulations to control drug importation (ibid).
importation of its active pharmaceutical ingredients and finished products, the structure of the US pharmaceutical supply chain, the scale of dispersed distributors and vendors, as well as the large number of products that require regulation (FDA, 2011a; 2011b).

Within the US pharmaceutical supply chain, the mandate of the Food and Drug Administration is to ensure the quality of medicines in the supply chain – both in domestic manufacturing as well as through international procurement – that depend on strict standards of quality assurance and pharmacovigilence (FDA, 2011a). As a result of a robust regulatory infrastructure in high-income countries like the US, all pharmaceutical manufacturers, distributors and suppliers are subject to stringent regulations of GMP, GDP as well as GPP. With respect to imports, the US Food and Drug Administration Strategic Priorities, 2011-2015 highlights the importance of electronically or physically screening every product that enters the supply chain for compliance with regulatory requirements (Fincham, 2011). By furthermore investigating and dismantling "illicit diversion networks," the US Food and Drug Administration and associated federal investigation units claim to preventing “most” cases of infiltration of products (Lutter, 2005).

However, Light (2010) and others have suggested that the Food and Drug Administration simply does not have the resources to monitor foreign manufacturing sites or the inspection and testing of imports. It should also be noted that inspections at ports of entry are only based on a “snapshot” of information about the safety and history of the

9 Based on continuous monitoring of the supply chain, for example, regulators in the US were able to assist in an investigation where a settlement in excess of $750 million was agreed to with GlaxoSmithKline, in connection with the drug company’s distribution and manufacture of several "contaminated and substandard" medicines over a period of several years (US Department of Justice 2010).

10 Even established generic manufacturers like Canada’s Apotex have continued to face FDA warning letters about the rigorousness of their quality assurance programs (Singer 2010).
product. This poses a clear limitation, as the US Food and Drug Administration lacks the authority to require information on the manufacturers, distributors, or transporters of a drug product in a foreign country, be it active pharmaceutical ingredient source information, test results for product purity, consistency, or contamination, or certification of shipping, that are critical in the monitoring of imported product risks (Oxfam, 2011).

Another agency that is active in addressing “counterfeit” pharmaceuticals in the US is the Immigration and Customs Enforcement (ICE), and particularly its National Intellectual Property Rights Coordination Center. It reported that out of 29,842 intellectual property rights (IPRs) seizures by US Customs and Border Protection and US Immigration and Customs Enforcement in 2011, 1,239 were counterfeit pharmaceuticals, which the US Immigration and Customs Enforcement maintains is a significant undervaluation of the scale of the problem (ICE, 2012). An inter-agency group comprised of the US Food and Drug Administration, Customs and Border Protection, Immigration and Customs Enforcement, the Departments of Justice, State, and Commerce, and the Agency for International Development, furthermore published a seminal report in 2011. The Counterfeit Pharmaceutical Inter-agency Working Group Report to the US Vice President and Congress (2011) produced a report recommending the adoption of a track-and-trace system that would enable a more accurate measurement of the problem, while also flagging products hit hardest by counterfeiters.

The proposed track-and-trace strategy exposes broader limitations with the trademark framework: namely, it assumes that a drug traded within the “formal” supply chain is of adequate material quality and that the task of the US Food and Drug Administration is to prevent "unauthorized" products from entering the market. There have been reported cases, however, both of poor quality medicines traded and consumed within the formal
supply chain – as the GSK settlement in Footnote 8 illustrates – as well as other classes of poor quality medicines that fall outside the scope of the "counterfeit" definition. Moreover, the FDA (2011a) suggests that over 80% of active pharmaceutical ingredients are imported in the US from 130,000 importers at 300 ports of entry (Fincham, 2011). This makes the task of inspecting every package significantly more difficult.

Advocating for increased law enforcement of trademark violations can conversely also significantly limit access to quality, generic medicines, as the focus becomes intellectual property protection rather than protect public health from ineffective medicines. While not a substantial concern in wealthier countries where a relatively high proportion of the population have access to essential medicines, the following section will discuss these implications in the context of low- and middle-income countries, where this could have adverse effects. In examining the policy recommendations pursued within higher income countries, how the problem of poor quality medicines is defined, and therefore conceptualized, is critically important, as it guides policy and action. In the US, the problem is still defined as one of “counterfeit medicines,” as outlined in Section 201 [321] (g) (2) of the US Food, Drug and Cosmetic Act as:

"...a drug which, or the containers or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, (...) and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor."

Importantly, this definition of “counterfeit medicines” frames the problem, as Gokakumar and Shushikant (2010) show, within the domain of customs and law enforcement agencies by focusing on trademarks: these stakeholders are charged with monitoring the supply chain for unauthorized products that “bear the trademark, trade
name, or other identifying mark” at the points of manufacture, distribution and dispensing, in order to secure the formal pharmaceutical supply chain (Bate, 2008). While formally prioritizing patient safety, it can be argued that the work of national medicinal regulatory authorities in higher income countries (a) identify the patent holder as a primary victim, while also (b) placing within the domain of regulatory and law enforcement agencies the responsibility of minimizing exposure to medicines that may violate trademarks, rather than quality.

The European Union

The European Commission of the European Union has taken a similar approach to framing the problem of poor quality medicines. With respect to pharmaceuticals, the European Union has emerged as one of the most intense pursuers of stricter intellectual property enforcement (Oxfam, 2011). Outlined in "Trade, Growth, and World Affairs," this strategy was highlighted as a critical means of safeguarding and enhancing competitiveness of European business (EC, 2010). Particularly, revision of the internal customs regulation in 2003 (1893/2003) expanded the power of border officials to detain imports, exports, and in-transit goods, including pharmaceuticals, suspected to infringe any type of intellectual property, including products that may be contested under civil trademark infringement.

A study by Miller and Anand (2009) reveals, however, that over a period of 18 months between 2008 and 2009, at least 19 shipments of “legitimate,” generic medicines in transit through the European Union and intended for low- and middle-income countries, were seized or temporarily detained by customs officials for alleged infringement of patent rights. In some cases, the consignments were seized under the "confusingly similar"
trademark infringement standard, either at the behest of multinational pharmaceutical companies or on the independent authority of customs officials (Mehdudia, 2010; ICTSD, 2009). In none of the cases did the medicines infringe intellectual property in country of origin or in the recipient country (Oxfam, 2011).

EU regulation 1383/2003 has been under international scrutiny since at least 2008 and is currently under revision. Opponents have pointed to the fact that it is inconstant with Article 41 of TRIPS Agreement. By imposing their more extensive domestic intellectual property standards on the exporting and importing countries, the European Union is exceeding their WTO obligations, as the TRIPS Agreement does not require the detainment of in-transit goods, or even the checking of the intellectual property status of products that are in transit. In 2010, India and Brazil furthermore initiated independent disputes before the WTO (2010) alleging that 1383/2003 violates several WTO rules – including detainment and checking of the intellectual property status of in-transit goods – and in fact conflicts with the European Union commitments to prioritize public health under the Doha Declaration on TRIPS and Public Health. European Union policymakers refuse to acknowledge this perspective and have continued to export 1893/2003 clauses in trade negotiations as well as through bilateral technical assistance, including at the WHO (Oxfam, 2011).

In addition to protecting its ports of entry through customs regulations, EU members states have also sought a treaty to criminalize the “manufacture, supply or sale of counterfeit” drugs and other medical products and devices. In October 2011, the MEDICRIME Convention was initially signed by 15 of the 47 members of the Council of Europe (2011), making it the “first international treaty against counterfeit medical products
and similar crimes involving threats to public health.” While the protection of public health has been articulated as the principal motive for the convention, however, the convention risks being undermined for three reasons.

First, Bate and Attaran (2011) argue MEDICRIME criminalizes the deliberate falsification or intentional “offer to supply counterfeit products,” which could affect legitimate manufacturers of unintentional mistakes, i.e. bad batches, which occur frequently. Secondly, this could affect access to generic medicines, as generic launches or products in transit may not violate intellectual property rights in the country of origin and destination, but may be criminalized by this treaty (ibid). Lastly, as a result, this could severely affect the relationship between the EU and other manufacturing countries, such as India and Brazil, who have voiced their concern over the EU’s strategy against drug quality and safety, particularly as the process has lacked transparency and consultation from other stakeholders (ibid). In the following section, the approach by the US and EU will be contrasted with a number of low- and middle-income countries.

2.3.4 Low- and Middle-Income Countries

While high-income countries have placed emphasis on protecting their regulated, formal supply chains and framing poor quality medicines as a trademark violation that can be criminalized in trademark law, governments of low- and middle-income countries must contend with the presence of informal markets and more fundamentally financial and infrastructure constraints. Despite greater ubiquity of a distinct form of market vulnerability to poor quality medicines, state governance and law enforcement strategies have nevertheless been emphasized. In this section, three distinct classifications of the problem
will be presented from four low- and middle-income countries: Kenya, Nigeria, China, and India. There are three reasons for the selection of these countries.

First, these countries represent a diverse range of populations and gross domestic products among low- and middle-income countries (China: 1.34 billion, US$7.3 trillion; India: 1.21 billion, US$1.68 trillion; Nigeria: 170 million, US$239 billion; Kenya: 43 million, US$35 billion) (CIA, 2012; IMF, 2011). Moreover, each of the countries also has sizable domestic drug production capacity, producing both active pharmaceutical ingredients and finished medicines (mainly generics) for domestic consumption, but importantly also for export, regionally and globally. Lastly, each of the four countries will offer an example of a novel approach, both in defining but also in responding to the problem: Kenya’s adaptation of the EU’s criminalization approach, Nigeria’s perceived success against counterfeits, India’s whistleblower scheme, and China’s state-controlled regulation. It is important to reinforce the fact that this section will not present an in-depth analysis of each country, but rather a snapshot of notable features vis-à-vis framing the problem of poor quality medicines.

Kenya’s Anti-Counterfeiting Act (2008)

In 2008, Kenya enacted an Anti-Counterfeiting Act, providing several measures aimed at targeting the general availability of counterfeit goods in the country (MSF, 2008). The drafting of the Anti-Counterfeiting Act was strongly supported by external actors, including IMPACT, worked more closely with the Ministry of Industry rather than the Ministry of Health (MSF, 2008). While the bill does have some positive aspects, it also contains several provisions that could limit the government’s ability to provide access to
essential medicines, such as to the estimated 1.4 million Kenyans living with HIV/AIDS (ibid). Some commentators have argued that the expansive definition of what constitutes a counterfeit medicine may target generic medicines that are legally available in Kenya, because they may infringe intellectual property rights held by someone anywhere in the world, even if not patented in Kenya (MSF, 2008).

The MSF Essential Medicines Access Campaign (2011) furthermore indicates that the bill needlessly confuses counterfeiting with violations of non-trademark intellectual property rights, while also weakening existing Kenyan legislation allowing parallel imports. This would certainly delay generic competition while doing nothing to improve the quality or safety of medicines. However, while high-income countries have the resources to monitor their supply chain and investigate spurious medicines, Kenya remains limited. Moreover, while it is too early to comment on the consequences of the Anti-Counterfeiting Act, public health experts have pointed to the failure by Kenya to prioritize a framework that places the safety risks of poor quality medicines along with an appropriate response.

In April of 2012, the Kenyan High Court accordingly ruled against the Anti-Counterfeiting Act, stating that it was too “vague and could undermine access to affordable generic medicines since the Act had failed to clearly distinguish between counterfeit and generic medicines” (UNAIDS, 2012). This challenge by the Kenyan High Court, along with civil society support, has highlighted the inappropriateness of transferring strategies employed in higher income countries, such as the MEDICRIME Convention, within low- and middle-income countries. Particularly noting the potential impact this Act could have on access to generic medicines underscores the lack of harmonization and coherence in how
countries define the problem, and more importantly differences between higher and lower income countries with respect to best strategies.

**Nigeria: Scaling up Regulatory and Law Enforcement Measures**

Unlike Kenya, where a resource limited government welcomed the consultation of members of IMPACT, Nigeria is a substantially larger and wealthier country, with almost four times the population and seven times the GDP of Kenya (CIA, 2012; IMF, 2011). Nigeria, however, has significant challenges with corruption, including in its pharmaceutical sector (Garuba, Kohler and Huisman, 2009). Accordingly, prior to 2001, a number of studies revealed that upwards of 40% of the medicines traded and consumed in Nigeria were fake or counterfeit, while 68% of medicines were unregistered (Akunyili, 2008). In 2001, Dr. Dora Akunyili, whose sister had died from tainted insulin, became the director of the Nigerian Food and Drug Administration (NAFDAC). During her tenure, the NAFDAC implemented sweeping strategies and safeguards that studies reveal have reduced the presence of counterfeit medicines by over 80% between 2001 and 2004 (Akunyili, 2006).

In addition to reorganizing its eight directorates to reduce corruption, NAFDAC recruited regulatory authorities, as well as restructured and modernized regulatory processes by adopting new standard operating procedures and guidelines. Moreover, the existing drug distribution system, as well as databases on health related activities were updated, with additional legislative changes increasing penalties for deliberate counterfeiting (ibid). The Port Inspection and Enforcement department furthermore provided help to the agency to address the problems resulting from inspections gaps and poor enforcement activities (Wertheimer and Norris 2009).
In addition, NAFDAC embarked on a massive campaign to create awareness of the problem to the general public. Thus, with the increased capacity of drug regulatory and enforcement officers, awareness campaigns resulted in enlistment of the public, providing them with the tools for identifying medicines of spurious quality. In 1993, the NAFDAC established the Nigerian Counterfeit and Fake Drugs and Unwholesome Processed Foods Decree that classified a ‘fake drug’ as:

“(a) any drug product which is not what it purports to be; or
(b) any drug product which is so coloured, coated, powdered or polished that the damage is concealed or (...) which is not labelled in the prescribed manner or which (...) bears any statement, design, or device which makes a false claim for the drug or which is false or misleading; (...) 
(e) any drug product which is not registered by the Agency (...)”

Departing from the emphasis on trademarks by the US Food, Drug and Cosmetic Act, the Nigerian characterization of the problem as one of fake medicines focused on deliberate misrepresentation – clauses (a) and (b) – as well as enforcing registration of drug products with the registry. Recognizing Nigeria’s insufficient capacity for a comprehensive regulatory and quality assurance infrastructure, the NADAC instituted the appropriate punitive instruments that would enable law enforcement to respond to “misrepresentations” and “unregistered” products.

While no longer centralizing the patent holder as the primary victim, the Nigerian characterization of ‘fakes’ nonetheless confers the problem to law enforcement. Despite the Nigerian response to poor quality medicines and having received global praise in prioritizing public health, engaging the public and tackling corruption and supply chain vulnerabilities, it has come at tremendous cost, institutionally and personally. Raids of local markets where pharmaceuticals are sold formally and informally demonstrate both the high rates of poor
quality medicines still prevalent in the country – ranging between 15-30% (Akunyili, 2008) – as well as the illicit nature of the trade in Nigeria: local merchants and traders have begun firing back, necessitating the support of the military in these raids. While the Nigerian response has been hailed as a great success story, there are critical challenges, particularly as corruption is pervasive as Garuba, Kohler and Huisman (2009) show, with drug registration and inspection of ports posing the greatest sources of vulnerability.

**China: An Axiom of State Control**

China is one of the world’s top producers of medicines across the quality spectrum (Nelson, 2006). Despite its membership to the World Intellectual Property Organization since 1980, and the World Trade Organization since 2001, China and India have been identified as the two greatest sources of poor quality medicines (Bronshtein, 2008). Consequently, China has consistently appeared on the US Trade Representative Special 301 Watchlist of countries failing to adequately protect intellectual property rights and responding to IP infringement (ibid). However, much like Nigeria’s transformation of its pharmaceutical regulatory agency, China has attempted to take steps in responding to poor quality medicines, particularly with its growing pharmaceutical market.

In “The Pharmerging Future,” China is identified as the fastest growing market for medicines over the next decade, expected to climb to third globally by 2013 (Hill and Chui, 2009). Domestic responses to this demand have resulted in thousands of generic pharmaceuticals companies proliferating throughout the country, often operating outside the formal supply chain (Schwartz and Wong, 2006). In one example, the deliberate counterfeiting of drugs in the Chinese city of Yiwu, with a population of 650,000, was shown
to account for over 26% of the city’s tax revenue, enlisting over 30,000 wholesale distributors (Hill and Chui, 2009). China has since announced that over 192,000 deaths occur every year from the consumption of poor quality medicines in China (Schwartz and Wong, 2006).

At the 2010 International Conference of Drug Regulatory Authorities organized by the WHO, the Director of Drug Supervision and Inspection at the State Food and Drug Administration highlighted key strategies undertaken by China in tackling poor quality medicines (Sun, 2010). In developing legal mechanisms for responding to the problem, Articles 48 of the Chinese Drug Administration Law, identifies a drug as counterfeit either if “ingredients in the drug are different from those specified by national drug standards” or “a non-drug substance is simulated as a drug or one drug is simulated as another” (ibid). Furthermore, a drug “shall be treated as a counterfeit drug” if:

“(1) use is prohibited by regulations of the drug regulatory (...) under State Council;
(2) it is produced or imported without approval, or marketed without being tested;
(3) it is deteriorated;
(4) it is contaminated;
(5) it is produced by using drug substances without approval number (...);
(6) the indications or functions indicated are beyond the specified scope”

From this classification, two deductions can be made about the Chinese framing and response to poor quality medicines. First, there is a strong emphasis on centralized state control and regulation (Schwartz and Wong, 2006). Sub-sections (1), (2), and (5) highlight the need for products to be registered, approved and catalogued by the drug regulatory body under the State Council. A second derivation is the strong punitive component of ‘counterfeiting’ in China, where its chief drug regulatory official was sentenced to death in 2007 for taking bribes to approve untested medicines. In November of 2011, for example,
over 1,700 suspects were arrested, and over US$315 million in counterfeit medicines were confiscated in a week-long raid. This has come as a response to the criminalization of poor quality medicines, while commentators have questioned whether these raids can restore public trust, as the problem is pervasive throughout the country, and a lack of transparency or public accountability has resulted in authorities often being implicated (Bronstein, 2008).

India: “Spurious Medicines” and Whistleblower Schemes

India is often considered the “pharmacy of the world,” as its robust generic drug industry serves as the main source of medicines for most countries in low- and middle-income countries (MSF, 2007; Srinivasan, 2011; Daemmrich, 2009). Because India is the greatest supplier of essential medicines to low- and middle-income countries (over 67% according to MSF, 2007) due to its low cost, there has been notable attention to the safety, efficacy and quality of the medicines that are exported. Interestingly, in the Indian Drug and Cosmetic Act and Rules of 1940 and 1945, respectively, a central piece of legislation regulating the manufacture, sale, and quality of drugs and formulations, provides a definition of “spurious drugs” under section 17-B.4:

“1. If it is manufactured under a name which belongs to another drug; or
2. If it is imitation of, or is a substitute for, another drug or resembles another drug in a manner likely to deceive or bears upon it or upon its label or container the name of another drug unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other drug; or
3. If the label or container bears the name (…) purporting to be manufacturer of the drug, which individual or company is fictitious or does not exist; or
4. It has been substituted wholly or in part by another drug or substance; or
5. If it purports to be the product of manufacturer of whom it is not truly a product.”

By focusing on “spurious” medicines rather than counterfeit, fake or poor quality, the Indian state instead is suggesting that the central challenge is an inability to determine the
quality, composition and provenance of medicines. This is not to suggest that India does not have a problem with poor quality medicines, but rather that a lack of ability to determine these features has exacerbated the trust between health system and patient. In 2003, the Indian Ministry of Health and Family Welfare commissioned a report (‘Mashelkar Committee Report’) that identified the following contributing factors to the proliferation of “spurious” medicines:

“Lack of enforcement of existing laws; weak penal action; very remunerative trade; large-scale sickness in small scale pharmaceutical industry; availability of improved printing technology that helps counterfeiting; lack of coordination between various agencies; too many retail and wholesale outlets; inadequate cooperation between stakeholders; lack of control by importing/exporting countries.”

In addition to strengthening its regulatory capacity and exploring anti-counterfeiting packaging technologies (CII, 2009), India has also initiated a whistleblower scheme, that is intended to “burst the fake medicines racket with rewards of up to 2.5 million rupees” (60,000CDN) for informers (Jayaraman, 2009). The ambitious scheme, overseen by the government’s Central Drugs Standard Control Organization, was prompted by media reports of a high prevalence—as much as 25%—of spurious drugs on the market. Yusuf Hamied, managing director of Cipla, India’s leading generics maker, told Nature Medicine he was furious over attempts by the foreign corporations to treat genuine Indian generic drugs as counterfeits just because they could not patent their original products in India. “Such an interpretation means I cannot ship my generics through their ports,” Hamied says. He cites a Feb 2009 incident in which a shipment of Cipla’s HIV drugs was held up by officials in Amsterdam en route to Peru.

While examples of how some low- and middle-income countries have framed and responded to the problem of poor quality medicines, this list is not by any means exhaustive.
They were mainly to highlight specific strategies by key drug producing countries, as well as the complexity in framing and responding to the problem. The following section will subsequently outline the framing and approach that has been undertaken by multinational pharmaceutical countries.

2.3.5 Multinational Pharmaceutical Companies

According to Cockburn et al (2005), multi-national pharmaceutical companies have historically been hesitant of releasing information on ‘counterfeit’ medicines, fearing reputational damages to their branded products (Outterson and Smith 2006). A convergence of increased public awareness along with the proliferation of poor quality medicines, particularly in many middle-income countries, constituting a significant emerging markets for medicines, has led multi-national pharmaceutical companies to formalize anti-counterfeiting strategies.

The International Federation of Pharmaceutical Manufacturer’s Association (IFPMA) is also an important stakeholder during the 1992 meeting organized by the WHO that led to the present definition of counterfeit medicines. Particularly because the IFPMA represents the research-based pharmaceutical industry, is has strongly defended the protection of intellectual property rights, focusing on the criminalization of trademark violations. As a result, civil society groups have been vocal in criticizing the WHO for their affiliation with the IFPMA. Indeed, the IFPMA has been very supportive of the IMPACT, which a number of public health and civil society groups, along with member-states of the WHO have recently condemned for forwarding an IP agenda on poor quality medicines, rather than a public health one. Following Resolution WHA63.23 in 2010 indefinitely
blocking the activities of the IMPACT, IFPMA (2010) released their Ten Principles on Counterfeit Medicines, particularly with the intent of reinforcing their “commitment” to public health:

1) “Medicine counterfeiting is first and foremost a crime against patients.
2) Counterfeit medicines threaten the full spectrum of legitimate medicines.
3) Patents have nothing to do with counterfeiting and counterfeiting has nothing to do with patents.
4) All substandards are not counterfeits.
5) A medicine that is authorized for marketing by one regulatory authority but not by another should not be regarded as counterfeit.
6) Government regulatory and enforcement authorities must be fully vested with the proper power and adequately resourced to fight counterfeits.
7) Stopping the international trade in counterfeit medicines is vital.
8) All stakeholders across the pharmaceutical supply chain must be made aware of health threats posed by counterfeit medicines and collaborate.
9) Global cooperation is needed.
10) The leadership of the World Health Organization is crucial.”

Another organization that has been active vis-à-vis drug quality is the Pharmaceutical Security Institute (PSI), a trade organization established by the Brand Protection and Product Security directors of 14 major multi-national pharmaceutical companies. The PSI maintains the most comprehensive global database of counterfeit drug information, but researchers, the WHO, health authorities, and the public are not given access to this database (Outterson and Smith 2006). The reason for this, the PSI argues, is that the sources as well as methods for collecting the data is sensitive, and would compromise their ability to continue their work should “counterfeiters learn how and where we collect the data” (Guido, 2011). Against a recent economic analysis, from an industry perspective, it is more profitable to frame the problem as one of abuse of intellectual property (Bate, 2009). Similarly, pharmaceutical companies have a strong incentive to discourage the use of TRIPS
flexibilities by confusing these drugs with criminal counterfeits, and Sell (2008) has argued that these companies are using IMPACT to pursue this agenda.

2.4 Conclusion

In this chapter, the problem of variability in drug quality was described, while pointing to the importance of drug regulation in ensuring access to safe and effective medicines within the pharmaceutical supply chain. Following a review of the data outlining the scale and scope of the problem, the Chapter also outlined the various terms that have been used in the literature to describe variability in drug quality. Subsequently, the Chapter provided an overview of the various classifications, as well as responses, by the multiple stakeholders that are affected, including the patient and her community, the WHO, regional and national strategies by high- as well as low- and middle-income countries, and finally by pharmaceutical companies.

Following a brief overview of the research methodology and limitations in Chapter 3, the thesis will refocus on the various stakeholders that were outlined in Section 2.3, and map their organization and interaction within the pharmaceutical supply chains of higher, as well as low- and middle-income countries. In Chapter 4, it will be argued that each faces distinct vulnerabilities, necessitating context specific responses. This will be followed in Chapter 5 by suggesting the need for a re-classification of the problem as one of drug quality, rather than contemporary focus on counterfeits.
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~ CHAPTER THREE ~

Research Methodology

According to Teddlie and Tashakkori (2003), a research undertaking should incorporate multiple perspectives, from problem identification through to the drawing of final inferences. Indeed, empirical research is said to be particularly compelling when different methods and different data lead to the same result (White, 2011). The combination of empirical and qualitative research, however, will not necessarily lead to similar results: rather than one validating or invalidating the other, they are instead more likely to indicate different constructions of the studied phenomenon. If this is the case, criteria will need to be developed to assess the meanings of the congruencies and such discrepancies (Flick, 2007). These relationships are often established and the criteria sustained by the extent to which the strengths of one approach compensate for the limitations of the other.

As a research methodology, triangulation was derived from the practice in navigation and surveying where two precise bearings are used in order to calculate the position of a third (White, 2011). In this instance the two initial bearings are not used to check or verify the other but, rather, to complement each other in order to identify the particulars of the third; in other words, to obtain different but complementary data on the same topic. In research, however, the usual intention is to establish how different approaches or strategies relate to one another. Empirical researchers, for example, might seek to establish how different approaches or strategies check, validate or corroborate one another and qualitative researchers might seek to establish how they enhance understanding of, or elaborate one another (Brannen, 2005).
What neither can do, however, is seek confirmation of what they triangulate. Any attempt to do so would be based on fallacy (Hart, 2005). The best that can be hoped for is that triangulation illuminates aspects of a phenomenon or indicates different frames of reference to broaden the interpretive repertoire (ibid). Herein, three criteria are required: internal validity, external validity and reliability of the analysis (Newman et al, 2003). The three dimensions of internal validity include: face validity (does the analysis/framework measure what it is supposed to measure), concurrent validity (does the analysis/framework correlate with those that have been previously validated) and predictive validity (is there statistically significant correlation between the analysis/framework and subsequent concrete observation) (White, 2011).

External validity, also called generalizability or applicability, is a measure of the extent to which research results can be extrapolated. Both breadth and depth of sources and data will typically increase the extent to which research findings can be generalized. The third criterion for triangulation is reliability, which is the extent to which research is consistent in what it measures (White, 2011). Ideally, triangulation of research should be both valid and reliable, although the former carries more importance, as it indicates the extent to which research has achieved what it set out to do (Cryer, 2006).

Since reliability rests on the assumption of a single, observable and objective reality, and thus presents problematic when applied to qualitative studies, the related concept of dependability is appropriate. The latter represents a measure of the extent to which a reader, on the basis of the evidence presented concurs with the findings of the research (White, 2011). The primary mechanism to enable them to do so is “thick description,” or where the richness of the description indicates the density of the layers of meaning with which the
interpretation has had to deal. This enables auditability to the reader, enabling her to follow the interpretive process and understand the findings derived from it (ibid).

In this thesis, triangulation is used within an analytic methodology for mediating between multiple perspectives. The definition of mixed methods is research in which the investigator "collects, analyzes, mixes, and draws inferences from both quantitative and qualitative data in a single study or a program of inquiry" (Creswell and Plano Clark, 2007). The key word here is 'data', no reference is made to empirical or qualitative methods (White, 2011). So, in terms of this definition mixed methods research validly incorporates the term mixed methodology research.

Triangulation as a method is used in this thesis for mediating between various data that is obtained from publicly available documents. A comprehensive document analysis was derived from a number of sources. These include: international organizations (among them, the World Health Organization, the International Medical Products Anti-Counterfeiting Taskforce, the International Federation of Pharmaceutical Manufacturers and Associations, INTERPOL, Medicines Sans Frontiers, Oxfam, etc), national medicinal drug regulatory authorities (the US Food and Drug Administration, the US Pharmacopeia, the European Union, and the National Agency for Food and Drug Administration and Control of Nigeria, among others), multinational pharmaceutical companies as well as publications and field studies by academics and other authors from around the world. Analysis of the findings was also based on publications that were sourced from the University of Toronto libraries, as well as from a 2010 Conference in Toronto, Canada by the International Pharmaceutical Academy on "Combating Counterfeit Medicines."
The reports that were analyzed were predominantly published between 2008 to 2012, although other studies and publications from 1999 to 2008 were also incorporated. Out of over 600 publications, over 350 were selected and cited in this thesis. Although no rigorous criteria for inclusion were developed, these included: reliability of sources, originality of ideas, verifiability of research methodology, appropriateness to thesis topic. Preference was therefore reserved for: primary sources of data, reports from reliable international organizations such as the WHO and/or research labs, publications in peer reviewed journals, and arguments based on reliable evidence. These reports were moreover supplemented by a survey of available technology platforms, proposed both by national regulatory bodies as well as proprietary companies, for forensic drug quality assessment. Many of the latter were derived from the scientific literature, as well as from a 2008 conference by the technology working group of the International Medical Products Anti-Counterfeiting Taskforce.

In addition to these reports, an extensive literature review of relevant publications was undertaken, ranging from public health, infectious disease, public policy, political science, economics, evidence based medicine, and quality systems theory. The following terms were searched in the query (one from each group): (a) ‘drugs’, ‘medicines’, ‘medical’, ‘pharmaceuticals’, ‘therapeutics’, and (b) ‘quality’, 'spurious', 'counterfeit', 'substandard', ‘fake’, 'poor', ‘adulterated’, ‘falsified’, ‘falsely-labeled’, ‘inauthentic’, ‘mis-branded’, ‘non-genuine’, and ‘unauthorized’. Additional searches for ‘quality systems’, ‘information asymmetries’, ‘corruption’, and ‘trust’ were undertaken with the terms in group (a).

This search was also undertaken on Summon (http://query.library.utoronto.ca/), a multidisciplinary unified search index that combines databases, books and journals from
publishers and open access sources, together with the University of Toronto library
catalogue and local collections. The Summon index allows deep searching, including full
text for the majority of e-journals. Notably, the four terms that appeared in the literature
more frequently include: “counterfeit medicines” returned 3,286 result, followed by
“spurious medicines” (550), “substandard medicines” (265), and “falsely-labeled medicines”
(5).

The analysis of the thesis was grounded in the study objective, namely examining the
prevalence of poor quality medicines from a public health perspective. A problematitization
and triangulation of available documents led to the challenging of the current framing of a
counterfeit medicine, and moreover prompted the criteria for a new classification of drug
quality based on material quality and main channels of distribution. This was furthermore
supported by three quality frameworks – quality-by-enforcement, quality-by-regulation and quality-
by-evaluation – that were analyzed based on the following criteria: how the issue is framed, the
primary victim that the framework identifies, as well as the target stakeholder and proposed
intervention by each framework.

3.1 Research Limitations

There are a number of inherent and significant research limitations that must be
acknowledged. In the first instance, the methodology of this thesis is entirely analytical, as no
fieldwork was conducted. As a result, all the data is based on primary and secondary data
that would be accessed through the University of Toronto libraries as well as keyword
searches online. The publications and documents were moreover based on public
availability. This may potentially be a limitation, as much of the work in this field that is
undertaken by multi-national pharmaceutical companies is confidential, and may not be represented. Moreover, any local studies or reports, particularly from low- and middle-income countries, that have not been translated or made publicly available would also have been missed. Similarly, no key informant interviews or surveys were conducted, furthermore limiting the explanatory capacity of the findings to available documents, rather than first-hand accounts from stakeholders who are directly engaged.

Another critical research limitation is that an established qualitative research methodology, e.g. grounded theory was not used. While triangulation and analysis of the available data may illuminate key ideas, there are limits to analytic rigour in the absence of content analysis or qualitative research software. For example, neither the analysis of the results from the web searches, nor the criteria for including publications were sufficiently transparent. While these criteria would ideally be elucidated, the analytic triangulation methodology utilized in this thesis suggests that if sufficient data from multiple and diverging sources are analyzed, it should yield sufficiently valuable conclusions.

It should also be noted that although it has been a strength rather than a limitation, the interdisciplinary of this thesis added complexity to the analysis. Broaching the fields of pharmaceutical sciences, political science, information sciences, quality systems theory as well as trade and law, the harmonization of its findings may require further substantiation within each field. Here again, the triangulation methodology suggests that coherence in the analysis indicates potential convergences that may have been difficult to attain in a single discipline. Further suggestions for addressing some of these limitations are presented in Chapter 7 of this thesis.
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While comprehensive data on drug quality variability remains limited, the WHO (2009a; 2010) claims that the pharmaceutical supply chains of wealthier countries remain less vulnerable to the problem of poor quality medicines, as outlined in Section 2.2. As was subsequently argued, where access to medicines through regulated pharmaceutical supply chains is low, the demand for informal markets for medicines increases (WHO 2004a; Lybecker, 2007). While these informal and often poorly regulated markets pose a greater risk due to greater uncertainty of the quality, provenance and composition of medicines sourced, higher income countries are not immune to vulnerabilities in the supply chains.

The following chapter will therefore begin by outlining the distinct vulnerabilities posed by the increased globalization of supply chains over the past twenty years, as well as the proliferation of online pharmacies on pharmaceutical supply chains of higher income countries (Woo, Wolfgang and Batista, 2008) (4.1). This will be followed by exploring the vulnerabilities in low- and middle-income countries (4.2), where it will be suggested that informal markets and limited capacity for pharmacovigilence and drug quality regulation often lead to greater variability in drug quality, as well as greater prevalence of poor quality medicines, posing a significant health risk to patients and health systems.

It will subsequently be argued that while distinct vulnerabilities between higher and lower income countries exist, the central challenge can be explained by a number of information asymmetries between stakeholders (4.3). Linking these information asymmetries to the responses by the stakeholders will be further explored in Chapter 5, where an
argument will also be made for an alternate framework for information asymmetries offering a more appropriate reflection and response to the challenge of variability and poor quality of medicines.

4.1 Vulnerabilities in Drug Supply Chains: High-Income Countries

As has been shown in Sections 2.1 and 2.3.3, higher income countries have benefited from greater regulatory capacity for pharmacovigilence and pharmaceutical supply chain management (Bate, 2008). While variability in drug quality remains a more pressing public health and health systems problem in low- and middle-income countries, there is an emerging literature that has also suggested increasing vulnerabilities within pharmaceutical supply chains of higher income countries (Mackey and Liang, 2011). Regulatory authorities within high-income countries have mainly pointed to two main sources of vulnerability in accessing quality medicines: the “globalization of supply chains” as well as proliferation of online pharmacies (Woo, Wolfgang and Batista 2008). This means a greater proportion of active pharmaceutical ingredients as well as finished medicines are increasingly imported from, primarily, middle-income countries such as China and India (ibid). This globalization of supply chains therefore poses a new set of regulatory challenges supplementary to regulating domestic manufacturing and circulation of medicines.

This is captured in Figure 4.1 (inspired by Lybecker, 2008 and Yankus, 2006), representing an abstraction of the pharmaceutical supply chains of higher income countries, as well as its vulnerabilities at the ports-of-entry and online pharmacies. In addition to domestic manufacturing, high-income countries import most of their medicines through international drug procurement. These imports of finished products and APIs as well as
purchasing medicines from online pharmacies – which will be discussed in section 4.1.2 below – expose vulnerabilities in the supply chain, as the provenance, composition and quality of these products can sometimes be unknown, as will be discussed below.

![Diagram of drug supply chain](image)

**Figure 4.1. Vulnerabilities of drug supply chains: high-income countries.** In higher income countries, a greater proportion of medicines are procured through domestic manufacturing, while drug importation from regulated international drug production sites is also significant. In addition to the medicines and APIs that are imported through the ports of entry, many of which increasingly come from middle-income countries, the proliferation of online pharmacies pose a danger to the patient and other stakeholders along the supply chain.

### 4.1.1 Globalization of Supply Chains for Drugs and Raw Ingredients

As stated in the previous section, since the late 1990s, an increasing proportion of both finished pharmaceutical products and active pharmaceutical ingredients are imported from abroad (Woo, Wolfgang and Batista, 2009). This includes the 300 US ports of entry that are accessed by over 130,000 importers, procuring medicines from over 300,000 foreign facilities (Fincham, 2011). According to Woo, Wolfgang and Batista (2008), manufacturing
sites in India and China alone comprise over 40% of all US Food and Drug Administration registered foreign sites. A number of factors have contributed to this “globalization of supply chains.” These include the growing cost of medicines (particularly biologics and drugs for chronic disease management), the fiscal incentives for outsourcing the production of APIs and medicines to emerging drug manufacturing countries, as well as the rising rate of mergers and acquisitions that have granted multinational pharmaceutical companies from the US, Europe and Japan greater control of generic companies in middle-income countries such as India.

It can be argued that the cost savings to drug manufacturers by outsourcing drug production could translate into lower prices and greater access to medicines for patients. It should also be noted, however, that a globalization of procurement practices may also lead to reduced awareness of the provenance, composition and quality of medicines, as has been widely reported, including Dangerous Doses, where the authors provides an extensive list of medicines that have penetrated the US pharmaceutical supply chain (Eban, 2005). The top five drug classes that are counterfeited and/or imported into US supply chains include: alimentary (including diet pills, as well as medicines for lowering cholesterol and erectile dysfunction), anti-infectives, cardiovascular, central nervous system, cytostatic (anti-cancer medicines) (Miller and Duggan, 2010). As Woo, Wolfgang and Batista (2008) furthermore explain, globalizing supply chains requires more brokers, distributors, re-packagers, and import-export firms to facilitate transportation, warehousing, and distribution of the medical products. This exposes opportunities for stakeholders to purchase medicines that may not be of sufficient quality or composition, or may threaten public health.
Many medicinal regulatory authorities, such as the US Food and Drug Administration, have admitted of gross under-resourcing for regulatory resources of foreign sites, such as those allocated to inspection and testing, relative to the rapid growth of imported drugs and APIs (Fincham, 2011; WHO, 2009a). In an effort to control the domestic pharmaceutical supply chain, one strategy by regulatory bodies has been to commit to greater electronic or physical screening of shipment of drugs, biologics, medical devices, and cosmetics for compliance with applicable regulatory requirements (Woo, Wolfgang and Batista, 2008).

At least from studies within the US, the admissibility decisions are alarmingly only based on a “snapshot” of information about the safety and history of the product at ports-of-entry (Mackey and Liang, 2011; Woo, Wolfgang and Batista, 2009). This poses a limitation as the US Food and Drug Administration lacks the authority – beyond voluntary and limited memorandum of agreements – to require information on the manufacturers, distributors, or transporters of a drug product in a foreign country, be it active pharmaceutical ingredient source information, test results for product purity, consistency, or contamination, or certification of shipping or disposition information, that have become useful in the monitoring of imported product risks (ibid).

Since 2004, the US Food and Drug Administration has on multiple occasions proposed the adoption of Radio Frequency Identification technologies to secure the pharmaceutical supply chain, in addition to more robust track-and-trace pedigree (FDA, 2006a; Lefebvre et al. 2011). Some authors have opposed efforts to standardize the utilization of radio frequency identification (RFID) due to cost and infrastructure demands that would have to be borne by distributors, wholesalers and manufacturers who have thus far been reluctant (Mackey and Liang, 2011). Paxton (2011) furthermore states that radio
frequency identification systems are difficult to implement, would require interoperability between different actors, as well as an ability for systems to communicate using standard protocols, and the added costs and logistical challenges of changing internal processes of shipping and handling. Mackey and Liang (2011) furthermore shows that there are funding challenges in implementing radio frequency identification technologies, as just the cost of implementation a US Food and Drug Administration e-pedigree mandate has been estimated at $84,000 for individual pharmacies to $1.3 billion for large-chain pharmacies (Law and Youmans, 2011).

While there are often a limited number of wholesalers within high-income countries (e.g. over 90% of all pharmaceuticals within the US supply chain go through only three regulated wholesalers), distributors would play an important intermediary role between these wholesalers and hospitals/pharmacies. Resistance by distributors to standardize radio frequency identification and other track-and-trace pedigree systems is based on the fact that it could affect their slim profit margins: in addition to the possibility of pedigree systems revealing the list of distributor’s vendors and clients. It would also require greater human and capital resources to manage.

4.1.2 Proliferation of Online Pharmacies

An additional challenge when patients seek access to lower cost medicines is direct procurement of pharmaceuticals over the Internet, often without the need for a prescription (St Jean, 2011). Where online pharmacies cross jurisdictions, they may furthermore avoid meeting regulatory requirements (Veronin and Youan 2004). A study by the US Food and Drug Administration in 2006 concluded that in more than 50% of cases, medicines
purchased over the internet from websites that conceal their physical address have been found to be counterfeit, including those for cancers and cardiovascular diseases, according to the WHO (2009b). The same US Food and Drug Administration (2006b) study also warned that 85% of drugs that were advertised as being of Canadian origin were actually from other countries, many of which were determined to be ‘counterfeit’. In another study by Columbia University in 2008, out of 159 websites offering controlled drugs, over 85% did not require a prescription (CASA, 2008).\(^\text{11}\)

The ease of setting up bogus internet pharmacy sites and the willingness of consumers or unethical resellers to send them money has led to difficulties in regulating this market. The Royal Canadian Mounted Police, for example, have investigated over 157 suspicious websites between April 2010 and April 2011, leading to numerous high-profile seizures and arrests across Canada (St Jean, 2011). Globally, the International Criminal Police Organization (INTERPOL) has also been coordinating an international week of action to tackle the online sale of “counterfeit and illicit” medicines. *Operation Pangea* has thus far shut down 290 websites, seized over one million pills and made 76 arrests (ibid).

While these various efforts by regulatory and law enforcement authorities in high-income countries have limited the prevalence of poor quality medicines in the pharmaceutical supply chain, there are emerging vulnerabilities that will test their resources

\(^{11}\) One strategy undertaken in 2008 by the Royal Pharmaceutical Society of Great Britain (RPSGB, 2009), the professional and regulatory body for pharmacists in the United Kingdom, as well as the UK Medicines and Healthcare Products Regulatory Agency, includes providing approved and registered online pharmacies with a logo and registration on the ‘General Pharmaceutical Council’ website. Public service announcements, including the ‘Real Danger’ campaign launched in 2011, served to inform the public that medicines ought to be purchased from registered online pharmacies only, as they were recognized by the UK regulatory authorities and subject to regulation (RPSGB, 2009).
and capacities. In the following section, however, the distinct vulnerabilities in many low- and middle-income countries will be discussed. Rather than the threat of online pharmacies, and in addition to the challenges of globalized supply chains, it will be argued that these countries report limited drug regulatory capacity, while moreover suffering from the proliferation of informal markets where the quality, composition and provenance of medicines are often unknown.

4.2 Vulnerabilities in Drug Supply Chains: Low- and Middle-Income Countries

All available sources – including news reports, drug quality studies, and estimates by organizations such as the WHO – indicate a much higher prevalence of variability in drug quality within low- and middle-income countries (IMPACT 2010). In addition to resulting in significantly higher rates of morbidity, mortality, and drug resistance in these countries, the pervasiveness of variability in the quality of medicines has furthermore led to significant deficits in both public health capacity as well as confidence between patients and the health system (White, 2004; Wertheimer and Norris 2009). The challenge of ensuring the quality of medicines must be understood against the backdrop of two billion people, predominantly in low- and middle-income countries, that lack regular access to essential medicines that the WHO (2004b; 2004c) estimates leads to over ten million avoidable deaths a year. This global drug gap has been explained in the literature as a convergence of numerous market and governance failures (Kohler 2007; Pennefather, et al 2010).

4.2.1 Factors Exacerbating the Drug Access Gap

In high-income countries, demand for medicines is often met by a combination of domestic manufacturing capacity and drug procurement through strong purchasing power
(Wertheimer and Norris, 2009). According to an IMS report of the top 20 pharmaceutical performers, every company listed was based either in North America, Europe or Japan (MMandM, 2011). Collectively, these three regions furthermore consume 85.6% of the global share of pharmaceuticals, according to a WHO (2006) *Commission Report on Intellectual Property Rights, Innovation and Public Health*, while South-East Asia and sub-Saharan Africa account for only 4.6% and 1.1%, respectively. In addition to physical access to medicines, however, transparent networks of drug distribution and a dynamic quality control model centralized within responsive regulatory agencies are needed to establish credibility and trust between the health system and patient (Falagas et al, 2007). In many low- and middle-income countries, the drug access gap is exacerbated by a number of these market and governance failures (Kohler, 2006).

First, in economic terms pharmaceuticals are said to be price inelastic, wherein demand does not dictate price, which remains very high (Lybecker, 2008). Justifying the large margins between manufacturing cost and market price, multi-national pharmaceutical companies have pointed to the high operational costs, e.g. clinical trials, research and development, marketing (DiMasi et al, 2003). Some figures for the cost of bringing a typical new molecular entity to market have been as high as $802 million (DiMasi et al, 2003) and $1.32 billion (DiMasi et al, 2007; PhRMA, 2009), while Kieff and Epstein (2011) highlight the low success rate of drug development.\(^\text{12}\) The perceived necessity of medicines and a lack

\(^{12}\) There is significant controversy around the cost of bringing a drug to market. The figures by DiMasi et al (2003, 2007) and PhRMA (2009) have been heavily challenged since their publishing. Angell (2004), for example, shows that this figure is a gross over-representation of the true cost of drug development, particularly since pharmaceutical companies release little data on how they derive their research and development costs and other expenses, including marketing and failed clinical trials, are often included in these estimates. Recent estimates, have
of suitable substitutes have resulted in a market model where costs such as research and development or marketing are transferred to the buyer (ten Ham, 1992).

Monopoly pricing of medicines can moreover be indirectly protected for pharmaceutical companies in member states of the WTO by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Although flexibilities have since been introduced, TRIPS signatory member states are required to grant a patent holder twenty years of market exclusivity on pharmaceuticals, and therefore prevent competition which would lower price. Outterson and Smith (2006) show how for brand name drugs protected under patents, while the marginal cost of production over commercial price remains low, pricing ratios can be upwards of 200:1 (Moon and t’Hoen, 2000). This would be more difficult, Outterson and Smith (2006) argue, in the absence of strictly enforced intellectual property laws, as generic competition would lower commercial price to a range closer to marginal cost of production.

In 2000, the Doha Declaration on TRIPS and Public Health reiterated existing flexibilities to the TRIPS Agreement that promote access to medicines – namely compulsory licensing and parallel importation – as well as the impact that drug prices may have on access. Further mechanisms for pooled procurement have moreover led to price reductions (particularly for HIV/AIDS, tuberculosis and malaria), high drug prices still pose a significant barrier to access. According to the 2011 WHO World Medicines Report, per capita pharmaceutical expenditures ranged from as little as US$ 7.61 in low-income countries to US$ 431.6 in

therefore offered more modest figures for the cost of drug development. The review paper by Morgan et al (2011), which evaluates existing figures, argues for a figure closer to US$92-883.6 million, while Light and Warburton (2011) suggest a more accurate median drug development cost of $149 million.
high-income countries, with considerable country variation within individual income groups (WHO, 2011). For many patients served by health systems in low- and middle-income countries, additional challenges of limited and unreliable access to affordable health insurance or medicines through the public sector have resulted in over 90% paying for medicines out-of-pocket (WHO, 2004c; Cameron et al., 2009).

According to Flynn et al. (2009), this saturation in purchasing power by households as well as fixed percentage that is spent on pharmaceuticals by health systems in resource-poor settings creates economic disincentives to make patented medicines affordable: lowering prices to reach a larger market is unlikely to increase returns to producers despite a higher unit sales. This was echoed by Amartya Sen (1999), who described markets as "notoriously defective" in dealing with public goods. With medicines, Sen further argues, markets eventually create an “artificial” and “unpredictable scarcity”, leading to a “market failure of undersupply” (Greeve 2008; Pogge, 2005).

These “market failures” are further exacerbated by limited financial, technical, and human resources within many low- and middle-income countries, diminish their capacity for drug manufacturing, or public health or regulatory investments (Kohler, 2007; Moon and t’Hoen, 2000). The August 30, 2003 amendment to the Doha Declaration and TRIPS Agreement was intended to explicitly address limitations in manufacturing. By stipulating that WTO member states, under a health emergency – as individually defined by each state – can take advantage of flexibilities under Article 31 of the TRIPS Agreement to import compulsory licensed medicines from countries with manufacturing capacity (Kohler, 2007). Despite the legal authorization, governments of low- and middle-income countries, for a variety of political and trade related reasons, have not fully taken advantage of this
mandated right to bypass property rights in accessing essential medicines (Greve, 2008). Inspired by Lybecker (2008) and Yankus (2006), Figure 4.2 highlights existing vulnerabilities within the pharmaceutical supply chains of many low- and middle-income countries.

**Figure 4.2. Vulnerabilities of drug supply chains: low- and middle-income countries.** A lower proportion of medicines are typically procured through domestic manufacturing, while drug importation from regulated international drug production sites is also significantly lower than in higher income countries. In addition to the proliferation of local, informal markets where the provenance, quality and composition of medicines is often unknown, variability in drug quality is exacerbated by limited capacity for regulation of the pharmaceutical supply chain due to human, technical and financial resource gaps.

As shown in Figure 4.2, a significantly lower proportion of medicines are produced domestically or imported or procured from international markets, as compared to higher income countries. Two distinct vulnerabilities will be outlined in the following sections, including the proliferation of local, informal markets where the provenance, quality and
composition of medicines is often unknown, as well as limited capacity for regulation of the pharmaceutical supply chain due to human, technical and financial resource gaps.

4.2.2 Drug Regulatory Capacity Gaps

Even when medicines are available and affordable, many low- and middle-income countries face additional capacity gaps in drug regulation. According to the WHO (2010, 2012), only about 20% of the 193 member states have effective medicine regulation; of the remaining countries, about 50% implement medicine regulation at varying levels of development and operational capacity, while 30% either have no medicine regulation in place or a very limited capacity that hardly functions, limiting the capacity for monitoring the quality of medicines.

While Ombaka (2009) suggests that as much as half of all procured medicines may be “lost” during delivery, the WHO (2004c) suggests two thirds of the Member States have either inadequate or no means of controlling drug quality, with only two WHO (2009a; 2009b) pre-qualified laboratories operational in the entire continent of Africa. This was corroborated at a 2009 meeting organized by the WHO, where African regulators noted that 29 of the 46 countries in sub-Saharan Africa that were sampled had minimal medicines regulatory capacity, while 14 had none at all (WHO/AFRO 2009).

There are a number of financial and technical challenges to improving the quality and safety of medicines in poor countries. First, government authorities responsible for keeping poor quality medicines out of the supply chain are "chronically underfunded" (Oxfam, 2011). This is compounded by a lack of adequate, trained human resources, as high turnover results from low salaries, lack of incentives, and poor morale that can
undermine effectiveness of regulatory mandates (WHO 2010). This may subsequently create opportunities for corruption, which the WHO (2009c) Good Governance for Medicines program has identified as a major impediment to ensure access to quality medicines. Particularly when laws have not been enacted to mandate regulation, health authorities are left unable to set up basic administrative processes to identify which medicines may be lawfully sold in the country (Oxfam, 2011).

Where regulations are in place, difficulties with enforcement have led to little if any monitoring of what is produced, imported and traded.\(^{13}\) In the absence of capital, technical and human resources that compromise the effectiveness of drug regulatory authorities or operational quality-control laboratories, even buying from regulated pharmaceutical sources may not offer an assurance of quality or safety. This was highlighted in the WHO (2009d) report that evaluated the quality of key anti-malarial medicines in ten sub-Saharan African countries. Some of the countries where alarming proportions of medicines failed international quality metrics include Senegal (44%), Madagascar (30%), and Uganda (26%) (interestingly, medicines procured from the public sector of Uganda, possessing some regulatory capacity, were free from any quality defects).

4.2.3 Informal Markets

Many of these market and regulatory failures – including drug access gaps, excessive cost of medicines relative to income, as well as limited capacity for drug regulation – have resulted in unmet needs for safe and effective medicines that are not readily satisfied by the

\(^{13}\) Oxfam (2011), for example, reports that the country of Belize only has one inspector, working in the absence of any formal registration process for medicines; meanwhile, Lesotho, with a population of over two million, is said to have only 21 trained pharmacists, with just 3 in the public sector.
types of regulated sources that have evolved in high-income countries. For those seeking lower cost alternatives, these factors have enabled an expansion of the pharmaceutical market structure, creating opportunities for the trade of medicines outside the regulated pharmaceutical supply chain. These "informal" markets often operate outside the jurisdiction of regulated supply chains, while also providing a significant proportion of effective medicines in many low- and middle-income countries, as users of such informal markets often have limited options of accessing essential medicines elsewhere (Wertheimer and Norris, 2009; Seiter, 2009).

Unlike regulated markets that enable the capacity for quality control of medicines at the point of manufacture, distribution and dispensing, poorly regulated or informal markets present opportunities for many unauthorized points of entry, enabling misunderstanding of what is being acquired (Goodman et al 2007; Kesselheim 2008). These poorly regulated, local markets therefore follow a structure profuse with indeterminable manufacturing and distribution conditions, posing a clear public health risk, as therapeutic safety and efficacy demand knowledge of the provenance, composition and quality of medicines (Pennefather, et al 2010). Subsequent therapeutic failure or adverse events can result in a lost of confidence in the health system and the systems of drug control and enforcement (Gautam, 2008). Unlike formal markets that principally have a mandate of protecting a closed supply chain through quality control monitoring, unregulated markets present many unauthorized points of entry that enable misunderstanding of what is being acquired (Goodman et al, 2007; Kesselheim, 2008).

Some countries, such as India, have used the term "spurious" medicines to denote products where quality, manufacturing and distribution conditions are difficult to ascertain
(Mashelkar, 2003). The growing prevalence of such spurious medicines can be attributed to a number of factors. First, informal markets are said to be operating within a "high reward, low risk" environment (Bate, 2008). This means that the profits gained from selling poor quality medicines are significant due to the pricing ratio of medicines, described in Chapter 2, while the risk of being caught or penalized is low, particularly as regulatory and law enforcement capacity is limited in many countries. According to the WHO, more than US$4.1 trillion is spent on health services worldwide each year, while pharmaceuticals total $750 billion annually in global sales, and may account for up to 50% of total health spending in some developing countries (WHO, 2009c).

Another figure that is frequently cited in the literature comes from the US Center for Medicines in the Public Interest. In 2006, it proposed, but never explained, its projection that the informal pharmaceutical sector represents 10% to 15% of the legitimate market, with predictions that revenues will reach $75 billion by 2011 (WHO, 2006; Nelson et al, 2006). It should be noted, however, that the Center for Medicines in the Public Interest is a non-governmental organization that is principally funded by the pharmaceutical industry, and "was originally a project of the Pacific Research Institute, an older corporate front established in conjunction with Philip Morris to fabricate academic support for the tobacco industry" (Fang, 2009). It is therefore surprising that their estimates, which have never been justified, have been repeatedly cited, including by the WHO (2006).

Concurrently, the risk of operating within the informal pharmaceutical supply chain can be remarkably low (WHO, 2006). The high number of dispersed actors creates multiple points of entry, especially as a diffuse omnipresence of informal vendors in urban areas remains a difficult market to control (Wertheimer and Norris, 2009). While registered drug
distributors and vendors can be subject to regulation and enforcement, little is known about informal local vendors and pharmacies as they lack the training to evaluate the quality of medicines (Nelson et al, 2006). This task is made more difficult as access to more sophisticated equipment and technology for copying chemicals has become more prevalent (Fernandez, 2008). There are also many opportunities for policy arbitrage that are not in the interest of the end-user within semi-stable markets that link multiple agents who subsequently take advantage of high demand by simultaneously acting as producers and consumers (Greve, 2008). This ultimately creates a market structure profuse with spurious medicines, where manufacturing and distribution conditions and therefore provenance, composition and quality are difficult to ascertain.

In Chapter 5, the vulnerabilities in the pharmaceutical supply chains described in this Chapter will be discussed through the framework of information asymmetries – representing transactions where one party has more or better information than the other – influencing trust between the patient and the health system. It will be argued that in environments where information asymmetries are more structural, e.g. resource-poor settings in low- and middle-income countries, there is a greater need for reliance on mechanisms for evaluating quality and thereby mediating trust between the stakeholders in health systems.

In proposing three distinct quality frameworks (quality by enforcement, quality by regulation and quality by evaluation), Chapter 5 will argue that the counterfeit approach – represented by the quality by enforcement framework – has shown efficacy in some higher income countries in reducing the prevalence of poor quality medicines. Meanwhile, the quality by regulation (i.e. strengthening regulatory capacity) as well as the quality by evaluation (i.e. enabling material quality evaluation) frameworks, it will be argued, would
have the most efficacy, particularly in many low- and middle-income countries where regulatory gaps and informal markets introduce uncertainty.

4.3 Conclusion

In Chapter 4, the distinct vulnerabilities experienced in high-incomes countries, as well as low- and middle-income countries, were presented. In the former, the globalization of supply chains, i.e. procurement of active pharmaceutical ingredients and finished medicinal products from foreign production sites, as well as the proliferation of online pharmacies were identified as the primary sources of medicines with potentially indeterminate provenance, quality and composition. This would explain why higher income countries turn to greater regulation of existing supply chains, including by customs officials, as well as enforcement of trademark infringements by online pharmacies.

Conversely, in many low- and middle-income countries, variability in the quality of medicines begins with gaps in access to medicines, which together with gaps in regulatory capacity, have led to a proliferation of informal markets where patients acquire medicines. In these countries, a focus on law and regulatory enforcement is limited, as regulatory capacity and penetration is limited in poorly regulated, informal markets. In Chapter 5, it will be argued that these informal markets represent information asymmetries, necessitating a new classification of the problem that is based on local experiences. By promoting a drug quality concept that emphasizes material quality rather than “intention to deceive,” Chapter 5 will end by arguing for developing distinct quality frameworks, to be outlined in the Discussion (Chapter 6).
4.4 References


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~ CHAPTER FIVE ~

Results: Information Asymmetries and Defining Drug Quality

Medicines regulation, as discussed in Section 2.3, is needed to ensure that all pharmaceutical products on the market are safe, effective and consistently meet approved quality standards (WHO, 2003). As was shown in Chapter 4, however, all countries experience varying forms and degrees of vulnerabilities that may introduce medicines with indeterminate provenance, composition and quality into the pharmaceutical supply chain. It has moreover been suggested that in higher income countries, well-resourced, formal regulatory mechanisms often exist, while pharmaceutical supply chain management is more rigorously enforced. In these countries, the principal risk of medicines with poor or unknown provenance, composition and quality is at the ports of entry, including the importation of increasingly foreign-sourced APIs and finished medicinal products, as well as online pharmacies, where little regulation often exists (Woo, Wolfgang and Batista, 2008).

Like wealthier countries, low- and middle-income countries also face challenges of monitoring the ports of entry, particularly as limited manufacturing capacity may lead to greater reliance on importation to satisfy the drug needs of populations. As per capita spending on health is also significantly lower in low- and middle-income countries, they may rely more readily on lower cost medicines procured from other low- and middle-income countries. These lower income countries may also subsequently experience greater regulatory lapses, as documented in drug-exporting countries such India and China, where regulatory mechanisms for drug quality control have been shown to exist for domestic consumption and export.
In addition to the ports-of-entry, Section 4.2 furthermore highlighted two additional vulnerabilities that low- and middle-income countries in particular may experience, that may introduce uncertainty with respect to drug quality, composition and provenance. First, reduced technical, human and capital resources have limited the capacity of many countries to institute the needed institutional and regulatory mechanisms necessary for monitoring the pharmaceutical supply chain. For example, out of 26 national medicines regulatory authorities that constitute 88% of the population of sub-Saharan Africa, only 4 (15%) undertook all five main regulatory functions (marketing authorization, licensing, inspection, quality control and pharmacovigilence), while only 8 (30%) undertook quality control (WHO, 2010a).

In addition to limited regulatory capacity, the convergence of reduced levels of health spending, greater gaps in access to medicines, and lower household purchasing power in most low- and middle-income countries have moreover led to the emergence of informal markets where individuals obtain medicines. While figures do not exist as to the scale of these informal markets relative to the formal and more regulated pharmaceutical supply chains, anecdotal evidence and various research teams have suggested these informal markets constitute a significant source of medicines, particularly for the most marginalized populations in both urban and rural settings. These informal markets often operate outside the jurisdiction of national medicines regulatory authorities, thereby introducing uncertainty in the provenance, composition and quality of the medicines that are traded and consumed.

In the following chapter, these varying vulnerabilities of pharmaceutical supply chains will be explored through the framework of information asymmetries in health systems. In Section 5.1, it will furthermore be suggested that information asymmetries with respect to
the provenance, composition and quality of medicines can lead to a loss of trust between the patient and health system, as described by Bloom, Standing and Lloyd (2008). This will be followed in Section 5.2 by proposing the challenge that begins with the lexicon by which the problem is defined, particularly as key stakeholders in many low- and middle-income countries are increasingly and publicly voicing their mistrust with the current ‘counterfeit’ and ‘substandard’ frameworks. Rather than fixating on these terms that emphasize intent to deceive, that many authors have argued pursue the protection intellectual property rights, a new taxonomy for drug quality will be presented that emphasizes material quality, and thus public health.

To justify this shift from the current WHO characterization of the problem as one of counterfeit medicines that emphasizes “intent to deceive,” Section 5.3 will rigorously deconstruct the concept of quality, its centrality to a public health focused strategy, and moreover why this can lead to a greater level of trust between the various stakeholders. In Section 5.4, three distinct quality frameworks will subsequently be presented: quality-by-regulation, quality-by-enforcement, and quality-by-evaluation. With respect to the problem of poor quality medicines in low- and middle-income countries, it will be shown that the evidence suggests quality-by-enforcement has limited effect, quality-by-regulation must be reinforced, while quality-by-evaluation has remained an under-utilized opportunity. Lastly, Section 5.5 will present areas of research beyond the scope of this thesis that would present exciting future opportunities.
5.1: **Asymmetries in Information Economics**

While comprehensive data on the scale and scope of poor quality medicines remains unavailable, Section 4.2 presented evidence of significantly higher prevalence rates in most low- and middle-income countries (IMPACT, 2010; Newton et al, 2011). In Chapter 4, it was furthermore shown that these higher prevalence rates correlate to greater vulnerabilities in the pharmaceutical supply chains of these low- and middle-income countries, as limited regulatory capacity and the prevalence of informal markets expose buyers to medicines without known provenance, composition and quality.

According to Cohen, Mrazek, and Hawkins (2007), there are seven key decision points in pharmaceutical systems, where processes may be vulnerable to corruption: manufacturing, registration, selection, procurement, distribution and prescribing and dispensing. The authors furthermore provide a methodology for a diagnostic tool to assist regulatory authorities with assessing the vulnerability to corruption at these core decision points (ibid). In the absence of regulatory oversight or transparency with respect to these decision points, the buyer may be unable to make rational economic or health decisions, as they could acquire products that may not have the perceived characteristics and qualities.

A useful framework for understanding vulnerabilities in health systems, including those within pharmaceutical supply chains, comes from the field of information economics, a branch of microeconomic theory that studies how information affects economic decisions. Information economics begins with the assertion that information has economic value, as it allows individuals to make economic choices, such as purchasing medicines from a particular vendor. The literature on the importance of information flows for the functioning of the markets is extensive (Stigler, 1961; Bellver and Kaufman, 2005). Stiglitz (1999) has even
argued that access to information and transparency ought to be considered as a human right.

Transparency is herein defined by Kaufmann (2002) as the “increased flow of timely and reliable economic, social and political information, which is accessible to all relevant stakeholders” (Vishwanath and Kaufmann, 1999). Beyond the human rights and the market efficiency arguments, it has also been argued that transparency is moreover critical for human development because it increases the efficiency in the allocation of resources, providing incentives for redistribution and inclusiveness (Bellver and Kaufman, 2005). In this regard, the concept of transparency is closely linked to accountability, as information can reduce uncertainty among actors within a free-market (Florini, 1999).

An imbalance in power occurs in transactions (or decisions) where one stakeholder has more or better information than the other, which is also described as information asymmetries. With respect to the pharmaceutical system, a report by the World Bank’s Human Development Network (HDN, 2002) highlighted three key principles that may limit transparency and exacerbate corruption. The first example is the principal-agent problem, which arises when one stakeholder, the ‘agent’, has some information that another stakeholder, the ‘principal’, cannot observe directly (or vice versa), and where the objectives of the two do not align (ibid). With respect to pharmaceutical systems, and notably the purchasing of medicines, this can lead to the inappropriate enforcement of laws and regulations, such as inadequate or ineffective quality assurance procedures.

In the second example, moral hazard, the authors highlight the need for appropriate incentives to maximize the possibility of optimal performance. This applies when the actions of a stakeholder are not verifiable, or private information is transmitted. In this case, moral
hazard, representing a situation where there is a tendency to take undue risks because the costs are not borne by the party taking the risk, connoted the “endogenous variables which cannot be directly observed or perfectly controlled” (HPN, 2002). This principle explains the “low risk, high reward” environment in which poor quality medicines have been explained.

Herein, stakeholders may have little incentive to high quality medicines, as the costs of deliberately selling poor quality medicines may be less than the likelihood of being detected. Many economists have argued that this problem of moral hazard can best be controlled by the implementation of specific incentives that reward good performance, serving as a check against incomplete information.

The last principle described in HPN (2002) is that of information asymmetries, where one party knows certain relevant information of which the other party is unaware. Arrow (1963), Ruger (2008), and others have described information asymmetries as a particular limitation of health systems in free-market enterprises, as the conditions for efficient market allocation may remain unattainable. These information asymmetries produce market failures that necessitate public intervention, including with respect to regulation in the pharmaceutical supply chain (Ruger, 2008).

5.1.1 Informal Markets and Information Asymmetries

In many low- and middle-income countries, a number of inherent information asymmetries exacerbate the presence of informal markets. In addition to gaps in access to defined quality medicines through the formal pharmaceutical supply chains, deficiencies in professional and institutional regulatory capacity significantly reduce the risk of operating in informal markets, as a diffuse network of informal vendors remains a difficult market to
control (Pennefather et al, 2010). While registered drug distributors and vendors can be subject to regulation and enforcement, little is known about informal local vendors and pharmacies as they often lack the training to evaluate the quality of medicines (Nelson, Visuranga and Chang 2006).

Markets for medicines in high-income countries offer consumers a certain degree of protection, as the products traded and consumed are subject to regulatory mechanisms at the point of manufacture, distribution, dispensing and sale. In contrast, the structure of markets for medicines in many low- and middle-income countries are characterized by more “laissez-faire” and "caveat emptor" – or ‘buyer beware’ – forces, often resulting from selectively applied regulation (Tu and Ma, 2007). These less structured markets are capable of selling a full range of products, but the composition, provenance and quality of these products is often difficult to ascertain by the economic actors within those markets.

The gaps in regulatory structure present opportunities for many unauthorized points of entry that enable misunderstanding of what is being acquired (Goodman et al, 2007; Kesselheim, 2008; Seiter, 2009). A critical problem in low- and middle-income countries is the paucity of available information on the drugs available in local markets. Assuming that resources within a “laissez-faire” market are allocated using a price mechanism, as described

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14 In regulated markets, the seller typically has a responsibility to ensure that the product or service that is sold abides by the regulatory standards of said market. With respect to medicines, for example, national medicinal regulatory authorities such as the US Food and Drug Administration ensure that products sold to patients pass safety and efficacy standards. Where markets are more poorly regulated or insufficient information is available to the buyer, i.e. informal markets, a situation arises where the buyer has to be more vigilant of what she is buying. This is captured in "caveat emptor," latin for 'let the buyer beware', indicating either that regulation or information is insufficient and the buyer ought to be more vigilant.
by von Hayek (1945), access to relevant information would enable local economic agents to confidently make decisions on how to most cost effectively allocate health resources.

When available information in a transaction is incomplete, e.g. when medicinal composition, provenance and material quality are unknown, there can be negative public health consequences. It can moreover promote the "low risk, high reward" environment described above, promoting criminal behaviour that includes the trade of medicines of poor quality (Savedoss and Hussman, 2006; Bate, 2008). Lack of information additionally enables tremendous variability in the price of even high standard drugs, further complicating the use of medicine price as a signal of quality and value.\(^\text{15}\)

Another dimension of information asymmetry within the health system involves the patient attributing ineffectiveness of a medicine to the severity of an illness (or iatrogenic factors of a strained health system) rather than the composition or quality of the medicine (Bloom, Standing and Lloyd, 2008). Similarly, drugs that do not produce an immediately observable therapeutic effect enable suppliers to reduce or altogether omit active pharmaceutical ingredients. A cholesterol-lowering drug like atorvastatin calcium, for example, can be produced at a fraction of the cost of either obtaining the correct API or obtaining cheaper versions of unknown quality (Outterson and Smith 2006).

Limited capacity for monitoring drug use for therapeutic effectiveness or adverse events and the widespread predominance of these information asymmetries globally have led experts to conclude that cases where poor quality medicines are detected can only be the "tip

\(^{15}\) Health Action International (HAI, 2010) conducts annual global surveys of the price of selected medicines available in different countries. In 2009 they found a 20,000-fold range in the price of the antibiotic ciprofloxacin and in 2010 they demonstrated a 5,000-fold range in the price of insulin (See: http://www.haiweb.org/medicinesprices/).
of the iceberg" (Mukhopadhyay, 2007). In 2004, for example, a batch of Ringer’s lactate infusions destined for Medicines Sans Frontiers in Darfur was “serendipitously” discovered to be contaminated with fungal growth (Caudron et al, 2008). In a subsequent investigation by the WHO, the over 2000 batches were reported to have past through three intermediaries – including UN agencies and relief organizations – with eventual recalls only having recovered 15% of the batches (ibid).

5.1.2 The Concept of Trust in Health Systems

Bloom and Standing (2001) have argued that information asymmetries are an inherent feature of all health systems – as multiple stakeholders are involved with varying degrees of information – and may further complicate access to "competent health care," including quality medicines. Their effect, however, remains more pronounced where health markets are unorganized, porous and/or poorly regulated. Because health systems of many low- and middle-income countries may reflect a historical legacy of the "construction and subsequent decay" of particular institutional arrangements, households have increasingly relied on community-level institutions to "regulate" markets and organize social protection (Bloom, Standing and Lloyd, 2008).

This is also reflected in data on health expenditures, as a very high percentage of health care transactions in lower income countries take place through "self-treatment," including the purchasing of medicines from local and often informal markets (Cederlof and Tomson, 1995; Whyte, Van der Geest, and Hardon, 2003). Such "unorganized" markets have been described as suboptimal in terms of efficiency, equity and quality (Hsiao, 2000). In such environments, the concept of trust emerges as a critical relational and "socio-
psychological" phenomenon that serves as an impotent “social lubricant” (Thiede, 2005; Arrow, 1963; Hall, 2001).

As a means of managing information asymmetry, trust is also conceptually linked to social capital as the "glue" which creates functioning institutions, reducing the complexity and risks that come from the autonomy of others, such as drug vendors in informal markets (Woolcock, 2001; World Bank, 1999). Herein, trust offers a correction to economic individualism in understanding critical challenges and building institutional and ethical legitimacy (Gilson, 2003).

Bellver and Kaufman (2005) have highlighted the important role that transparency can have in building trust in institutions among citizens. Within pharmaceutical supply chains, greater transparency with respect to the provenance, composition and quality of medicines would enable buyers as well as consumers of these products to develop trust, as well as reinforce concepts of good governance, including independence, accountability and integrity of markets (ibid). In the following section, the need for greater governance as well as transparency will be argued to promote trust between stakeholders, linking information asymmetries to how the problem of poor quality medicines is defined. To satisfy the mandate of the WHO, namely that poor quality medicines are principally a public health problem, it will be argued that ‘counterfeit’ classifications, emphasizing “intent to deceive,” undermine the central challenge of material drug quality, while furthermore exacerbating information asymmetries and diminishing trust between the various stakeholders in pharmaceutical supply chains.
5.2: Quality and Counterfeits: What Are We Measuring?

At the 63rd World Health Assembly in 2010, a broad coalition of WHO member-states supported a resolution that called for international focus on the problem of poor quality medicines. Beyond mere dissatisfaction at the scale and speed of activities that the WHO and its partner institutions were engaged in, resolution WHA63.10 expressed concern that the activities and partnerships of the IMPACT could undermine its public health mandate in which the problem of poor quality medicines was framed. The following year, at the 2011 World Health Assembly, the “Working Group on Substandard/Spurious/Falsely-labeled/Falsified/Counterfeit Medical Products” was formed and subsequently charged with two tasks: (a) providing clarity on the role of the WHO in the prevention and control of medicinal products of compromised quality, safety and efficacy, and (b) investigating the relationship between the WHO and IMPACT (WHO, 2011a).

At the very core of the issue was the way the problem was defined (WHO, 2011b). As described in Section 2.2, the WHO has currently prioritized and defined the problem with respect to “counterfeit medicines,” which emphasizes "deliberate mislabeling as to identity or source.” Through the Rome Declaration, the IMPACT has also expressed its aim of the “promotion and promotion of public health,” and clarified the fact that counterfeit medicines are “principally a public health problem.” (IMPACT, 2010). From this, it follows that the patient is subsequently identified as the principal victim of these products.

There are, however, growing practical uncertainties between “counterfeit medicines” and other classifications, including substandard, fake and spurious medicines, as the WHO
has acknowledged that the “deliberate” and “fraudulent” intents to deceive can often be
difficult to prove from analysis of the content of a drug preparation (Wondemagegnehu,
1999). In India, for example, while nearly 30% of drugs are considered of poor material
quality, or “substandard,” only 0.5% would fall within the WHO “counterfeit” definition
(Bate and Porter, 2009). While IMPACT has proposed a change to its definition of
“counterfeit medicines” by incorporating the concept of “false representation,” a footnote
causes circular logic, wherein “false representation” is stated to be counterfeiting done
“fraudulently and deliberately” (ibid).

Furthermore, while the current and proposed definitions of “counterfeit” medicines
state that patent disputes must not be “confused” with the issue of drug counterfeiting, the
definitions do not explicitly state that patent violations are not counterfeiting. The new
definition therefore does not clarify whether “counterfeiting” must be done deliberately or
whether criminal intent or careless behaviours are necessary elements (Bate and Porter,
2009). According to legal analyses by Third World Network (2008), the proposed re-
definition of counterfeit also applies to false representations of identity or source applied to
“the product, its container or other packaging or labeling information,” raising the
possibility that generic versions of off-patent drugs could be considered counterfeit on the
basis of similar trade dress or drug labeling.

For this reason, numerous WHO member states, including India and Brazil, have
used the World Health Assemblies over the past three years to highlight the activities of
IMPACT, arguing its re-definition of “counterfeit” medicines is an "indirect attack" on their
generic drug industries (Gopakumar and Shahukant, 2010). In a 2008 WHO Report to the
Secretariat, for example, IMPACT had recommended that member-states lacking specific or
effective legal instruments for combating “counterfeit” medical products resort to non-specific legislation related to trademark protection (WHO, 2008). While this pragmatic approach provided a window for the member-states that lacked effective regulatory infrastructure to enforce legal instruments in combating the problem, the objections to the WHO Secretariat warned that it could lead to an abandonment of the public health (WHO, 2011b).

What these efforts at the WHO demonstrate, is a call by member-states to recentralize the problem as one of drug quality to avoid the limiting applications of terms like fake, counterfeit or substandard (ibid). While the term spurious has also been used, its application extends only in so far as requiring further elucidation: it denotes a pharmaceutical product for which composition and quality have not been determined. These efforts furthermore suggest the call by member-states to move beyond a ‘counterfeit’ framework that prioritized legal and enforcement strategies (Gopakumar and Shashikant, 2010).

Two conclusions follow from these pursuits by WHO member-states at the World Health Assembly since 2010. First, there is an acknowledgement that resource constraints in many low- and middle-income countries have lead to poor capacity to regulate the formal pharmaceutical supply chain, while informal markets furthermore pose a challenge to drug quality evaluation. Moreover, if the public health consequences and the material quality of medicines are identified as the central challenges, the responses and strategies at the national and international level ought to centralize the patient as the principal victim, rather than the patent holder, which represent legal and enforcement mechanisms, as will be argued in Section 5.5 and 5.6.
5.2.1 A New Taxonomy for Drug Quality

These reflections by WHO member-states, as articulated by the *Working Group* and the World Health Assembly Resolution, on the ideal strategy for pursuing the problem of drug quality have necessitated, in the first instance, a reconceptualization in how the problem is defined, particularly as countries lack agreement in defining the problem. The following section will therefore present a classification that is based on a number of variables that focus principally on material drug quality. Figure 5.1 below, adopted from Seiter (2009), illustrates the broad spectrum of classifications of variable drug quality.

**Table 5.1. Classification of Drug Quality Based on Material Quality and Distribution**

<table>
<thead>
<tr>
<th>Class of medicines vis-à-vis quality</th>
<th>Main markets; channels of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Proprietary or generic drug of known provenance, quality and composition</strong>, including active pharmaceutical ingredient (API) that corresponds to international pharmacopeia</td>
<td>All countries; distributed through both formal and informal supply chains</td>
</tr>
<tr>
<td><strong>2. Deliberate copy misrepresented as proprietary or generic branded drug containing correct quality and composition</strong></td>
<td>Mainly high- and middle-income countries; distribution via Internet or non-medical informal outlets</td>
</tr>
<tr>
<td><strong>3. Deliberate fake of proprietary or branded drug</strong> containing incorrect quality and/or composition (i.e. over-, under-, no-concentration of API, or alternate composition)</td>
<td>Mainly middle-income countries where original drug has significant market share; sold through formal distribution chains and informal channels</td>
</tr>
<tr>
<td><strong>4. Deliberate fake of generic branded drug</strong> containing incorrect quality and/or composition (i.e. over-, under-, no-concentration of API, or alternate composition)</td>
<td>Low-income populations within low- and middle-income countries; predominantly through informal channels</td>
</tr>
<tr>
<td><strong>5. Copy (‘mimic’) of known proprietary or generic drug that does not intend to misrepresent</strong>, but also do not contain correct concentrations of API</td>
<td>Low-income populations within low- and middle-income countries; predominantly through informal channels</td>
</tr>
<tr>
<td>6. Registered drugs that contain wrong or incorrect amounts of the right ingredients (e.g. contaminated, mislabeled, expired) from failures in quality assurance</td>
<td>Low- and middle-income countries with a weak regulatory system; through formal, including public-sector outlets, as well as informal channels</td>
</tr>
</tbody>
</table>
**Class 1** represents much of the world’s drug supply, including proprietary and generic medicines of known provenance – with ascertainable information on manufacturing and distribution – as well as quality and composition that correspond to national and international pharmacopeia (WHO, 2009). Accordingly, medicines within this class would have known therapeutic safety and efficacy, enabling the health practitioner and patient to make a more informed decision on their use. Within regulated pharmaceutical supply channels, such as in high-income countries, these medicines are available through “formal” markets, including regulated hospitals, pharmacies and other authorized and monitored retailers. While this class poses a low risk to the patient if the drug is used appropriately (not accounting for otherwise adverse drug events), these products may nonetheless be available through informal channels, such as resale of intercepted or stolen shipments.

Class 2, 3 and 4 are collectively distinguished for being “deliberate fakes” that herein designate products that intentionally misrepresent the content, formulation, source and/or other components of the active pharmaceutical ingredient or excipient. Differences among these classes are based on the product that is being misrepresented and the concentration of active pharmaceutical ingredient. **Class 2** medicines include products made with the correct ingredients in the correct proportions to mimic proprietary pharmaceuticals. Because they imitate predominantly high-valued lifestyle drugs, these classes would be marketed at relatively high prices primarily in high- and middle-income countries, and distributed via the Internet and other non-medical outlets outside regulated markets. While they may contain the correct concentration of active ingredients and generally adhere to pharmacopeia standards, details of their manufacturing and distribution procedure are generally unreported.
Conversely, **Class 3 and 4** are non-equivalent products that are substituted for proprietary or generic medicines, respectively, but that are not truly functionally equivalent, e.g. do not always generate a biopharmaceutical response that closely matches, within specified limits, that of the medicine being substituted for. This can include products that contain too much, too little or no concentration of the correct API, or use an alternative active pharmaceutical ingredient altogether. According to studies, however, these products rarely contain any active ingredient or clinical benefit, and are sometimes prepared with toxic chemicals (Newton et al, 2006; Newton et al, 2008; Seear et al, 2011; Nair et al, 2011). While some deliberate fakes are easily discovered because of their obvious poor quality, more sophisticated technologies are enabling deliberate counterfeiters to make nearly indistinguishable copies; when manufacturers of pharmaceutical equipment send specifications for parts, for example, the information can be intercepted by unauthorized agents who outfit themselves with the same equipment (ibid; Fernandez et al, 2008).

It can be argued that these “deliberate fakes” – namely, Classes 2, 3, and 4 – collectively constitute what the WHO defines as “counterfeit medicines.” In placing emphasis on their “deliberate misrepresentation,” this classification fails to distinguish between products that can have therapeutic benefits (Class 2) and those that could pose safety risks to the patient (Class 3 and 4). Moreover, Class 3 and 4 are non-equivalent products that are substituted for proprietary or generic medicines, respectively, but that are not truly functionally equivalent (e.g. do not always generate a biopharmaceutical response that closely matches, within specified limits, that of the medicine being substituted for). This narrow distinction of drug quality as ‘counterfeits’ furthermore excludes other classes of medicines that could pose a public health risk.
Class 5 medicines, for example, would represent unregistered products that do not deliberately imitate proprietary or generic products, nor do they adhere to international pharmacopeia. Because available data is scant, this is a very poorly understood or reported class, with anecdotal examples suggesting high prevalence particularly within informal markets of poorly regulated supply chains (Singh et al, 2006). Because this class does not represent a direct infringement of intellectual property, it often falls outside the purview of the mandate of law enforcement and regulatory bodies. As a consequence, this group of medicines poses an elevated risk to patients, particularly in communities least likely to have the capacity to ascertain quality or identity. With Class 5 products, there is no deliberate intent to deceive, but consumers may mistake the different formulation for one they may be more familiar with.

Class 6 medicines represent another group that is under-represented in the lexicon of terms to describe the problem. This class includes registered products that contain wrong or incorrect concentrations of active pharmaceutical ingredient that result from failures in quality assurance. While similar to Class 3 and 4 non-equivalent products, substandard Class 6 medicines are not deliberately misrepresented. Rather, compromised quality in this class can be a result of inadequate adherence to GMP and GDP. Many compounds produced or procured as a specified formulation with specific biopharmaceutical properties, for example, become poorer in quality over time because they are improperly stored (prior to sale to the final user), while their external appearance and packaging may appear identical to the genuine article. Conversely, the current system of routinely using two to three year expiry dates is driven primarily by marketing considerations rather than measured stability properties of the formulation and may not reflect actual medicine quality. Indeed, a recent
direct test of the stability of an expired fixed dose combination artemether-lumefantrine antimalarial tablet in uncontrolled tropical conditions showed that chemical composition was stable as long as five years past the stated expiry date (Cockburn et al, 2005).

The viability and usefulness of these products is unknown, as the degradation of ingredients could modify the efficacy of the drug. Despite containing some clinically beneficial ingredients, these substandard drugs can therefore pose a significant epidemiological risk due to the changing health ecology as resulting from increased microbial resistance (White, 2004). This was documented in a 2004 study that found 53% of artemisinin based antimalarials sold in South-East Asia contained incorrect levels of this API although some was often present (Dondorp et al, 2004). As previously stated, Cockburn et al (2005) estimate that “substandard therapy” has contributed to a doubling of malaria deaths over the last 20 years. Significantly, in studies where direct measurement has been made of medicine quality in low- and middle-income countries, most were found to be substandard rather than outright fakes (Bate et al, 2009).

A 2004 study by the WHO, for example, revealed that out of 19 reported poor quality medicines cited elsewhere as evidence of counterfeiting, 18 were in fact “genuine but substandard” (Maponga and Ondario 2003; Syhakhang et al 2004; Caudron et al, 2008). Similarly, sampling of medicines in public, private and informal markets in India reveal a significantly higher proportion of substandard medicines relative to outright fakes. While only 0.24 to 0.47% of medicines sampled were found to be “counterfeit” in the trademark sense (Class 3), about 8.19 to 10.64% were of substandard material quality (Class 6).

What remains consistent across Classes 2 to 6 is the uncertainty as to the source or identity of the product. Even if medicines are of the correct quality or contain the correct
amount of active substance, their production and distribution in poorly regulated markets of low- and middle-income countries may not be within the control of the drug regulatory authority, if one is even established. Consequently, any associated defects and adverse reactions will not be easily recognized or monitored and, if needed, an effective product recall would not be possible. What should also be centralized is the possible therapeutic failure of using poor quality medicines, prolonged treatment periods and in extreme cases death. In 1995, for example, 119 children died in Haiti and India due to the consumption of paracetamol cough syrup prepared with diethylene glycol, a toxic chemical used in antifreeze (Falagas et al, 2007; Harris, Stevens and Morris, 2009).

5.3 Deconstructing the Drug Quality Concept

The classifications of drug quality offered above highlight the potential focus on two variables: “intent to deceive” (Class 2 to 5) as well as variability and inconsistency of the material quality of medicines (Class 3 to 6). Before examining the optimal framework in addressing the problem primarily in low- and middle-income countries, these two applications must be distinguished. Under the growing influence of industrial ideas about quality management, the ISO standards are increasingly considered as a frame of reference for quality assurance (London, 2005). ISO-9000 is the framework for constructing quality systems, defining a quality system as the organizational structure, responsibilities, procedures, processes, and resources to assure and improve quality (ibid).

The ISO 9004–2 goes further, defining quality as the "total composite of properties of an entity needed for fulfillment of explicitly stated or self-evident demands." Herein, "properties" substitute for possibilities realized while "explicitly stated or self evident
demands" represent the normative frame of reference. This definition has an inherent limitation, as the reference to a set of properties is not accompanied by a criterion to distinguish aspects related to quality from those that are not. The definition of quality was therefore revisited in ISO 9000:2000, where it was redefined as a "degree to which a set of inherent characteristics fulfills requirements" (London, 2005).

By incorporating a set of inherent characteristics with particular explicit requirements, this definition, Harteloh (2003) argues, meets the semantic rule expressed by the quality concept. Nonetheless, further elucidation is required in qualifying the inherent characteristics as well as explicating the requirements, possible through a continuous and reflexive revision by data producers and consumers (Pennefather et al, 2010). Data, however, becomes information on quality when it can be compared with a normative frame of reference - such as guidelines, standards, norms, and values (London, 2005). Quality indicators are moreover needed in conceptualizing the realization of these norms and values. As Harteloh (2003) argues, the formal, social construction of a quality system therefore requires adequate social interactions, or communication between stakeholders.

5.3.1 Systems Theory and Rational Control

A necessary requirement for enabling a user-focused quality system is some means of enabling the health system to mediate information on quality to the patient, or more directly, by allowing end-users to evaluate quality. According to Harteloh (2003), a central value in constructing such a quality system is rational control. In fundamental terms, rational control demands control of variability in the primary processes in order to adjust the
outcome to patient needs and professional requirements. At least three elements are thought to facilitate rational control in a quality system.

First, organizational structure and leadership are required to legitimize, facilitate and stimulate quality assurance (Harteloh, 2003). The primary process as a focus of quality assurance must also be followed by guidelines, standards - containing normative framework - and protocols, describing its actual realization. Underpinning this is a requirement for practical knowledge of quality assurance techniques, necessitating training and education. Whether health care professional or patient, quality assurance requires the collection of data, or a knowledge base that becomes information on quality by "applying a semantic rule in such a way that data exemplify the meaning of quality" (ibid). In this way, rational control becomes a guiding principle and blueprint of a quality system.

As a reflexive process, representing a circular relationship between cause and effect, rational control is also akin to the model of control mechanisms, a central axiom of systems theory (ibid). The latter suggests that reality consists of a set of disparate elements and relationships between them, which can be described by control mechanisms. Two of the most fundamental of such control mechanisms are feed forward - (re-)acting on input - and feed back - (re)acting on results or output. Within such a system, the internal equilibrium is thus governed by values as standards for quality, resulting in the latter transcending classification as a static property (i.e. effectiveness, efficiency), but rather becoming a dynamic capacity wherein judging quality requires comparing actual properties with patient expectations.
5.4 Conclusion

In Chapter 5, it was argued that although higher and lower income countries experience distinct vulnerabilities in their pharmaceutical supply chains vis-à-vis poor quality medicines, they are both based on information asymmetries, leading to adverse selection, potential market failure and notably opportunities for poor quality medicines to be traded and consumed. Particularly in many low- and middle-income countries, it was suggested that informal markets, which in these countries are pervasive, lead to asymmetries in the information that is known between the buyer and seller, which can ultimately undermine trust within the health system. It was subsequently argued that problem of trust was further exacerbated by a lack of clarity around how to define the problem, while Section 5.2.1 proposed a new classification for drug quality based on material quality, and main channels of distribution. Lastly, a deconstruction of the quality concept and examination of rational control - or the lack thereof – will be used to argue, in Chapter 6, for new frameworks in how the problem is framed and responded to. Indeed, Chapter 6 will present three frameworks – quality by enforcement, quality by regulation, and quality by evaluation.
5.5 References


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~ CHAPTER SIX ~

Discussion: Finding the Right Quality Framework

In the following Chapter, the literature on inherent information asymmetries will be used to explore how conceptions of quality are mediated to promote trust in health systems, with particular application to the material quality of medicines. Herein, three quality frameworks will be presented, each offering distinct conceptualizations of the problem of poor quality medicines, whom it identifies as the primary victim, and moreover who and what the primary responses ought to be.

In Section 6.1, ‘quality by enforcement’ will be introduced to describe the emphasis of legal and enforcement strategies that the current conceptualization of ‘counterfeit’ medicines has taken in many countries. This will be contrasted in Section 6.2 by the ‘quality by regulation’ framework that instead emphasizes strengthening regulatory capacity to promote quality systems. Finally, Section 6.3 will explore the opportunity for ‘quality by evaluation’, where emphasis is placed on enabling stakeholders to mediate trust by directly evaluating the material quality of medicines. Rather than select a single framework, it will be suggested that all three are central strategies that countries must undertake in mediating the quality of medicines, as well as promoting trust between patients and health systems.

6.1 Quality-by-Enforcement

In most higher income countries, particularly the United States and in the European Union, the challenge of poor quality medicines has been incorporated into a strategy that enforces trademarks and criminalizes the trade of ‘counterfeit’ medicines. This was
illustrated most clearly above in Section 2.3.3 in the definition of ‘counterfeit’ medicines in the US Food, Drug and Cosmetic Act. Similar to the current ‘counterfeit’ definition promoted by the WHO, Gopakumar and Shashukant (2010) argue member-states and other stakeholders have interpreted these conceptualizations of the problem as opportunities for legal enforcement of “unauthorized products” that “bear the trademark, trade name, or other identifying mark” in order to secure the pharmaceutical supply chain. This approach can be classified as the ‘quality by enforcement’ framework, represented in Figure 6.1 below.

![Figure 6.1. ‘Quality-by-Enforcement’](image_url)

**Figure 6.1. ‘Quality-by-Enforcement’**. In the ‘quality by enforcement’ framework, the issue of poor quality medicines is framed as one of ‘counterfeit’ medicines, emphasizing “intent to deceive” by the ‘counterfeiter’, and therefore emphasizing infringement of trademarks. It therefore identifies the patent holder (i.e. pharmaceutical company) as the principal victim, as it calls mainly on regulatory and law enforcement agencies to criminalize intellectual property infringement and to seize “counterfeits.”

This framework is akin to the pursuit of policing the pharmaceutical supply chain and punishing brand counterfeiting, which has been strongly promoted by authors such as Attaran, Bate and Kendall (2011), where the authors call on the criminalization of medicine counterfeiting internationally. At international forums like the WHO and the WTO,
policymakers particularly from the US and the European Union alongside members of the multinational pharmaceutical industry have pressured countries to embrace the argument that stricter enforcement of intellectual property is the "best remedy" to protect patients from poor quality medicines (Oxfam 2011). Consequently, at a WHO (2010a) Open Forum on IMPACT, a number of member states supported the call for a disbanding of the IMPACT. This reasoning is based on obligations by WTO member-states to criminalize intellectual property violation, including trademark infringements (or “counterfeits”) in their national legislation (Oxfam, 2011; WHO, 2011a).

The brand counterfeiting framework takes an indirect approach to prioritizing patient safety by expanding the definition of a “counterfeit” medicine, with the aim of criminalizing any “intentional manufacturing” of a product that may be “a false representation as regards identity and/or source.” It has been argued, however, that reliance on criminal trademark infringement has shown little to no effectiveness in addressing problems associated with variability in drug quality (Gopakumar and Shashukant, 2010; Wertheimer and Norris, 2009). A report by the International Intellectual Property Institute highlights the “unrecognized public health problem with particular consequences in the area of injury mortality and morbidity” for drugs with undetermined quality, stressing the obligation of governments to protect the health of its populations rather than defend intellectual property rights and criminalize offenders (Forzley, 2003). Similarly, Oxfam (2011) suggests that blunt instruments, such as criminalizing drug counterfeiting, cannot replace effective quality assurance standards and pharmacovigilence by a drug regulatory authority. Enforcing more stringent intellectual property protection may also create barriers to the production of and trade in generic medicines, through the criminalization of unintentional mistakes or
Examples of the application, and public response, to this framework were highlighted in Section 2.3.3, particularly in the examples of the European Union efforts through customs regulation 1893/2003 to enable border officials to detain imports, exports, and in-transit goods, including pharmaceuticals, suspected to infringe any type of intellectual property, including products that may be contested under civil trademark infringement (EC, 2003). While international pressure necessitated the European Commission to amend the regulation, higher income countries have continued to export its clauses in trade negotiations – including the European Union-India FTA that is being negotiated – as well as through bilateral technical assistance, as highlighted in 2.3.4 (Oxfam, 2011).

6.1.1 Limitations of the Quality-by-Enforcement Framework

It can therefore be argued that the ‘quality by enforcement’ framework suffers from three distinct limitations, summarized in Figure 3 below. Foremost, while nominally prioritizing patient safety, it can be argued that this framework in fact identifies the patent holder as the primary victim, reflected in the terminology used to define the problem (i.e. counterfeit). It furthermore places within the domain of national and international law enforcement agencies the responsibility of minimizing exposure to medicines that may violate trademarks. Wertheimer and Norris (2009) note, for example, that port authorities are responsible with the public health task of protecting the public from the importation of poor quality medicines. Similarly, a WHO report indicates that many member states do not have specific or effective legislation for combating counterfeit or spurious medicines, and manufacturing without the consent of an intellectual property owner, as is the case in 30% of generic drug launches (Bate and Attaran, 2010).
thus may resort to non-specific legislation related to intellectual property protection (Oxfam, 2011). The greater capacity and incentives of law enforcement authorities to prosecute deliberate counterfeiters ignores the broader category of medicines that may lead to public health challenges, but where an “intention to deceive” is either not present, or difficult to prove.

6.2 Quality-by-Regulation

The pharmaceutical supply chain is a complex system that is aimed with ensuring the right drug reaches the right people at the right time and in the right condition (Kaiser Family Foundation, 2005). In Section 2.1, it was shown that a core component of a functioning pharmaceutical supply chain is an effective drug regulatory infrastructure. This system aims to ensure that medicines acquired and traded in pharmaceutical supply chains and in international markets are: (a) safe, effective and of good quality; (b) accompanied by complete and correct product information, and (c) manufactured, stored, distributed and used in accordance with good practices (WHO, 2003). As shown in Chapters 2, 4 and 5, the vulnerabilities and challenges to national medicinal regulatory authorities are distinct among higher and lower income countries.

Especially among lower income countries, technical, financial and human resources have limited the capacity of effective regulation of the pharmaceutical supply chain. Economists, however, have suggested that state institutions, with sufficient support, can more “efficiently and effectively mediate information asymmetries” that arise from informal markets (Haas-Wilson 2001). This section therefore presents the ‘quality by regulation’ framework that highlights the opportunity for national and international stakeholders to
invest resources in strengthening regulatory capacity in an effort to control the trade and consumption of poor quality medicines.

This approach, while strongly favoured by member-states, has notable limitations, as significant technical, financial and human resources are required to establish a responsive regulatory infrastructure that can monitor the pharmaceutical supply chain. This strategy therefore mediates more successfully between patients and health systems, while it can also address the challenge of informal markets, where the quality by enforcement framework has previously failed (Gopakumar and Shahukant, 2010). The ‘quality by regulation’ framework is captured in Figure 6.2 below, while strategies at the international as well as national levels to promote regulation of medicines are also outlined below.

**Figure 6.2. ‘Quality-by-Regulation’.** In the ‘quality by regulation’ framework, the issue of poor quality medicines is framed as one of ‘spurious’ medicines, denotes the difficulty to ascertain the provenance, composition and quality of medicines (Mashelkar, 2003). This framework therefore acknowledges that poorly regulated, and often informal markets permeate the pharmaceutical supply chain in many low- and middle-income countries. It therefore identifies the patient who obtains medicines as the primary victim, as they are unable to mediate quality. This framework also calls on national medicines regulatory authorities to increase resources for monitoring the supply chain.
6.2.1 Strengthening Regulatory Capacity against Poor Quality Medicines

Recognizing its national challenges in 2007, China invested an additional US$1.16 billion over four years in its food and drug inspection and monitoring infrastructure (Jia 2007). However, while generic competition in many low- and middle-income countries has improved access to essential medicines, best practices are not always enforced and the international community has an opportunity to offer support in establishing a dynamic regulatory infrastructure to enforce best practices to ensure drug quality (Bate 2008). Whether through foreign support in regulatory capacity building, or the allocation of domestic resources, it is critical to communicate to all stakeholders the potential risk of drug procurement in the absence of effective and responsive regulatory mechanisms that can assure, or at least assess, quality.

Other challenges to building drug regulatory capacities in low- and middle-income countries also exist. Many of these countries will need to begin with a fundamental legal basis for regulation, adding administrative procedures for registering medicines and monitoring market. Bloom, Standing and Loyd (2008) also underline the importance of other context-dependent factors of health systems, such as governance structures and relative strengths of States, as institutional arrangements do not necessarily transplant well to different political economy contexts. Ensor and Weinzierl (2006) have called for a broader understanding of regulation, including strategies like contracting, self-regulation, accreditation, or "co-producing" regulatory arrangements that depend on partnerships between States, the private sector and civil society organizations.
International Collaborations

Against many other pressing health needs competing for priority, this will require investing in resources and technical expertise, currently not available to over 80% of WHO Member States (Outterson 2009). International organizations, such as the WHO, can therefore play a significant role in coordinating capacity building activities. Since 2001, for example, the WHO has managed pre-qualification for United Nations procurement of priority medicines for HIV/AIDS, tuberculosis, malaria and reproductive health, adding 40 to 50 new products each year (WHO, 2011b).

The program has widely been recognized for its success in ensuring quality, particularly among lower income countries, as well as recognizing the efforts of generic manufactures to improve compliance with international quality standards. However, only two WHO pre-qualified laboratories are operational in the entire continent of Africa. This situation is troubling as 29 of the 46 countries in sub-Saharan Africa reported minimal medicines regulatory capacity, and 14 none at all (WHO, 2009; WHO/AFRO, 2009). It is therefore critical that the WHO pre-qualification program be expanded, including at least all products on the model Essential Medicines List, which would require significant commitment from the international community. It should be noted, however, that the WHO pre-qualification program cannot be a panacea for three reasons: it does not have the budget or mandate to undertake drug quality monitoring on a global scale; the program’s methodology for including countries can be highly selective for middle-income countries; and national medicinal regulatory authorities need to strengthen their mandate to do so.

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16 In one study by the WHO (2010b), 73 out of 184 (or 39.7%) non-WHO pre-qualified antimalarials tested across six African countries failed quality testing, while only 3 out of 83 (or 3.6%) WHO pre-qualified samples were found to be of poor quality (also see 2010c).
While not focused on regulation, another example of an international program that promotes transparency and harmonization of drug quality data is the Medicines Transparency Alliance, a multi-stakeholder initiative launched in seven pilot countries to parallel existing government regulation. It establishes councils that include health authorities, local and international pharmaceutical companies, as well as civil society groups, who subsequently generate and share information about products in the market, with a shared interest in targeting trade of poor quality medicines. While it was only introduced in 2008, early evaluations in 2010 already show positive results in at least three of the seven sites, including in the Philippines, Jordan and Peru (Oxfam, 2011).

National Strategies for Regulatory Strengthening

Despite resource limitations, some low- and middle-income countries have also demonstrated the capacity to institute effective regulatory standards. The Nigerian national medicines regulatory authority, the NAFDAC, for example, has managed to implement broad-ranging strategies and safeguards that include organizational restructuring to reduce opportunities for corruption, supporting port and enforcement agencies with inspection, as well as incorporating “provider associations” to build trust with registered vendors and linking the legitimacy of NAFDAC with its capacity to protect public health (Bloom, Standing and Loyd 2008; Olapedo et al 2007).

One external study reported an 80% reduction in the prevalence of “counterfeit” medicines in Nigeria between 2001 and 2004 (Akunyili, 2006; NAFDAC, 2006). It should be noted, however, that like many estimates for “counterfeit” medicines, this figure did not distinguish between medicines that were of poor material quality, or products that were
either unregistered or violated intellectual property. Moreover, the study by Garuba, Kohler and Huisman (2009) highlights four essential areas of Nigeria's pharmaceutical sector where perceived vulnerabilities to corruption exists (registration, procurement, inspection, and distribution), suggesting challenges exist even in countries that have made substantial resource commitments to addressing the problem of drug quality variability.

There are also more cost and resource sensitive strategies for strengthening regulatory capacity. In 2002, for example, the Tanzanian Ministry of Health initiated nation-wide awareness campaigns that generated public support, but also developed databases of "unregistered" medicines against the products for sale in outlets across the country (TFDA 2010). Rather than punish vendors, Tanzanian inspectors chose to invite pharmacies found to be selling unregistered medicines to cooperate with authorities' efforts to track the source, quality and efficacy of products; only those that refused faced (well publicized) closures (Oxfam, 2011). To overcome resource constraints, other low- and middle-income countries have likewise formed collaborative regional partnerships to coordinate medicines registration and regulatory activities (Hill and Johnson, 2004). One example is the African Medicines Registration Harmonization Initiative, launched in 2009 with the participation of the WHO, to foster regionalization of certain aspects of medicines regulations (Oxfam, 2011).

Brazil is another model country for very rapidly creating effective national regulatory institutions. Following a period of military dictatorship, the re-democratization of Brazil in the mid-1980s resulted a decade later in the formation of the National Health Surveillance Agency (ANVISA, 1999; Oxfam, 2011) with the stated objective of promoting and protecting public health. Charged with overseeing the registration and regulation of
medicines, the agency modelled its policies on norms and guidelines set by the WHO, wherever possible. Today, Brazil enjoys an extensive system of drug regulation that mirrors many high-income countries, undertaking registration, quality assurance, inspection, pharmacovigilence, monitoring of clinical trials and oversight of marketing practices (Oxfam, 2011). A recent study by Ames and Souza (2012), however, revealed that “counterfeiting of drugs is a severe public health problem” in Brazil. Analyzing over 370 seizures between 2007 to 2010, the study suggested critical challenges, particularly with lifestyle medicines (erectile dysfunction and anabolic steroids), that could pose public health risks as the problem increases (ibid).

### 6.3 Quality-by-Evaluation

As was highlighted in Chapter 4 and 5, the integrity of health systems, and access to safe and effective medicines may be compromised in informal markets where the capacity for regulatory monitoring of the pharmaceutical supply chain is most limited. Emerging opportunities exist, providing patients with reliable tools and information to better judge drug quality, noted by Lucas (2008) to reduce information asymmetries. This opportunity is captured in the ‘quality by evaluation’ framework, presented in Figure 6.3 below. The strengths of the framework lie in enabling the primary victim of poor quality medicines, namely the patient, to play an active role in mediating trust by evaluating the material quality of medicines. Particularly in informal markets where regulations and enforcement of trademarks appear impotent, the quality by evaluation framework offers potential.
By recentralizing the patient and recognizing the public health implications of medicines with indeterminate provenance, quality and composition, the quality by evaluation framework identifies material drug quality evaluation as the principal response, furthermore pointing to a need for being able to compare chemical product signatures of accessible medicines at the point-of-use to known reference samples. Examination of technological responses to the problem show that it is becoming possible to achieve that goal in a distributed fashion using adaptive, open and commoditized technologies that deliver simple analytical chemistry functionality whose results can be communicated and analyzed using widely available consumer electronic computer and communication platform.
A number of recent publications have confirmed the feasibility and effectiveness of local drug quality evaluation in resource-limited environments using adaptive, open and commoditized technologies that deliver simple analytical chemistry functionality (Macleod and Matousek 2008; Fernandez et al. 2010). This is enabled by the increased affordability and accessibility of the broad spectrum of techniques for drug quality evaluation, supplementing physical inspection with overt methods such as unique identification labels (i.e. barcodes, holograms, radio frequency identification, inserts, etc.) to identify the provenance of medicines (Pennefather et al, 2010).

The pharmaceutical supply networks of high-income countries employ a broad spectrum of techniques for drug quality evaluation. This includes GMPs implemented before medicines are distributed as well as post-manufacturing market surveillance and product tracking systems. For product tracking and sampling, overt methods such as physical inspection are supplemented by the application of unique identification labels, including covert tags, barcodes, holograms and radio frequency identification package inserts that identify the source and provenance of medicines.

The effectiveness of these technologies, however, requires a formal regulatory infrastructure for monitoring the supply network to maintain product quality. Moreover, in many low- and middle-income countries with inadequate regulation of pharmaceuticals, medicines are often obtained in small quantities and devoid of original packaging, allowing package-based verification tools to be subverted using modern print and packaging technology (Newton et al 2009). Especially where markets are informal, non-destructive material verification becomes necessary and can include raman spectroscopy and telemicroscopy, which can be adapted to analyze single tablets by evaluating chemical
taggants, coatings features, or verifying the presence of active ingredients from spectral analysis of product composition (Pennefather et al, 2010; Martino et al 2010). Other simple chemical analysis kits, such as MiniLabs, that provide rudimentary assessments of deviations from reference standards with dissolution assays and colorimetric methods are also currently being field-tested (Risha et al 2007).

Emerging non-destructive material quality assessment technologies have also become popular, as they preserve the integrity of the product and packaging and can be applied sequentially at different points along the supply chain. Raman spectroscopy and telemicroscopy, for example, can be adapted to analyze single tablets by evaluating chemical taggants, coating features, or verifying the presence of active ingredients from spectral analysis of product composition (Ricci et al, 2008; Macleod and Matousek, 2008). The possibility of converting chemically specific spectra into unique digital identity codes enables overt tagging and the production of quantitative analysis of observed properties that can be shared over digital communication networks and algorithmically compared to digital reference standards (Pennefather et al, 2010). While this approach can also be subverted, successful ‘work-arounds’ come at a greater cost to the perpetrators.

For these peer produced spectral data feeds to become meaningful in promoting system-wide medicine quality improvements, these local results must be communicated to network based aggregation services. This is enabled by a communications environment built on cheap processors with high computation capabilities, interconnected in a pervasive network - the phenomenon we associate with standard internet protocols and telephony modalities or text messaging. The declining price of computation, communication, and storage have, as a practical matter, placed the material means of information in the hands of
a larger fraction of the world’s population by replacing traditional centralized, expensive and politically inaccessible communication technologies with globally accessible, cheap and decentralized network access.

As described by Pennefather et al. (2010), this enables a network based medicine quality data stream at any point along the supply chain, including point of dispensing and use. Such a repository of medicine quality assessment results would be comprised of summaries of both measured spectra and other physical parameters as well as local knowledge of the medicine's origin. That knowledge base in turn could support the creation of a community of practice focused on medicine quality validation and enable the study of social determinants factors that influence the ability of medicines to have the actions they were designed for (i.e. their biopharmaceutics).

Ultimately, such a system enables a necessary feedback loop for guiding both local and system-wide medicine quality efforts (Caudron et al, 2008). Contrary to recent estimates of the level of exposure to variable and poor quality medicines that are based on systematic random sampling, the quality by evaluation framework would promote local control, sustained with the option of sharing results (Caudron et al, 2008; Pennefather et al, 2010). These technical innovations would generate real-time medicinal quality data feeds, allowing all agents in supply networks to monitor and protect the quality of the goods and services they are responsible for. This in turn will promote transparency and trust in the pharmaceutical supply chain as there is now a possibility to reward quality.
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Access to safe and effective medicines remains highly variable globally. While comprehensive data on the necessary global scale does not exist, the WHO estimates that less than 1-2% of sampled medicines in high-income countries fail quality tests, while the figure can be upwards of 50% in some low-income countries, with some studies suggesting rates as high as 80% in regions of South-East Asia and sub-Saharan Africa. In Chapter 2, a number of reasons were forwarded explaining the gap in publicly available data as to the scale and scope of the problem.

Most significantly, no single international organization has the mandate or capacity to undertake such a comprehensive field study. In addition, many low- and middle-income countries, in particular, may experience gaps in technical, human and financial resources, leading to insufficient and/or unreliable regulation of the pharmaceutical supply chain. Moreover, local – and often informal – markets represent a significant source of medicines in many of these countries, presenting critical challenges in determining the provenance, composition and/or quality medicines being traded and consumed. Lastly, this thesis identifies insufficient global consensus in defining the problem as a critical barrier, both in determining the scale and scope of the problem, as well as identifying appropriate responses.

These features subsequently result in significant divergences in how the various stakeholders conceptualize, and respond to, the challenge of poor quality medicines. With an emphasis on elucidating the distinct vulnerabilities in the pharmaceutical supply chains of higher and lower income countries, triangulation work described in Chapters 3 and 4 lead to
two conclusions. First, in higher income countries, a globalization of supply chains for drugs and active pharmaceutical ingredients as well as online pharmacies pose the greatest risk to drug quality. Meanwhile in most low-income countries, the primary challenges included drug access gaps that propagate informal local markets, while gaps in regulatory capacity furthermore lead to limited capacity to monitor the quality of medicines in the supply chain. These vulnerabilities were furthermore explored in Chapter 4, where it was argued that informal markets and poor regulatory capacity result in asymmetries in access to information vis-à-vis drug provenance, quality, and composition. This can ultimately lead to therapeutic failure, morbidity and mortality from medicines of variable and poor quality, as well as a loss of trust between the patient and the health system if patient safety cannot be protected.

In order to highlight these public health challenges, the thesis subsequently argues for the need to re-conceptualize the problem from the counterfeit framework that emphasizes an “intent to deceive,” to one of the material quality of medicines, focusing on identifying and promoting medicines that are safe and effective. This shift from punishing “deliberate” violators of trademark infringements, to examining the conditions within a pharmaceutical supply chain that enable the monitoring and evaluation of drug quality furthermore highlights the opportunities of increasing trust between the patient and health system. Another outcome of drafting a new classification of medicines based on material quality is the opportunity for examining the problem of poor quality medicines through multiple frameworks; in this thesis, three are presented.

The quality-by-enforcement framework, most clearly incorporated within higher income countries, frames the issue as one of trademark infringement. This suggests the primary victim to be the patent holder, and thereby calls for greater enforcement measures that
criminalize intellectual property right infringement, as well as promote the seizure of “counterfeit” medicines. While its emphasis on intellectual property violations can deviate from the public health focus, as some authors have suggested, the framework does highlight the import roles of law enforcement as well as the judicial system, for punishing deliberate counterfeiters of medicines.

It was subsequently noted, however, that all instances of poor or variable quality medicines, particularly in many low- and middle-income countries, are not exclusively the result of deliberate counterfeiting. Instead, medicines are sometimes produced, traded and subsequently consumed that may be of poor or variable quality, where deliberate intent either cannot be substantiated, or is absent. Herein, quality-by-regulation frames the issue as one of poor capacity for regulating the pharmaceutical supply chain, most evident in countries with a high proportion of informal markets. In this framework, the patient purchasing the “spurious” medicine — or one for which the provenance, quality and composition is unknown — is identified as the principal victim, and greater investment in national medicinal regulatory authorities is promoted as the most effective response.

In addition to promoting greater regulation of the pharmaceutical supply chain, the quality-by-evaluation framework highlights the material quality of medicines as a critical challenge in promoting the trade and consumption of quality medicines. Unlike the former institutional model, the quality-by-evaluation framework identifies the patient consuming the poor or variable quality medicine as the primary victim. Moreover, it calls for greater capacity for health professionals and the public to evaluate the material quality of medicines. A brief survey of the overt, covert and forensic technologies was presented (see also Pennefather et al. 2010 in Appendix), which some countries have already implemented to
secure their pharmaceutical supply chains.

It should be noted that this thesis does not suggest the universality of a single quality framework in addressing the challenge of variability in drug quality. Instead, it highlights the need for context-specific strategies that examine the appropriate application of any and all strategies, based on the availability and limitation of resources locally. In many low- and middle-income countries, for example, the evidence suggests drug quality variability is more profound, regulatory capacity is more limited and a significant volume of medicines are procured from informal markets. In these countries, the most appropriate strategies, according to the framework presented, is making greater investments in strengthening regulatory capacity, as well as enabling health professionals and patients in evaluating the quality of medicines dispensed and consumed.

**7.1 Policy Implications**

A number of important ideas and potential policy implications can be extracted from this thesis. By invoking the human right of access to safe and effective essential medicines, the problem of variability in drug quality is identified principally as a public health challenge. The paucity of data on the scale and scope of the problem furthermore calls on all stakeholders to work together in undertaking a comprehensive assessment of the quality of medicines accessed locally. The results should furthermore be made publicly available so that national medicinal regulatory authorities and other local actors can identify gaps and vulnerabilities, and therefore respond accordingly. Primarily in low- and middle-income countries, it is also suggested that gaps in access to medicines as well as poor regulation, have propagated informal markets that pose information asymmetries and diminish trust between
the patient and other stakeholders in the health system. In order to promote trust and collective action, it is argued that greater regulation, as well as monitoring of local markets is necessary. Particularly as economists have argued that the state is most efficient in mediating trust with the public, as well as addressing information asymmetries in health systems, the thesis calls for greater investment in regulation of the pharmaceutical supply chain.

The thesis moreover presents a novel classification for drug quality that is more nuanced than the highly challenged definition of counterfeit medicines. The challenge by WHO member states of the mandate and activities of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) highlights the importance of coherence in how the problem is defined, as well as cooperation and consensus from major raw ingredient and drug exporting countries such as India and China. To this end, the three frameworks – quality-by-enforcement, quality-by-regulation and quality-by-evaluation – provide an opportunity for assisting policy makers in conceptualizing the appropriateness of a strategy for addressing variable and poor quality medicines.

As previously stated, rather than picking a single framework and its associated strategy, policy makers are recommended to draw attention to multiple frameworks. That said, the quality-by-regulation and quality-by-evaluation frameworks are highlighted as more appropriate in many low- and middle-income countries vis-à-vis public health, where the quality-by-enforcement framework can be misused to defend intellectual property rights. Importantly, the latter framework also provides an analysis that could be continued in the form of a feasibility study in local contexts. Unlike the publicly available literature that either highlighted the challenge of the problem, or the myopic field studies that report on narrow dimensions of the challenges, this thesis outlines the comprehensive range of challenges – including the
need for greater enforcement, investment in regulatory infrastructure for monitoring drug quality, as well as opportunities for focusing on material drug evaluation, which has thus far been limited to narrow and resource intensive studies, and conceptual feasibility models.

There are also critical implications for the WHO, that plays a critical role in mediating the framing and responding to the problem, notably in its affiliation with the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). However, critiques by member states have resulted in the WHO Working Group on Substandard/Spurious/Falsely-labeled/ Falsified/ Counterfeit Medical Products openly condemning the IMPACT for potential conflicts of interest and misaligned activities beyond public health. At the 65th World Health Assembly, member states will subsequently debate IMPACT’s future, as well as the WHO’s role in the prevention and control of drug quality. In addition to providing a more nuanced classification of the problem, the conceptual framing of quality that is presented in this thesis can inform the WHO’s analysis of its role, as well as its relationship with the IMPACT.

7.2 Future Directions

While this Masters thesis offer potential policy implications, there are a number of future areas of research. First, the WHO and national medicinal regulatory authorities should undertake comprehensive, independent market surveillance to both establish the true scale and scope of the problem, and moreover to identify gaps within drug supply chains. Member states could additionally undertake and fund surveillance to ensure the integrity of the global supply chain, incorporating randomized purchases of medicines from local markets, testing for compliance with drug regulatory procedures. The results of these studies should be made available to the public and performed in a manner that supports accurate
cross comparisons. Pharmaceutical companies can also assist by becoming more transparent with their data on this public health challenge, as well as alerting the public of potential cases of poor quality medicines. Here, the application of the classification chart can also provide a richer understanding of the problem beyond intent and authenticity.

There is also a critical need to undertake further research into the role of information asymmetries in pharmaceutical supply chains, and its effect on perceptions and actions of health professionals, consumers and patients. As awareness of the problem of poor quality medicines increases among the public, will there be an increase in mistrust, or can greater transparency and access to information vis-à-vis drug quality mediate trust between the patient and the health system? This question can be furthermore explored based on dispensing and consumption trends in regulated markets, such as those in higher income countries, against those in lower income countries, where informal markets and decreased reliance on regulatory mechanisms may require greater mediation of trust by the patient.

A further area of future research is a feasibility study that examines the strengths and limitations of the quality frameworks. Field-testing the proposed strategies in a variety of countries with varying resource gaps can better inform stakeholders of potential best practices that are appropriate to local contexts. Particularly as middle-income countries are emerging as important sources of pharmaceutical ingredients and finished medicinal products, there is increasingly a need for comprehensive and harmonized strategies for addressing variability in drug quality. Additionally, the various technological interventions for enabling patients and health professionals to evaluate drug quality can be evaluated for efficacy and appropriateness in ensuring drug quality. Far from the final word, this thesis serves as a first analytic effort in establishing capacity and envisioning future action.