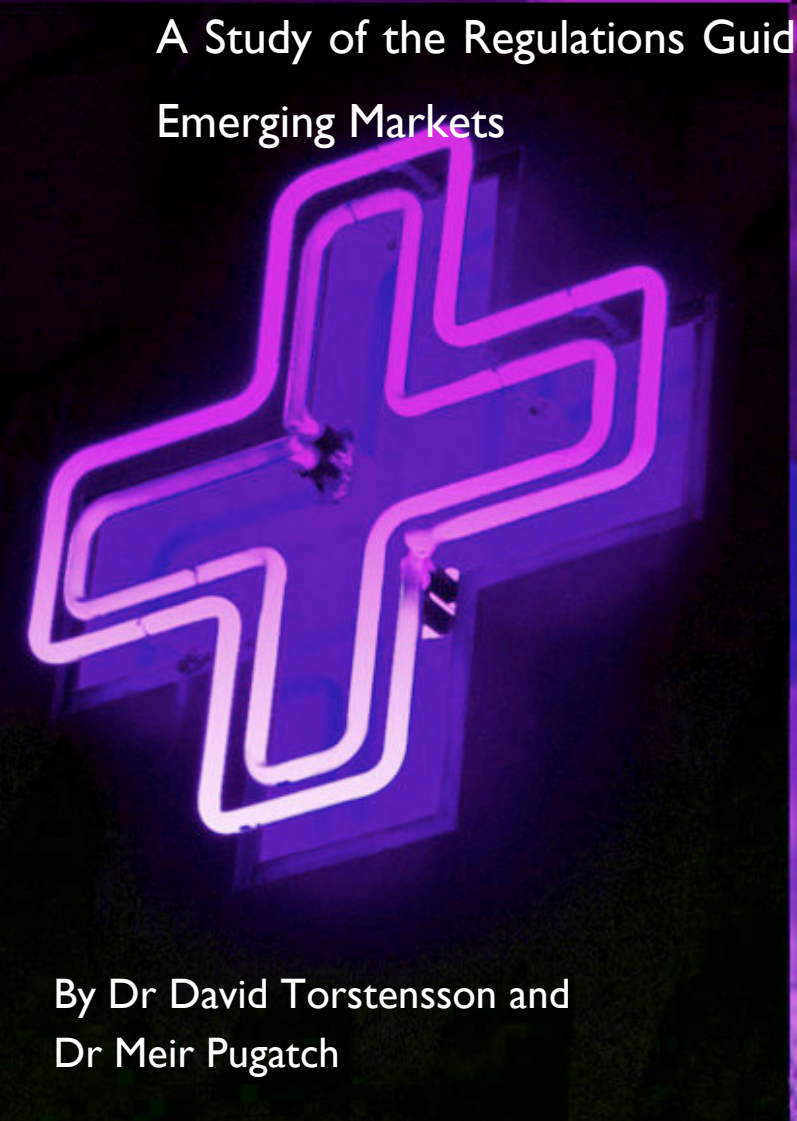
Keeping Medicines Safe

A Study of the Regulations Guiding the Approval of Medicines in Emerging Markets



By Dr David Torstensson and
Dr Meir Pugatch

STOCKHOLM NETWORK

Keeping Medicines Safe –

A Study of the Regulations Guiding the Approval of Medicines in Emerging Markets

By Dr David Torstensson and Dr Meir Pugatch

Executive Summary

Medicines and pharmaceutical treatments are today manufactured, sold, distributed and dispensed across the globe. Complex and interlinked supply and demand chains mean manufacturers, distributors, wholesalers, pharmacists, healthcare professionals and patients all make up a global network of producers, sellers and consumers of pharmaceuticals. The globalisation of the health care sector and the free movement of its goods and services has had enormous benefits: for example, patients can now access medicines that were in the past either not produced locally or far too expensive to import and access.

However, the globalisation of pharmaceutical markets and production has also increased the spread and prevalence of medicines which are unsafe. Broadly speaking, unsafe medicines can be divided up into two categories: counterfeit medicines and substandard medicines. Counterfeit medicines are defined by the WHO as being 'deliberately and fraudulently mislabelled with respect to identity and/or source'.[1] Substandard pharmaceuticals, on the other hand, are those which have been legally authorised for manufacturing and, more often than not, approved for market and sale by a national or regional Drug Regulatory Authority (DRA) but which do not meet the required quality or safety requirements for that particular drug or treatment.

This paper has attempted to show, firstly, just how serious a threat substandard and counterfeited medicines are to public health and, secondly, to discuss how the regulations of the production, sale and use of medicines can have an impact on the availability of these dangerous drugs. The paper began by examining the very nature of medical and pharmaceutical regulations: Why are they necessary? What are the concepts and ideas drug regulations are based on? And what are some of the essential best practices? It then moved on to examining how drug regulations have been designed in a number of countries (China, India, Brazil, Argentina and Turkey) which have experienced problems with substandard and counterfeited drugs. By examining each country separately it was found that because they all faced different sets of challenges, drug regulators and policymakers had responded to them differently. In some cases this had led to positive results; in other instances the results were less encouraging. The paper's final section provided some concrete examples of the lethal effects counterfeiting and substandard drugs can have on public health and how bad, non-existent or un-enforced regulations can play a serious part in this process.

The evidence from this paper's sample of China, India, Brazil, Argentina and Turkey shows that while the problems of substandard medicines and counterfeiting are widespread they also affects countries differently. The specific problems each individual country has to grapple with, depends on the legislative, regulatory, cultural, and socio-economic policies and make-up of that country. As such

[1] WHO, *The World Medicines Situation*, (Geneva 2004), p. 34-35

there are no easy or quick fixes. Some problems can be addressed relatively easily, while others require hard thinking, large resources, and national – or even international – coordination.

The paper made the following policy recommendations which were divided into two categories: general recommendations valid for all countries, and some country-specific recommendations.

General Policy Recommendations

- Recognise the problem. Governments in all countries (and across the world) must acknowledge the extent to which the production of substandard drugs and counterfeiting is a real threat to public health and safety. This is the first step towards action.
- There must be a better understanding at the regulatory, policy and public level of the differences between substandard and counterfeited drugs. While the effects of the two are often similar – detrimental and sometimes lethal health outcomes to patients – their causes are not always the same. Counterfeiting is the deliberate production of illegal, unsanctioned and mostly harmful medicines. Substandard drugs, by contrast, can be produced, sold and distributed by completely legitimate and authorised entities who are often unaware of their product being (or becoming) substandard.

Country-Specific Policy Recommendations

- **China**: China must do better at implementing its existing regulatory framework. While resources for the SFDA have been increased and there is improvement in national and international coordination, Chinese regulators and policymakers must make enforcement a greater priority.
- **India**: Indian drug regulations are highly disparate, inefficient and not well-enforced. Regulations should be streamlined and a clear regulatory framework and source of authority should be established. The current split between central and provincial functions does not foster efficiency or effectiveness. The resulting provincial and regional differences of rules, regulations and enforcement are at the heart of India's difficulties with substandard and counterfeited medicines.
- **Brazil**: Like China, Brazil's enforcement mechanisms and authorities need to be strengthened. Legislation introduced in 2003 to effectively outlaw similars by 2015 is a step in the right direction, but the long time frame leaves many potentially dangerous drugs in circulation.
- **Argentina**: Unlike Brazil, Argentina has not addressed the existence of non-bioequivalence tested similars and should do so. ANMAT should also introduce a more comprehensive system of pharmacovigilance which increases the burden of reporting onto health professionals.
- **Turkey**: Regulations of pharmacists and pharmacovigilance must be improved and implemented more effectively on the ground.

Contents

- Argentina
- Turkey
- Summary

Section 4: Final Thoughts and Policy Recommendations

Appendix

Introduction

Medicines and pharmaceutical treatments are today manufactured, sold, distributed and dispensed across the globe. Complex and interlinked supply and demand chains mean manufacturers, distributors, wholesalers, pharmacists, healthcare professionals and patients all make up a global network of producers, sellers and consumers of pharmaceuticals. The globalisation of the health care sector and the free movement of its goods and services has had enormous benefits: for example, patients can now access medicines that were in the past either not produced locally or far too expensive to import and access. The tremendous growth of the Indian generic medicines sector over the last two decades is a good example of this. Today Indian generics make up a substantial part of the US generics market and a growing share of abbreviated new drug applications.[2] In 2007 Indian companies made up 26.5% of applications granted. In 2008 this number had risen to 30%, and during the first quarter of 2009 this number reached 35% of the total abbreviated applications approved by the FDA.[3]

However, the globalisation of pharmaceutical markets and production has also increased the spread and prevalence of medicines which are unsafe. Broadly speaking, unsafe medicines can be divided up into two categories: counterfeit medicines and substandard medicines. Counterfeit medicines are defined by the WHO as being 'deliberately and fraudulently mislabelled with respect to identity and/or source'.[4] Substandard pharmaceuticals, on the other hand, are those which have been legally authorised for manufacturing and, more often than not, approved for market and sale by a national or regional Drug Regulatory Authority (DRA) but which do not meet the required quality or safety requirements for that particular drug or treatment. The United States Pharmacopeia (the USP is the official public standards-setting authority for all medicines, pharmaceutical and health products in the United States) defines substandard drugs as being 'genuine products that do not conform to the pharmacopeial standards set for them.'[5] The most common reasons why drugs become substandard are poor manufacturing practices, the use of impure formulation ingredients, and the inadequate quality of active ingredients (that is the main therapeutic ingredient of a medicine) which can be caused by, among other things, decomposition due to high temperatures and humidity.[6] There are also many instances when impure and toxic ingredients have been added to the manufacturing process rendering the medicines produced not only substandard but harmful. Crucially – and as will be illustrated below – these are not detected in the drug regulatory process and the drugs pass through the system undetected.

[2] Abbreviated drug applications are for generic drugs.
[3] *FiercePharma*, 'Indian drugmakers push into US generics market', March 6 2009, http://www.fiercepharma.com/story/indian-drugmakers-push-us-market/2009-03-06
[4] WHO, *The World Medicines Situation*, (Geneva 2004), p. 34-35
[5] United States Pharmacopeia, Drug Quality and Information Program, *A Review of Drug Quality in Asia with Focus on Anti-Infectives*, February
[6] O. Shakoor, RB Taylor, RH Behrens, 'Assessment of the Incidence of substandard drugs in developing countries', *Tropical Medicine and International Health*, Vol 2, No 9, pp 839-845, Sep 1997, p. 841.

Counterfeit and substandard drugs make up a growing share of the total drugs supply. Recent estimates by the WHO, the FDA and others put the number of counterfeit drugs between 10-15% of the total drugs market, with some areas in Asia and Africa reaching levels of almost 50%.[7] Estimating the amount of substandard drugs on the market is much more difficult. This is because so many substandard drugs are legitimately manufactured and regulatory approved medicines. However, the few studies that do exist have found that in some cases, and countries, the number of substandard drugs can be as high as 40% of the total sample size.[8] In 1997 a team of researchers using a survey of 96 samples of chloroquine, an anti-malaria drug, and selected antibacterials from Nigeria and Thailand, found that 36.5% of samples were substandard with respect to pharmacopoeial limits.[9] 36% of samples from Nigeria and 40% of samples from Thailand contained quantities of active ingredients that were outside British pharmacopeial limits. Six drugs had no active ingredient at all, a number over 6% of the sample size.[10]

The growing prevalence of counterfeit and substandard medicine in both developed and developing countries is a real threat to public health. In 2005-6 the Stockholm Network first began highlighting the serious effects of counterfeit medicines with the publication of two books: *A Sick Business* and *Coincidence or Crisis*. Now in 2009, we aim to highlight how both counterfeit and substandard drugs are a real and growing threat to public health. Most substandard and counterfeit drugs emanate from and are used in the developing world, either through direct consumption in the country of origin or in an importing country.

This study will focus on five emerging countries where these drugs are a real and growing problem: China, India, Brazil, Argentina and Turkey. The study of these countries is both relevant and timely for the following reasons. Looking at Asia, China has the fastest growing pharmaceutical market in the region. The sheer size of its domestic market, as well as its ambitions to become a leader in the export of medicines, makes it relevant to consider and analyse its regulatory environment. This is also the case with India, which in addition to its huge domestic market is one of the leading exporters of generic medicines. Brazil and Argentina, both with strong domestic pharmaceutical markets, are the most suitable candidates for a preliminary analysis of Latin American countries. Finally, Turkey is also a very interesting and relevant case, not least in light of the ongoing discussions on the possibility of becoming a future EU Member State. Clearly, regulation in developing markets also takes on a wider pan-European relevance in regard to patient safety, since the globalisation and parallel trade of pharmaceuticals means that substandard and counterfeit products now travel around the world with greater speed and ease and have the possibility of ending up in the hands of unwitting European patients. Indeed, substandard and counterfeit drugs also affect the developed world. This is

[7] Roger Cockburn et al, 'The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers', *PLoS Medicine*, 2(4), March 2005, http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020100
[8] O. Shakoor, et al, 'Assessment of the Incidence…', *Tropical Medicine and International Health*, p. 842-3. This was a study of chloroquine and anitmalarials
[9] Ibid.
[10] Ibid.

particularly true for generic drugs which are manufactured in developing countries and then exported to North America, Europe and Southeast Asia.

Because substandard drugs are more often than not (and in stark contrast to counterfeit medicines) approved by a national or regional drug regulator, it is imperative to examine where existing drug regulations have gone wrong and how they can be changed. The purpose of this paper is four-fold:

1) Highlight the problem that substandard drugs present to public health;
2) Explain how drug regulations in the developed and developing world work and why it is important to work towards an international "gold standard" of regulation;
3) Provide an overview of existing drug regulations and programmes of pharmacovigilance in five emerging markets in which substandard and counterfeit medicines are a real and growing problem: China, India, Brazil, Turkey and Argentina; and finally
4) Recommend how drug regulations and pharmacovigilance in these countries can be improved and how this can significantly reduce the prevalence of substandard medicines.

Accordingly, the paper is divided up into four sections. Section 1 will discuss the aim and goals of a regulatory framework which seeks to test and approve medicines for public use and explain why good regulatory standards are an essential part of maintaining high levels of public health, fighting substandard medicines, and building confidence in public health care and medicines. Medical professionals around the globe have over the past few decades realised the need for reforming regulatory standards and ensuring a high level and quality of regulations in all pharmaceutical markets. Since the 1980s there have been various initiatives from governments, regulators, industry and patients to harmonise and standardise regulations. This section will outline the progress that has been made and what remains to be done. Section 2 will outline, firstly, how substandard drugs and counterfeit medicines are affecting the five-country sample of China, India, Brazil, Argentina and Turkey. Secondly, this section will provide an overview of the existing pharmaceutical regulations and legislation (including the important area of pharmacovigilance and post-marketing surveillance) in these countries. Section 3 seeks to provide some practical and historical context to Section 2 by looking at what actually happens on the ground in the five-country sample. The purpose of this section is to examine what happens at the implementation stage and not just look at what is regulated or legislated in each individual country. For example, China has very strong and comprehensive regulations regarding the production, sale and dispensation of medicines. Yet despite this China also has one of the highest rates of substandard and counterfeit medicines in the world. The final section, Section 4, will summarise the previous three sections. It will seek to answer the question of whether there exists a global best practice model for the regulation and approval of medicines and, if one does exist, whether it is conceivable that it can be implemented globally.

Section 1: Regulating Medicines

Regulating medicine – then and now

The regulation of medicines and pharmaceuticals has its roots in the industrialisation and modernisation of Western Europe and North America during the 19th and 20th centuries. Beginning in the late 19th century the regional and national regulation of the safety of foods and drugs became enshrined in both European and North American law. In 1906 the United States Congress passed the Federal Food and Drugs Act which gave the United States Department of Agriculture's Division of Chemistry regulatory powers over the interstate transportation of food and drugs.[11] The Act followed a long line of proposed bills and many highly publicised scandals over food safety, the most notorious being Upton Sinclair's critical exposé of the American meat-packing industry, *The Jungle*. In Europe the British Medical Association began to express its concern over the safety of medicines during the 1880s. Legislation finally followed in the Therapeutic Substances Act of 1925 which began regulating the manufacture of biological substances.

Prior to this legislation both Western Europe and North America had begun to self-regulate and ensure the quality of medicines through the establishment of national pharmacopoeias. These bodies and their guidelines set standards of quality control and became the basis for national formularies; formularies that were later codified into national standards. In the United States the US Pharmacopeia was founded in 1820, the same year its first national formulary was published.[12] In Britain the first edition of the British Pharmacopeia was published in 1860 and provided an industry standard for the production of pharmaceutical drugs.[13]

Today the legislation and regulation of the manufacture, dispensation and use of pharmaceutical products is vast, complex and comprehensive. Governments across the world (including developed, developing and emerging market countries) view the regulation of medicines and pharmaceutical treatments as paramount to maintaining public health. Medicines and new medical treatments have to undergo a wide range of tests and safety procedures until they are allowed to market.[14] But standards of safety control and quality are not the same or even similar throughout the world. Not surprisingly the best and most rigorous systems of regulation can be found in those parts of the world with the most advanced health systems: North America, Europe, Japan, Australia, and Southeast Asia. Other countries, such as China, have very comprehensive regulatory systems in place, but there remains some doubt over whether these regulations and guidelines are being followed. As will be seen in Section 3 of this paper the issue of implementing and making use of rigorous drug regulations is as important as having those regulations on the books in the first place.

---

[11] US Food and Drug Administration, 'FDA History – Part 1', http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm

[12] US Pharmacopeia, 'USP History', http://www.usp.org/aboutUSP/history.html

[13] British Society for the History of Pharmacy and Royal Pharmaceutical Society of Great Britain, 'The evolution of pharmacy…The History of UK Medicines Regulation', http://www.rpsgb.org.uk/pdfs/museve2.pdf

[14] The procedures and regulations that determine market approval of drugs and treatments are detailed below.

The purpose of the next few pages is to outline what drug regulations consist of, what purpose they serve, what the best standards and practices are, and how it is essential for all countries – rich or poor – to design and maintain high-quality systems of pharmaceutical approval and safety monitoring.

Why regulate?

At their best, medicines and pharmaceutical treatments provide a relatively cheap, mobile and highly effective method of providing medical care. Many times they do not require either a medical professional or hospital to dispense the treatment but can be administered by the patient him or herself or by someone close to them. Still, for all their positive attributes medical drugs and treatments are by their very nature chemical compounds which can be poisonous to the human body. Indeed, even approved and high-quality medicines can be highly toxic, dangerous and cause great harm when not taken by the intended patient or in the correct sequence and amount. While their intended effects are always hoped to be benign, medicines and pharmaceuticals are potentially dangerous substances and thus need to be regulated accordingly. Indeed, it was a host of national drug tragedies which pushed authorities in Europe, the United States and Japan to set up systems of drug product authorisation between the 1930s and 1960s. In the US mistakes in the formulation of a children's syrup lead to several deaths and the setting up of a drug regulatory and safety system under the FDA.[15] The thalidomide tragedies in Europe during the 1960s prompted a similar reaction from European regulators.

Since the 1960s and 1970s there have been substantial increases in the number of regulations and rules guiding national drug authorisation processes. The increasing complexity of medicines and pharmaceutical technologies, as well as advances in drug testing and clinical trials, have meant that drug regulations have developed rapidly and a comprehensive approach has evolved at the best drug registration authorities. Due to the globalisation of the pharmaceutical market and the international interest in upholding the highest standards, initiatives to both harmonise and standardise regulations have taken place in a range of fora. In fact, since the 1980s there has been a push by governments and regulators from across the world, international bodies such as the WHO, and the pharmaceutical and medical industries to harmonise drug regulation.

Harmonisation and working towards a regulatory "gold standard"

Harmonisation was pioneered in Europe during the 1980s as the European Community attempted to harmonise national rules and regulations into a single pharmaceutical market. The key event in this process was the 1989 WHO Conference of Drug Regulatory Authorities in Paris, which provided the impetus for global harmonisation. On the back of this conference the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was launched. The ICH is a joint initiative that actively involves regulators and the pharmaceutical industry as equal partners in discussions of the scientific testing procedures which are required to

[15] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 'History and Future', http://www.ich.org/cache/compo/276-254-1.html

ensure, assess and maintain the safety, quality and efficacy of medicines. The working parties of the ICH are: the European Commission; the European Federation of Pharmaceutical Industries and Associations; Ministry of Health, Labour and Welfare, Japan; Japan Pharmaceutical Manufacturer's Association; US Food and Drug Administration (FDA); and the Pharmaceutical Research and Manufacturers of America (PhRMA). The WHO, the European Free Trade Association (EFTA), and Health Canada participate as observers. The purpose of the ICH is to develop the highest quality technical and scientific standards and harmonise these to create a global leading standard for the regulation and authorisation of pharmaceutical drugs. Since the 1990s the ICH Steering Committee has given priority to harmonising the regulatory requirements for the technical content for the sections reporting data submitted in the EU, US, and Japan. The first Guideline issued was E3, *Content and Format of Clinical Study Reports*. This guideline describes a single format for reporting the core clinical studies that make up the clinical section of a registration dossier. In total the ICH has issued (or is in the process of formulating) guidelines on 28 categories to do with the safety, quality and efficacy of medicines. These categories are summarised in the table below; the specific meaning of each category will be discussed separately below.

Table 1: Summary of ICH work[16]

Quality Guidelines – Best Practice methods to ensure the quality of a drug or drug treatment	Safety Guidelines – Best practice methods to ensure the safety of a drug or drug treatment	Efficacy Guidelines – Best practice methods to ensure the safety of a drug or drug treatment
1) Stability	1) Carcinogenicity studies	1) Clinical Safety
2) Analytical validation	2) Genotoxity studies	2) Clinical Study Reports
3) Impurities	3) Toxiokinetics and Pharmacokinetics	3) Dose-Response Studies
4) Pharmacopoeias	4) Toxicity Testing	4) Ethnic Factors
5) Quality of Biotechnological Products	5) Reproductive Toxicology	5) Good Clinical Practice
6) Specifications	6) Biotechnological Products	6) Clinical Trials
7) Good Manufacturing Practice	7) Pharmacology Studies	7) Guidelines for Clinical Evaluation by Therapeutic Category
8) Pharmaceutical Development	8) Immunotoxicology Studies	8) Clinical Evaluation
9) Quality Risk Management	9) Joint Safety/Efficacy (Multidisciplinary) Topic	9) Pharmacogenomics
10) Pharmaceutical Quality System		

While not seeking to harmonise regulations like the ICH, other international bodies, like the World Health Organisation (WHO), have developed similar sets of best practice advice and guidelines for

[16] Ibid. See Guidelines.

poor and developing countries. Indeed, the WHO has for many years been arguing for the necessity of high quality and comprehensive drug regulation across the world. In 2001 the WHO published the second edition of *How to develop and implement a national drug policy*. As the title suggests the purpose of this document is to provide a step-by-step guide to drug regulations and the establishment of a national drugs policy. *How to develop and implement a national drug policy* makes clear that this is an issue that affects all countries around the world; developing countries in particular. And that there are serious consequences to countries that do not develop and maintains such standards:

> In many countries drug quality assurance systems are inadequate because they lack the necessary components. These components include adequate drug legislation and regulations, and a functioning drug regulatory authority with adequate resources and infrastructure to enforce the legislation and regulations. Without these, substandard and counterfeit products can circulate freely. In addition, inappropriate handling, storage, and distribution can alter the quality of drugs. All these factors may have serious health consequences and lead to a waste of resources.[17]

In addition to the ICH and WHO initiatives, there have also been several important regional efforts towards pharmaceutical harmonisation. Often these have taken place within existing regional trade or security organisations. For example, The Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC), The Association of Southeast Asian Nations (ASEAN), and Mercosur (the Southern Common Market) are, or have, agreements in place relating to the harmonisation of drug regulations. CADREAC, which includes Turkey and most Eastern European countries, allows products approved within the EU to be recognized in other CADREAC countries. Mercosur has also adopted quite a lot of drug regulatory harmonisation but, according to the WHO, 'difficulties lie in the adoption and implementation of MERCOSUR agreements and resolutions by participant countries.'[18]

The ICH, WHO and regional efforts towards harmonisation are not only important in their own right, but they also illustrate a convergence of thought on the need for establishing and maintaining international regulatory standards for pharmaceuticals. Together they provide an overview of what makes a successful and comprehensive regulatory framework.

Drug regulation – from A to Z

Within the drug regulation literature there are three main areas or fields which encapsulate both what areas of control regulations should seek to cover as well as what standards they should uphold. These areas are: quality, safety and efficacy. Together these three cover most of the most important aspects of assuring that a drug is safe and suitable for human use and will have the intended therapeutic consequences. In addition, this paper will look at Good Manufacturing Practices (GMP)

[17] World Health Organization, *How to develop and implement a national drug policy*, 2nd edition, WHO Geneva, 2001, p. 3.
[18] WHO, *The World Medicines Situation*, 2004, http://www.searo.who.int/LinkFiles/Reports_World_Medicines_Situation.pdf p. 105.

and Pharmacovigilance as separate areas of drug regulations. These two are of particular concern and interest to the developing world and this paper's five-country sample.

Quality

The term quality in drug regulation parlance refers to the medicine or pharmaceutical product in question meeting a set of specified standards both for the product itself, as well as for the procedures and processes that went into the manufacturing and dispensation of the product. The WHO's definition of quality states that:

> The quality of a drug or device is one of the criteria for market approval and is reviewed as part of the registration process. Quality assurance covers all activities aimed at ensuring that consumers and patients receive a product that meets established specifications and standards of quality, safety, and efficacy. It concerns both the quality of the products themselves and all the activities and services that may affect quality.[19]

The WHO has specified a range of steps that are needed to reach and establish this level of quality. These include: i) the review of quality as part of product registration; ii) the formulation of norms and standards; iii) the licensing of facilities and personnel; iv) inspection of facilities and products; and v) controlling the quality of a drug.[20]

In terms of the responsibility for establishing and maintaining the quality of a drug, this is not limited to the development phase but also the production process. Instead, the requirement to ensure quality runs through the entire manufacturing and distribution process. For example, manufacturers are responsible for developing and manufacturing the highest quality products and adhering to a high standard of Good Manufacturing Practices (GMP).[21] (GMP is in itself an important element of drug regulations and not just relating to the quality of a product; it will be discussed in a separate section below.) Distributers and dispensers of medicines need to ensure that the quality of a drug is not adversely affected under transportation, storage or actual dispensation. This is of particular importance in tropical countries where, unless proper storage and transportation conditions are maintained, a medicine's active ingredient will degrade rendering it either useless or, quite possibly, harmful to patients.[22] And finally, the overarching responsibility for ensuring the quality and integrity of a medicine lies with each individual DRA. They are responsible for overseeing all other actors and ensuring that the quality of a medicine is not allowed to deteriorate at any point in this long and complicated supply chain. DRAs must ensure that GMP practices are followed by having frequent and comprehensive site inspections and through drug manufacturing, sale and processing licensing agreements. Similarly, the wholesale, retail selling and dispensation of pharmaceutical products must be a licensed and/or regulated activity for which DRAs have ultimate responsibility.

---

[19] World Health Organization, *How to develop…* , p. 52.
[20] Ibid. p. 50
[21] Ibid. p. 52.
[22] O. Shakoor, et al, 'Assessment of the Incidence…', *Tropical Medicine and International Health*, p. 841. Here the authors noted that the 'decomposition of active ingredients…is plausible when drugs are stored under conditions conducive to chemical degradation of the active ingredient, particularly in tropical countries.'

Poor quality and substandard drugs are affecting both the countries in this study's sample as well as other countries (rich and poor) to which these countries export drugs. For instance, a WHO study of quality failure rates across a range of different type of manufacturers shows that there are real problems in both Brazil and India (in the form of the Indian state of Rajasthan). The below table summarises the result of this study in Brazil and Rajasthan:

Table 2: Percentage of sample tracer medicines that failed quality testing[23]

Country	Public Facilities	Private	NGO
Brazil	18.8%	18.18%	15%
Rajasthan	6.0%	14.08%	0.0%

More detailed examples will be discussed below in Section 2 and 3, as will specific problems and grey areas in each country's individual regulatory framework which is contributing to these figures.

Safety

The safety of a drug is perhaps the single most important criteria a DRA has to ensure and establish, not only for the sake of the product itself but for the integrity of the whole health system. If the safety of medicines within a health care system cannot be verified or trusted then public trust and credibility in that health system will begin to erode and public health will be at serious risk.

Within today's DRAs the safety of a drug is mainly ensured by a system of controls and testing prior to the drug being made available for public use. The safety of a drug is appraised through a period of pre-clinical and clinical trials. The purpose of these trials is to establish whether or not the drug proposed for approval is safe for human consumption. Each new medicine has to undergo a complex and lengthy process of selection, testing and development in order to make it safe for human use and therapeutically effective (this is usually referred to as efficacy and will be discussed below).

A typical pharmaceutical R&D project consists of one pre-clinical stage and four clinical stages (clinical stages are also referred to as phases).[24] At the pre-clinical stage scientists attempt to isolate new chemical or biological entities using advanced screening and synthesizing techniques. This stage also involves initial safety tests on animals and various assessment studies, such as toxicology studies. Clinical phases involve safety trials on volunteers (phase I), small patient groups, (phase II), large patient groups (phase III), and regulatory and post-marketing studies (phase IV). Both pre-clinical and clinical testing is a long and complicated procedure taking many years to complete. Today most such pharmaceutical R&D projects take about 10 to 14 years to complete.[25] After market approval the

[23] WHO, *World Medicines Situation*, p. 101.
[24] For an overview of different pharmaceutical R&D phases see: Gambardella (1995: Chapter 2); Ballance, Pogany and Forstner (1992: Chapter 4); Economist, A Survey of the Pharmaceutical Industry, (1998: 4); ABPI (1996: 8-10); IFPMA (1998: Chapter 3); PhRMA (1999: Chapter 3).
[25] Pugatch, M.P. *The International Political Economy of Intellectual Property Rights* (Edward Elgar: Cheltenham, UK, June 2004), chapter 4.

most important safety monitoring tool is what is known as post-marketing studies or stage IV clinical trials. This is the process in which real patients on a mass-scale are making use of an approved drug or a medicine and adverse reactions are reported. The reporting and monitoring of these reactions is will be discussed separately below in the section on pharmacovigilance.

According to the WHO different types of medicines require different levels of testing. The key difference here being between generic drugs (that is drugs which contain the same active ingredient as a branded product and display a similar rate of absorption into the bloodstream, also called bioequivalence) and research-based branded drugs. The WHO argues that

> For products indicated for standard uses and containing established ingredients (such as most generic essential drugs) there is usually no need to re-evaluate the efficacy and safety of the active ingredients. Separate national clinical studies would not normally be required. Emphasis should be put on a review of other factors, for example, the presentation, bioavailability (when indicated) and quality of the product, and the accuracy of the accompanying information.[26]

The procedures used to test new chemical entities stand in stark contrast to this guidance for generics. For new drugs, the WHO argues that 'considerably more extensive information is required…to prove assurance of safety and efficacy'.[27] This includes detailed accounts of the chemical, pharmacological and toxicological data on the substance as well as clinical and pre-clinical studies and trials having been carried out on humans and animals.[28]

While WHO's argument regarding new drug substances is widely accepted in regulatory practice across the world, the assertion that generic drugs should not be re-evaluated with regard to safety and efficacy is more questionable. As will be discussed below, there are many examples when DRA approved generic drugs and manufacturers of generic drugs do not meet the same pharmaceutical standards as the drugs they were copying. Particularly since in many cases of substandard drugs it is the excipient (that is the inactive substance or substances used to carry an active ingredient in a medicine) which can cause as much damage to a patient as a sub-quality active ingredient.[29] As bioequivalence tests and other commonly used regulatory evaluations of generic medicines do not clinically test excipients this is a potentially grey area of regulation.

Efficacy

Efficacy refers to the 'potential maximum therapeutic response that a drug can produce.'[30] In other words, efficacy is the extent to which the drug in question produces the desired therapeutic effect on a patient. The testing of efficacy is mainly carried out during the preclinical and clinical trials phase of pre-market approval testing. It is during these preclinical and clinical trials that a medicine's efficacy

[26] WHO, *How to develop and implement…*, p. 55
[27] Ibid.
[28] Ibid.
[29] See JM Caudron, N Ford, M Henkens, C Mace, R. Kiddle-Monroe, J. Pinel, 'Substandard medicines…', p. 1065-6.
[30] The Merck Manuals Online Medical Library, 'Drug Action', http://www.merck.com/mmhe/sec02/ch012/ch012c.html

and potency are established. Efficacy is closely linked to basic safety and quality issues. If a medicine's quality and safety are compromised – through poor manufacturing process, use of toxic ingredients etc. – then its efficacy will also be affected. Just like quality and safety the efficacy of a medicine is dependent on the processes by which it is manufactured, transported, stored and dispensed. Indeed, the efficacy of a medicine is directly linked and affected by the quality of the product. If quality and safety standards of a drug or pharmaceutical treatment are not maintained then the efficacy and desired therapeutic effect will not materialise. Instead, there is the distinct possibility that patients may be harmed.

Pharmacovigilance

As mentioned above, Phase IV clinical trials (post marketing studies) are an essential part of the safety monitoring process and to DRAs. These trials provide crucial information on how a general population responds to a medicine or pharmaceutical treatment. This type of information and scale of use is virtually impossible to replicate in a laboratory or in pre-approval clinical trials. Yet, the information garnered from these Phase IV trials can only be of use if it is, firstly, collected in a systematic fashion and, secondly, put to good use by a DRA. Indeed, post marketing monitoring relies on DRAs and health systems having developed at least a rudimentary system of pharmacovigilance. Pharmacovigilance is a system having the capacity to, firstly, detect adverse effects from a medicine or medical treatment and, secondly, having detected adverse effects preventing the further use of the affected drug or treatment. This means having the capability of reporting Adverse Drug Reactions (ADRs), taking swift and decisive action by suspending market approval of the affected drug, recall of drug batches, and having a system of regional and national warning.[31] In the developing world systems of pharmacovigilance are sorely lacking (this will be discussed in more detail in relation to each individual country in Section 3 below).[32] Indeed, this is a major problem which has a number of causes. The WHO notes that:

> For many drugs…there is virtually no post-marketing safety monitoring. This is because comprehensive post-marketing surveillance [in the developing world] is constrained by many factors including: a general under-reporting because of lack of knowledge of ADRs, fear of medical negligence or non-compliance; specific under-reporting because of lack of patient follow-up; inability to measure cumulative toxicity because of the lack of systematic records of repeated use; and lack of information on populations at risk. In developing countries, other systemic factors that are relevant to DRAs come into play, such as difficulty in transmitting reports, and difficulties in DRAs implementing policy decisions so that health warnings are circulated in a limited way.[33]

Pharmacovigilance should be at the heart of any pharmaceutical regulatory regime and is of real importance in ensuring the widespread safety of a medicine or treatment. It is vital that both developing countries and emerging markets develop strict and comprehensive systems of pharmacovigilance. As the WHO notes, in many of the pharmacovigilance programmes that do exist

[31] World Health Organization, *How to develop…* , p. 52.
[32] See JM Caudron, N Ford, M Henkens, C Mace, R. Kiddle-Monroe, J. Pinel, 'Substandard medicines in resource-poor settings: a problem that can no longer be ignored', *Tropical Medicines and International Health*, Vol 13, No 8, pp 1062-1072, August 2008, p. 1064.
[33] WHO, *The World Medicines…*, p. 103

the reporting and monitoring remain sketchy and often overly reliant on the sponsor/drug manufacturer to do the bulk of the monitoring.[34]

Good Manufacturing Practices

While primarily viewed within the context of assuring the quality of a medicine or pharmaceutical product, GMP has a direct effect on both the safety and efficacy of a drug. In its 2007 compendium *Quality Assurance of Pharmaceuticals* the WHO described GMP as 'that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and…are aimed primarily at diminishing the risks inherent in any pharmaceutical production.'[35]

Poor standards of GMP are a serious problem in both the developing world as well as in the five country sample of China, India, Brazil, Turkey and Argentina examined in this paper. A 1999 WHO study found that more than 4 in 10 countries surveyed did not have laws regarding manufacturing and distribution practices of pharmaceuticals nor did they have inspections carried out of said facilities by regulatory representatives.[36] This survey also found that less than half of countries surveyed required GMPs or sampled and tested products either in production or in retail outlets. Other studies support this finding. In 1997 the WHO studied the number of manufacturing violations in a number of emerging and developing countries and found that the average GMP violation rate was around 15%.[37] Some countries did particularly poorly. For example, Estonia had 6 manufacturing facilities with 5 inspections, recording a total of 5 violations and a GMP violation score of 100%.[38]

In summary, while it is fruitful to discuss the areas of drug regulations in terms of quality, safety and efficacy issues, this should not cloud the fact that these three are all interrelated and interdependent. It is, for example, impossible to have a high quality medicine that is unsafe for the intended end-user. As well as focusing on all three of these areas successful DRAs also need to consider a number of additional policy issues. According to the WHO some of these key issues are the following:

- Government commitment to drug regulation, including the need to ensure a sound legal basis and adequate human and financial resources;
- Independence and transparency of the drug regulatory agency;
- Stepwise approach to drug evaluation and registration; definition of current and medium-term registration procedures;
- Commitment to good manufacturing practices (GMP), inspection and law enforcement
- Access to drug control facilities;

[34] Ibid.
[35] WHO *Quality Assurance of Pharmaceuticals, A compendium of guidelines and related materials,* Volume 2, 2nd edition, 'Good Manufacturing Practices and inspection', WHO Press, Geneva 2007 p. 17.
[36] WHO, *The World Medicines Situation*, 2004, p. 97.
http://www.searo.who.int/LinkFiles/Reports_World_Medicines_Situation.pdf
[37] Ibid. p. 101.
[38] Ibid.

- Commitment to regulation of drug promotion;
- Regulation of traditional and herbal medicines;
- Need and potential for systems of adverse drug reaction monitoring (pharmacovigilance); and
- the international exchange of information[39]

While some of these issues will not be relevant to all countries (not all countries, for instance, have a large or well-developed herbal medicines sector) as a general overview of some of the key policy issues, the above is a good summary.

Having discussed some of the key elements that guide a successful drug regulatory system, this paper will now turn to examining the specific examples of DRAs in China, India, Brazil, Argentina and Turkey.

[39] WHO, *How to develop*…, p. 8-9.

Section 2: Drug Regulations in China, India, Brazil, Argentina and Turkey

> In the industrialised world drug regulatory authorities have developed strict standards and controls to ensure drugs are effective and safe. However, in the less-developed world, lack of human and financial resources within the health sector as a whole limits the capacity of drug regulatory agencies, resulting in a suboptimally regulated environment in which substandard drug production can persist without detection.[40]

The regulation of pharmaceuticals and medical treatments is a vital if hugely complicated and demanding task. Drug authorities all around the globe – regardless of the wealth or status of their respective country – face a very difficult set of challenges. By and large, emerging and developing countries do not have the resources to develop the same type of regulatory capability as countries in North America, Europe or Southeast Asia. As the above quotation illustrates, this is indeed an important factor in creating an environment in which the production of substandard medicines can take place. However, this is not the sole explanation for why substandard medicines persist in some countries and regions and not in others. In fact, there are many countries in which the financial and material resources are available but for a wide variety of reasons – social, political and geographical – the production of substandard and counterfeited medicines is not being effectively curtailed.

The purpose of the following pages is to describe the regulatory systems of five developing countries: China, India, Brazil, Argentina and Turkey. Given the concise nature of this paper, we have limited our analysis to these countries. Nevertheless, as explained above in the Introduction these countries individually and collectively represent an important sample from which policy many lessons can be learnt on how to tackle substandard and counterfeit medicines.

China

The development of China since the late 1970s has been staggering. Rarely has a country, an economy or a people changed so much in such a short space of time. With the market reforms instituted under the leadership of Deng Xiaoping during the 1980s and 1990s, China has transformed itself from an economically under-developed poor nation to being (measured by purchasing power parity or, PPP) the second biggest economy in the world.[41] Since the 1970s the Chinese economy has experienced more than a ten-fold increase in the size of its GDP and a vast improvement in living standards and expansion of personal wealth. The staggering growth of the Chinese economy has increased China's importance and stature in the world. The country is now viewed as a global power and on a range of international issues from global security policy, anti-terrorism, world trade, economic development, the proliferation of nuclear weapons, through to climate change, China's participation is viewed as vital.

---

[40] JM Caudron et al, 'Substandard medicines in resource-poor settings…', p. 1062.
[41] CIA Factbook, China, 'Economy Overview', https://www.cia.gov/library/publications/the-world-factbook/geos/ch.html

In many ways China has experienced some of the same growing pains of rapid industrialisation and economic modernisation that Western countries experienced during the 19th and 20th centuries. This includes the production of poor quality goods and services and false advertising. Scandals involving Chinese goods that are hazardous to human health are a staple of both the domestic and international news-cycle. Recent examples include the 2007 mass recall of over 10 million Chinese manufactured toys by international toymaker Mattel due to health and safety concerns over the use of lead paint and tiny magnets on the toys.[42] Similar health and safety concerns were raised about the quality of Chinese manufactured liquid milk and milk powder in 2008.[43] For health care, pharmaceutical policy and drug regulations this has some rather serious implications.

The pharmaceutical context

To begin with, China's pharmaceutical industry – in terms of both domestic consumption and production – is increasing rapidly. From 1997 to 2007 the production value of China's domestic pharmaceutical industry increased from 137.1bn yuan to 667.9bn yuan.[44] An increase of almost 500%. Similarly, export trade volume during the same period increased almost tenfold, rising from $3.4bn to a total of $24.6bn.[45] The total pharmaceutical market (excluding traditional and complementary medicines) is estimated to be worth over $30bn.[46] This is almost the same as the total value of the pharmaceutical market in Latin America.[47] But with this massive expansion in both the consumption and production of medicines has come a host of problems.

According to the United States Pharmacopeia's 2004 drug quality review counterfeiting in China is rife and the use of substandard medicines is widespread.[48] The review estimated that 99% of the 3,000 varieties of medicines made in China since the 1950s have been imitations. While not all of these medicines are bound to be counterfeits or substandard, there are a number of studies which suggest that many Chinese produced pharmaceutical drugs are of poor quality. For example, a 1998 nation-wide Chinese survey found that 13% of the 20,000 batches of medicines tested were either counterfeit or fell below minimal pharmaceutical standards.[49] Similarly, surveys of drugs used outside of China, but produced in China, have found high levels of substandard and counterfeit medicines.

The clearest sign that China has serious and endemic difficulties within its drug regulatory structure came in 2005 when the head of the State Food and Drug Administration (SFDA) Zheng Xiaoyu was arrested on corruption charges. During the course of his trial it was revealed that the SFDA director

[42] See MSNBC, 'Mattel issues new massive China toy recall', August 14 2007, http://www.msnbc.msn.com/id/20254745/
[43] See BBC News, 'China tainted milk scandal widens', 19 September 2008, http://news.bbc.co.uk/1/hi/world/asia-pacific/7624498.stm
[44] Information Office of the State Council of the People's Republic of China, *Status Quo of Drug Supervision in China*, July 2008 Beijing http://former.sfda.gov.cn/cmsweb/webportal/W43879541/A64028182.html?searchword=%28generic%29
[45] Ibid.
[46] PwC, 'Investing in China's Pharmaceutical Industry', 2nd edition, p. 5. http://www.pwc.com/en_GX/gx/pharma-life-sciences/assets/en-pharma_03-26-small.pdf
[47] IMS Health, 'Total Unaudited and Audited Global Pharmaceutical Market by Region', March 2009.
[48] United States Pharmacopeia, Drug Quality and Information Program, *A Review of Drug Quality in Asia with Focus on Anti-Infectives*, February 2004, p. 15-6.
[49] Ibid.

had taken bribes of $850,000 in exchange for approving untested medicines.[50] In a sign of just how seriously the Chinese government took his actions, Zheng was executed in July 2007. The magnitude of Zheng's actions were emphasised by the court that handed down his death sentence:

> Zheng Xiaoyu's grave irresponsibility in pharmaceutical safety inspection and failure to conscientiously carry out his duties seriously damaged the interests of the state and people…His misdeeds led to approval of many medicines that should have been blocked or taken from the market, including six fake drugs.[51]

The arrest and execution of Zheng was a huge blow to both the credibility of the SFDA and of China's drug regulatory system. In the immediate aftermath of the execution the SFDA announced new plans to reform its activities, with the twin goals of making them less susceptible to corruption and providing greater oversight of the food and drugs markets. Before getting into the detail of these changes it is worth outlining what the role of the SFDA looked like prior to 2007 and how China's legal and regulatory framework was originally formulated.

The SFDA and the regulation of food and drugs in China

The SFDA was first launched in March 1998 as a result of a government re-organisation of regulatory functions relating to health care. In 2003 the SFDA's powers were expanded by increasing its regulatory responsibility to also include food safety.[52] Guided by 2002 regulations and legislation the SFDA was charged with doing the following:

1) Drafting drug regulations;
2) Drafting quality management standards;
3) Registering new and imitation drugs;
4) Issuing production licenses;
5) Formulating qualification certification systems for drug wholesale and retail enterprises as well as licensed pharmacists;
6) Examining drug reappraisal requests;
7) Guiding the work of the national drug inspection institutes; and
8) Punishing those who make fake or poor quality drugs.[53]

The 2002 Drug Regulations and Legislation are detailed and prescribe comprehensive guidelines and statutes for the production, sale and dispensation of pharmaceutical drugs. On issues related to quality control and manufacturing and clinical practices – as outlined in the previous section, these are key areas in fighting substandard medicines – Chapters II, V and VIII of these regulations all address

[50] See MSNBC, 'China's top drug regulator gets death sentence', May 29 2007, http://www.msnbc.msn.com/id/18911849/
[51] China Daily, 'Former SFDA chief executed for corruption', July 1, 2007, http://www.chinadaily.com.cn/china/2007-07/10/content_5424937.htm
[52] Hepeng Jia, 'China Syndrome – a regulatory framework in meltdown?', *Nature Biotechnology* 25, pp. 835-7, 2007 http://www.nature.com/nbt/journal/v25/n8/full/nbt0807-835.html
[53] United States Pharmacopeia, Drug Quality and Information Program, *A Review of Drug Quality in Asia with Focus on Anti-Infectives*, February 2004, p. 15-6.

issues related to the manufacturing process.[54] Chapter II, 'Control over Drug Manufacturers', outlines how drug manufacturers must be licensed, how an acceptance inspection must take place upon receipt of a manufacturing license application, and a Drug Manufacturing Certificate must be issued prior to any manufacturing taking place.[55] Article 5 of that chapter specifically makes it clear that 'the drug regulatory department…at or above the provincial level shall organize inspections of drug manufacturers in accordance with the Good Manufacturing Practice for Pharmaceutical Products (GMP)…and issue a certificate to the manufacturer that complies with the GMP.'[56] On the inspection of drugs the regulatory authorities at all levels of government – central, provincial, autonomous region, or municipality – are charged with 'regularly make[ing] announcements on drug quality according to the results of sampling and testing'.[57] In other words, local and state authorities are instructed by government regulation to continuously monitor and maintain the quality of medicines and pharmaceutical treatments.

Similarly, the Drug Administration Law of 2001 makes it very clear what the responsibilities of a drug manufacturer are:

> A drug manufacturer to be established shall meet the following requirements: (1) having legally qualified pharmaceutical and engineering professionals, and the necessary technical workers; (2) having the premises, facilities, and hygienic environment required for drug manufacturing; (3) having the institutions and personnel capable of quality control and testing for drugs to be produced and the necessary instruments and equipment; and (4) having rules and regulations to ensure the quality of drugs.[58]

When it comes to post-marketing monitoring, China has instituted a form of pharmacovigilance through a network of reporting adverse drug reactions. In 1998 China joined the WHO Collaborating Centre for International Drug Monitoring. In 2004 the Chinese set up the Measures on Administration and of Reporting and Monitoring of Adverse Drug Reactions. Since 2002, centres and local stations have been set up to monitor ADRs. According to its own figures, China is now approaching the expected level of ADR reporting of a developed country of 400 cases per million people.[59]

These changes together with the above outlined legislation and regulations show how China has, since before the 2003 launch of the SFDA, maintained a relatively comprehensive system of pharmaceutical regulations. But it is also clear that China has a real problem with the production and consumption of counterfeit and substandard pharmaceuticals. As was alluded to above, in the immediate aftermath of

[54] State Food and Drug Administration, Drug Regulations, http://eng.sfda.gov.cn/cmsweb/webportal/W45649038/A48335997.html
[55] Ibid.
[56] Ibid. Chapter II, Article 5.
[57] Ibid. Chapter VIII, 'Inspection of Drugs', Article 59.
[58] Drug Administration Law of the People's Republic of China, Chapter II, 'Control over Drug Manufacturers', Article 8.
[59] Information Office of the State Council of the People's Republic of China, *Status Quo of Drug Supervision in China*, July 2008 Beijing. http://former.sfda.gov.cn/cmsweb/webportal/W43879541/A64028182.html?searchword=%28generic%29

the execution of Zheng Xiaoyu a number of regulatory changes were presented in 2007 to tackle some of these issues. They are the amended Measures on the Administration of Drug Registration which came into effect on October 1 2007. The purpose of the amendments is to 'increase drug safety by enhancing quality and supervision requirements' in the following areas:[60]

1) **Narrowing the Scope of New Drugs:** Prior to these amendments minor changes in drug formulations were made to change a drug and re-register it as a new drug. The result was that over 10,000 new drug formulations a year were registered as new drugs, despite the fact that the Chinese pharmaceutical industry is not R&D intensive spending only about 1-2% of revenue a year. These new measures make it tougher for manufacturer's to register new drugs unless there are substantial improvements in the safety, quality or efficacy of a drug.
2) **Creating a Regulatory Procedure for Generic Drugs:** The definition of copied drugs has been changed from "follow-on drug" to generic drug: an 'applicant for manufacture of a generic drug is required to submit comparison data/materials between the generic drug and original drug…biological drugs must comply with the new drug registration procedures rather than the generic drug registration procedures.'[61]
3) **Transparency:** The amended measures push the SFDA and local authorities towards greater levels of transparency and cooperation with manufacturers and applicants. This also involves limiting the involvement of officials with a possible conflict of interest as well as informing all parties privy to a decision (registration or licensing) of their rights of appeal etc.
4) **Approval Authority:** Approval authority is being divested from a single official to a body of officials. Moving away from individual decision-making to collective decision-making is thought to minimize corruption. Some of the approval authority for re-registration and supplementary registration will be delegated to the local and provincial authorities.
5) **Verification of Application Materials:** The new measures introduce much tougher scrutiny and verification of registration and application material. All submitted material needs to be checked and verified with on-site inspections of non-clinical trials, clinical trials and manufacturing facilities. New rules are also much tougher on applicants who submit false data.
6) **New Speedier Approval Times:** Shorter approval times: i) 90 days for new drug clinical trial applications; ii) 150 days for new drug manufacture applications, iii) 160 days for existing drugs or generics. Imported drugs may be subject to longer periods of review.
7) **Clinical Trials:** No major changes; major consequence of this is that biological drugs are subject to full clinical trials.[62]

[60] Wilmerhale (Law firm) *Briefing Series*, 'China Reforms Drug Registration', July 2007.
[61] Ibid.
[62] Ibid.

All in all these changes constitute a shift in thinking whereby the SFDA has increased its focus on drug safety through greater use of inspections and widening of the approval process to being a collective decision instead of an individual one.

Do these changes and the already robust regulations from 2002 mean that China is well on the way to achieving parity with Europe, North America and Japan in its drug regulatory structure? The simple answer is, 'no'. As will be seen in section 3, China has serious problems with the implementation of its laws and regulations. Indeed, as Qiang Zheng, director of the Center for Pharmaceutical Information and Engineering Research of the Beijing-based Peking University, said in relation to the execution of Zheng Xiaoyu, 'The problems of SFDA are related to both the scientific regulation and the larger scope of political and business environments in China'.[63]

This point is worth bearing in mind as we examine the drug regulatory systems of the other four countries in this sample.

India

While not quite as eye-popping as China's, India's growth and transformation over the past few decades has been equally impressive. Since 1997 India has averaged economic growth rates of over or close to 7% per year.[64] Indeed, in 2001, the American investment bank Goldman Sachs bunched India together with Brazil, China and Russia, to become known as the BRIC countries, a set of economies viewed as having the potential of becoming the richest nations in the world by 2050.

Over the past decade the Indian economy has developed in complexity with sophisticated service-based industries gaining in prominence. The best examples of this change are the Indian Information Technology-Business Process Outsourcing (IT-BPO) sector and the domestic pharmaceutical industry, both of which have experienced tremendous growth over the last decade. In 1998, IT-BPO sector revenues were 1.2% of Indian GDP. By 2009 this had grown to an estimated 5.8%, an almost five-fold increase in the space of a decade.[65] Similarly, the IT-BPO's sector's share of total Indian exports has grown from less than 4% in 1998 to almost 16% in 2008.[66] Illustrating the international competitiveness of this sector, two-thirds of overall 2008 industry revenues are made up of exports.[67]

The Indian pharmaceutical industry has experienced a similarly strong growth trajectory: between 1996 and 2006, nominal sales of pharmaceuticals increased by 9% per year, outperforming the global average of 7%.[68] Showing the strong potential for future growth but also reflecting the relative smallness of this market, India's pharmaceutical market remains only the twelfth biggest in the world.

---

[63] Quoted in Hepeng Jia, 'China Syndrome – a regulatory framework in meltdown?', *Nature Biotechnology* 25, pp. 835-7, 2007 http://www.nature.com/nbt/journal/v25/n8/full/nbt0807-835.html
[64] CIA, The World Fact Book, India, 'Economy Overview'.
[65] NASSCOM (Indian trade body for Indian IT and BPO businesses), 'The IT-BPO Sector in India, Strategic Review 2009', Executive Summary, p. 6, http://www.nasscom.org/Nasscom/templates/NormalPage.aspx?id=55772
[66] Ibid.
[67] Ibid.
[68] Deutsche Bank Research, Asia Current Issues, 'India's pharmaceutical industry on course for globalisation', April 9 2008, p. 1,

Its total sales of €10bn make up only 2% of total global sales.[69] But looking at generic drugs and the size of India's share of the global generic market, India is much more dominant. Actually, Indian pharmaceutical companies have specialised almost exclusively in the production of generic drugs and the generic industry has become one of the biggest in the world. Its share of the global market in generic drugs is substantial at around 20%.[70] Moreover, Indian generics also dominate the Indian domestic market. For 2006-7 70% of domestic demand was met by local manufacturing and of this 95% of drugs sold were generics.[71] Many of the biggest producers of generic drugs in the world are Indian firms. Examples of these include Ranbaxy, Cipla and Dr. Reddy's. Ranbaxy is India's biggest drug company with sales of $1.73bn for 2007 and, as part of Japanese Daiichi Sankyo Co, one of the biggest generic pharmaceutical companies in the world.[72] All three of these companies export medicines and drugs globally and have production facilities in both India and abroad.

As pharmaceutical markets have increasingly become more international and interlinked, Indian generics have found their way into the biggest pharmaceutical markets in the world: North America and Europe. In fact, Indian generics now make up over one-third of new Abbreviated New Drug Applications (ANDAs) in the United States. This demand for Indian generics is likely to continue to grow in both the developed and developing world.

In poorer developing countries with limited pharmaceutical production capabilities of their own, Indian generics are of real importance. Indeed, many poorer countries rely on India for a large number of their imports of generic medicines. As a disproportionate amount of substandard and counterfeited drugs affect poorer and developing countries, this is a real and growing issue for them. Indeed, as will be explored in more detail below in Section 3, the substandard quality of many Indian drugs presents serious health risks to patients and is an issue of both national and international concern. Recent major studies of counterfeiting and substandard drugs have shown the extent to which India produces the largest share of the world total. Given the nature of substandard drugs it is difficult to estimate exact sums, but the scale of both counterfeiting and substandard drugs is alarming. For instance, in 2008 the OECD estimated that 75% of the world's total supply of counterfeited and/or substandard drugs came from India.[73]

But the size and global influence of the Indian pharmaceutical industry is a relatively recent phenomenon. The following pages outline how this industry was built and explains how many of the regulatory and policy decisions made in the early stages of development continue to have a profound impact on the Indian pharmaceutical industry and the laws and regulations that monitor it. Indeed, current drug regulations need to be understood in the context of how the domestic Indian

[69] Ibid. p. 4.
[70] Ibid. p. 3.
[71] Padmashree Gehl Sampath, India's Pharmaceutical Sector in 2008 Emerging Strategies and Global and Local Implications for Access to Medicines, Commissioned by the Department for International Development (DFID), UK Government, p. 13.
[72] Bloomberg News, 'Daiichi to take control of Ranbaxy for $4.6billion', June 11 2008.
[73] *Asia Times*, 'Fake drugs a bitter pill for India', June 7 2008, http://www.atimes.com/atimes/South_Asia/JF07Df01.html

pharmaceutical industry was built and in particular how patent law and the regulation of intellectual property has shaped the industry.

The building of the Indian pharmaceutical industry

Up until the late 1960s the domestic Indian pharmaceutical industry was limited in both size and capability. Medicines and pharmaceutical treatments were mainly imported with only cheap bulk drugs produced domestically. From 1970 there was a sharp policy shift with successive Indian governments launching and supporting the idea of building a more substantial domestic pharmaceutical capacity. To achieve this, a host of legislative and regulatory measures were introduced. They included: the relaxation of patent rights, import restrictions on pharmaceuticals, limits on foreign-ownership and steep tariffs on medicines and treatments.[74] Of these measures, the most important (and arguably the most influential in creating India's generic-dominated pharmaceutical industry) was the decision to exclude medicines and drugs from product patent protection. Broadly speaking, up until 2005 Indian law did not provide product patents for medicines and drugs, instead an Indian patent would only cover the process whereby a medicine or pharmaceutical drug was discovered, not the end product itself. The 1970 Patent Act provided food, drugs and chemicals with only such process patents.[75] Chapter II of the Act, article 5, made clear that product patents were explicitly not allowed for medicines or drugs, instead 'only methods or processes of manufacture' were patentable.[76] The Act stated that: 'no patent shall be granted in respect of claims for the substances them selves, but claims for the methods or processes of manufacture shall be patentable.'[77]

The distinction between a process and a product patent is of real significance and has played a major part in creating the regulatory conditions from which India's generic industry could flourish and grow into today's global giant. To begin with, there is much less in the form of legal and regulatory protection for a process patent, as opposed to a product patent. For example, in the development of a medicine it is (in the vast majority of cases) the product itself which is the piece of intellectual property one is seeking to protect with a patent rather than the process by which a drug or chemical compound was discovered or developed. By not allowing patent protection for end products and substances, but only processes, the 1970 Indian Patent Act did not make illegal the direct copying and manufacturing of, what in other countries would be, patent protected medicines. Thus, through a relatively straight-forward process of reverse engineering, Indian pharmaceutical manufacturers could break down the ingredients of a medical compound or drug and then re-assemble a similar copy of the medicine or drug using the same Active Pharmaceutical Ingredient (API). Through this process a new generic drug would be made. If a patent did exist for a specific process to assemble the drug, this could effectively be bypassed by either developing a new process of assembly or slightly changing the

[74] Deutsche Bank Research, 'India's…', p. 3.
[75] Business.Gov.In, 'Managing A Business, Managing Your Intellectual Property, Patents' http://business.gov.in/manage_business/patents.php
[76] Office of the Controller General of Patents, Designs and Trademarks, Government of India, The Patents Act 1970, Chapter II, 'Inventions Not Patentable', Article 5, 'Inventions where only methods or processes of manufacture patentable [sic]'. http://business.gov.in/outerwin.htm?id=http://www.patentoffice.nic.in/ipr/patent/patAct1970-3-99.html
[77] Ibid.

patented one. In fact, many firms have developed such expertise in reverse-engineering and the manufacture of generics that there has developed a niche market for these businesses. The continued success of Indian drugs firms in manufacturing cheap generics relies on their ability to produce the kind of generic-based R&D which has made them experts in reverse engineering of APIs. This is especially in relation to the processes of producing a generic drug where the patent (covered by, as will be outlined below, new patent laws) for the therapy has expired but there may be patents on production processes. Examples of such firms include Unichem Pharmaceuticals, Matrix Pharmaceuticals, and Divi's Laboratories.[78]

In 2005 India amended its patent law and introduced a host of new measures. Chief amongst these was allowing product patents for medicines and drugs. Arguably, the 2005 Patents Amendment Act introduced product patents into Indian pharmaceutical patent legislation. This legislative change has, and is having, a big impact on India's pharmaceutical industry. For example, R&D expenditure by the top 5 Indian firms increased by 47%, from $131million in 2004 to $192.3million in 2005.[79] Similarly, since 2002, statistics show that the biggest companies invest between 5-10% of their total revenues in R&D.[80] Today the Indian pharmaceutical industry consists of roughly 20,000 licensed companies (the vast majority of which are small to medium sized enterprises) employing approximately 500,000 people.[81]

Current Indian drug regulations

Unlike China, Indian drug regulations have not been developed in a centralised and deliberate fashion. There exists no equivalent to the Chinese SFDA, the American FDA or the EU's EMEA. Instead, authority over medicines and pharmaceutical drugs is spread out over various layers of the Indian central government and state governments. As will be shown, this is the single most important and impactful characteristic of the Indian system of drug regulations.

At the central government level, pharmaceutical policy is made in all of the following government departments and agencies: the Ministry of Chemicals and Fertilizers (chiefly through the 2008 creation of a Department of Pharmaceuticals); the Ministry of Commerce and Industry (the Department of Intellectual Property Protection); the Ministry of Health and Family Welfare; and the Ministry of Science and Technology (Department of Science and Technology and the Department of Biotechnology). In terms of regulatory authority and enforcement the key player among these agencies and departments is the Central Drugs Standard Control (CDSC), which is under the Directorate General of Health Services, Ministry of Health and Family Welfare.

The CDSC is instructed under the Drug and Cosmetics Act to carry out a range of regulatory and quality control functions concerning medicines and pharmaceuticals. However, the CDSC shares this

[78] See Padmashree Gehl Sampath, India's Pharmaceutical Sector in 2008… , p. 18-9.
[79] Padmashree Gehl Sampath, India's Pharmaceutical Sector in 2008… , p. 22-4.
[80] Ibid.
[81] Deutsche Bank Research, Asis Current Issues, 'India's pharmaceutical industry on course for globalisation', April 9 2008, p. 4.

responsibility with State Governments which also, under the Drug and Cosmetics Act, has specific regulatory functions and responsibilities. A brief outline of the differences between the two is available on CDSC's website:

> Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities are responsible for approval of New Drugs, Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organisations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.[82]

The above extract makes clear how some of the most important elements of drug regulation (the regulation of the manufacturing, sale and distribution of medicines) are delegated to the State level. Table 3 below provides a more detailed account of how regulatory responsibilities and jurisdictions have been divided up between Central and State authorities.

Table 3: Division of regulatory authority and responsibility, Central versus State government, India[83]

Functions undertaken by Central Government	**Functions undertaken by State Governments**
Statutory functions	Statutory functions
Laying down standards of drugs, cosmetics, diagnostics and devices.	Licensing of drug manufacturing and sales establishment.
Laying down regulatory measures, amendments to Acts and Rules.	Licensing of drug testing laboratories.
To regulate market authorization of new drugs.	Approval of drug formulations for manufacture.
To regulate clinical research in India.	Monitoring of quality of Drugs & Cosmetics, manufactured by respective state units and those marketed in the state.
To approve licenses to manufacture certain categories of drugs as Central Licensing Approving Authority i.e. for Blood Banks, Large Volume Parenterals and Vaccine and Sera.	Investigation and prosecution in respect of contravention of legal provisions.
To regulate the standards of imported drugs.	Administrative actions.
Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).	Pre- and post- licensing inspection.
Testing of drugs by Central Drugs Labs.	Recall of sub-standard drugs.

[82] Central Drugs Standard Control Organization, Central Authorities http://cdsco.nic.in/html/CDSCO%20Contact%2025-9-08.htm

[83] Apart from the title, this table has been copied verbatim from the CDSC's website. See, CDSC, Drugs Control Administration, http://cdsco.nic.in/html/Drugs_ContAd.html

Publication of Indian Pharmacopeia.
Other Functions
Coordinating the activities of the State Drugs Control Organizations to achieve uniform administration of the Act; and policy guidance.
Guidance on technical matters.
Participation in the WHO GMP certification scheme.
Monitoring adverse drug reactions (ADR).
Conducting training programmes for regulatory officials & Govt. Analysts.
Distribution of narcotic drugs for use in medicinal formulations.
Screening of drug formulations available in Indian market.
Evaluation/Screening of applications for granting No Objection Certificates for export of unapproved/banned drugs.

As this table makes clear, on many critical issues of quality and safety regulations, there is divided authority between Central Government and the governments of individual Indian States. For example, while the CSDC is charged with laying down standards of drugs and approving new drugs, State governments have the responsibility for approving drug formulations. That is, State governments approve what substances (for example, excipients in generic drugs) go into the manufacturing process and medicines. Similarly, while the central authorities are responsible for regulating clinical research and the testing of drugs in Central Drug Labs, they are only in charge of approving licenses for the manufacture of specific categories of drugs: blood banks, large volume parenterals and vaccine and sera. State governments hold responsibility for, firstly, the majority of licensing of drug manufacturing and sales; secondly, licensing drug testing laboratories; and, finally, pre- and post- licensing inspection. State governments have the ultimate responsibility when it comes to ensuring that good GMP practices and safety and quality procedures are in place and are being followed by manufacturers, sellers and distributors of medicines and pharmaceuticals.

This division of power and responsibility between state and central government on many of the fundamental practices relating to ensuring the quality, safety, and efficacy of medicines (such as inspections and licensing and the ensuring of high-quality GMP standards) poses a real problem to the integrity of Indian medicines and public health. Poor manufacturing practices – either at the time of approval or subsequent to approval – are one of the main reasons why medicines which have gained regulatory approval become substandard. While it may be that some state governments have very

good inspection methods and rates, others may not. Standards will invariably vary and with it the quality and safety of medicines. In addition, state governments are also charged with monitoring the quality of drugs and medicines as well as investigating, prosecuting and recalling of substandard drugs. Again, while some states will have the budgets and capacity to carry out these tasks comprehensively, others will not and the standard and quality of medicines will thus vary across the whole country. In fact, there are many examples of this happening and this issue has been raised and noted by many policymakers and stakeholders within India. This February the *Business Standard* (one of India's largest financial newspapers) pointed out how the lack of a national standard and centralised regulation is a real public health issue:

> Currently new drugs and marketing of imports are authorised by the drug controller general of India but state drug authorities authorise the manufacture of drugs which have been around for four years. A drug manufactured in one state can be sold anywhere in the country. The competence of state regulators varies. The setup, for example, in Maharashtra where major pharmaceutical firms are located is quite elaborate but some states have barely any infrastructure. The market is currently flooded with states-approved fixed dose combinations, hundreds of which were banned in 2007 because they were irrational (didn't make any sense) or even harmful.[84]

Furthermore, this article made clear that 'the prevalence of spurious and substandard drugs is a scandal' and outlined how, if no reforms were undertaken, these drugs 'will continue to be widely sold in the market, affecting the poor the most.'[85]

In other important areas of drug regulations, such as pharmacovigilance, India has only recently instituted a national policy framework. Based on its poor record of pharmacovigilance, in 2003 the Indian Government was forced to take action and launched a National Pharmacovigilance Programme. This Programme consists of a National Pharmacovigilance Centre, Peripheral Pharmacovigilance, Regional Pharmacovigilance, and Zonal Pharmacovigilance.[86]

Indian drug regulators face a mammoth task of regulating the medicines and pharmaceutical treatments used in a country of over 1 billion people with much less in the way of physical infrastructure and economic development than China. Yet, from the above it would seem that the regulatory framework now in place and the division of power and authority between central government and state governments has not worked. As will be seen in section 3, substandard and counterfeit drugs coming from India are a serious problem not only for Indians, but for patients in both the developed and developing world which are importing increasing amounts of these medicines.

---

[84] *Business Standard*, 'Let a hundred spurious medicines thrive', February 4 2005.
[85] Ibid.
[86] National Pharmacovigilance Protocol, Ministry of Health & Family Welfare, Government of India, http://cdsco.nic.in/html/Pharmacovigilance%20Protocol%20.pdf

Brazil

Like India and China, over the course of the last two decades Brazil has transformed itself from a developing country into an emerging economic and international power. While not as expansive as either India's or China's, the Brazilian economy has grown at a relatively constant and consistent rate since major economic reforms were introduced by President Fernando Henrique Cardoso in the mid-1990s. Indeed, between 1997 and 2007, Brazil's GDP has averaged 2.8% growth.[87] So far the economy seems to be weathering the financial crisis and global economic downturn fairly well.

Today, Brazil's pharmaceutical market is one of the fastest growing in the world. By the end of 2007 it was estimated as being worth close to $13bn, that is, roughly the same as the size of the Indian market.[88] Average growth rates for the foreseeable future are expected to be high, topping 7% per year.[89] One of the most important factors driving this is the growth of a standardised, regulated and tested generics industry displacing the manufacturing of drugs labelled as 'similars'. As was suggested above, this regulated generics industry is a relative newcomer to Brazil. Generics (that is, copies of drugs tested for safety through some form of bioequivalence testing) were only introduced to Brazil in the late 1990s and early 2000s. At the time of introduction these drugs made up a very small segment of the overall market. But by 2007 generic sales topped $1bn, giving generics a market share of almost 10%.[90] The generics market is expected to continue growing at a rapid pace and to double its market share by 2012.[91]

<u>The Brazilian health care system</u>

The Brazilian Constitution guarantees universal health care benefits to all, and charges the Federal Government with the ultimate responsibility for ensuring the health of the nation. Article 196 of the Constitution reads: 'Health is a right of all and a duty of the State and shall be guaranteed by means of social and economic policies aimed at reducing the risk of illness and other hazards and at the universal and equal access to actions and services for its promotion, protection and recovery.'[92] That the Government of Brazil is charged with this type of responsibility is an important point. It is particularly worth bearing in mind when analysing pharmaceutical policy and trying to understand Brazil's long-term commitment to non-research based medicines, whether they are in generic form or in the less scrutinised form of "similars".[93] In fact, with regard to pharmaceuticals, Article 200 of the Constitution states that not only should the Government regulate the production and use of medicines, but it should also 'participate in the production of drugs, equipments, immunobiological

[87] World Bank, 'Brazil at a Glance', September 24 2008. http://devdata.worldbank.org/AAG/bra_aag.pdf
[88] *Medical News Today*, 'By 2012, Legitimate Generics will Account for 20% of Brazil's Pharamceuticals and Healthcare Market', 19 July 2008, http://www.medicalnewstoday.com/articles/115503.php
[89] Ibid.
[90] Ministry of Foreign Affairs of Denmark, Consulate General Sao Paulo, 'Brazil:Generics Turnover Soars 44%', http://www.gksaopaulo.um.dk/en/menu/CommercialServices/News/BrazilGenericsTurnoverSoars443.htm
[91] *Medical News Today*, 'By 2012, Legitimate Generics…'
[92] Federative Republic of Brazil, 1988 Constitution with 1996 reforms, Article 196, Edmund A. Walsh School of Foreign Service, Center for Latin American Studies, Georgetown University, http://pdba.georgetown.edu/Constitutions/Brazil/english96.html#mozTocId339966
[93] Both of these terms – generics and similars – have a specific meaning within a Brazilian context and will be defined and explained below.

products, blood products and other inputs'.[94] The Brazilian Government's activism and involvement in all aspects of health care and pharmaceutical policy is more easily understood with this in mind. In addition, the fact that most Brazilian health insurers do not reimburse patients for prescription drugs means that a substantial majority (80%) of drug purchases are made by individual patients.[95]

With regards to the regulation of medicines and pharmaceuticals the main governmental player is the National Health Surveillance Agency (ANVISA), a governmental agency under the purview of the Ministry of Health. ANVISA's role within the wider health system is central. Its purpose is to safeguard the general health of the Brazilian population. ANVISA thus has a very broad mandate with responsibilities for public health and the health care system. The agency describes its role in the following way: 'The institutional purpose of the agency is to foster protection of the health of the population by exercising sanitary control over production and marketing of products and services subject to sanitary surveillance.'[96] Its wide range of responsibilities include: coordinating the National System of Health Surveillance; epidemiological surveillance; pharmaceutical price monitoring; establishing standards regarding contaminants, toxic waste and the like; the issuing and revoking of GMP certificates; prohibiting the continued manufacture of goods and services deemed to be unsanitary or represent a risk to public health; revising and updating the pharmacopeia; and controlling the quality of goods such as food and pharmaceutical drugs.[97] ANVISA's responsibility thus extends far beyond medicines regulation into all aspects of public health and the health care system. Within the Agency there exists a General Office of Drugs that oversees many of the agencies policies and responsibilities with regard to medicines. The specific regulatory powers of ANVISA – and the legislation and regulation upon which it relies on – are discussed in more detail below.

Current Brazilian drug regulations and policy

The current make-up of the Brazilian pharmaceutical market is largely dependent on its history and, specifically, legislation from the late 1990s which brought in the current regulatory drug classifications used by ANVISA and others. This has divided up the pharmaceutical market into 3 major segments: innovative or original drugs, generics, and similars. In essence these classifications boil down to the various clinical or bioequivalence tests a medicine or drug has to undergo before being allowed to market. Innovative or original drugs are those which have been developed through lengthy research and testing procedures and are the equivalent to the same branded drugs in North America and Europe. Generics are those which have been approved for market through a process of bioequivalent testing. Similars are those which have not undergone tests for bioequivalence (the exception being drugs registered after 2003 which also have to be tested prior to approval – see below for details). Similars are largely the legacy of the copied-drugs industry built during the 1980s. This division was first instituted in the so-called Generics Law of February 1999 which was actually a series of

[94] Federative Republic of Brazil, 1988 Constitution with 1996 reforms, Article 200, Edmund A. Walsh School of Foreign Service, Center for Latin American Studies, Georgetown University, http://pdba.georgetown.edu/Constitutions/Brazil/english96.html#mozTocId339966
[95] US Commercial Service, Department of Commerce, 'Top US Export Prospects, Brazil, Pharmaceuticals', January 2005
[96] ANVISA, homepage, http://www.anvisa.gov.br/eng/index.htm
[97] ANVISA's General Competencies, http://www.anvisa.gov.br/eng/institution/competencies.htm

amendments to the existing 1976 drug regulations statute. Article 3 of this new legislation defined these three categories as follows:

> i) Similar Drug product - that which contains the same drug(s), presents the same concentration, dosage form, route of administration, strength and therapeutic indication, preventive or diagnostic, of the reference drug product registered at the federal agency in charge of sanitary surveillance, being allowed to differ only in characteristics related to size and form of the product, expiry date, packaging, labeling, excipients and vehicles, always being identified by its trade mark:
>
> ii) Generic Drug- drug product similar to a reference or innovative product, expected to be interchangeable with the latter, usually produced after the expiration or waiver of patent protection or of other exclusiveness rights, its effectiveness, safety and quality being proven, and designated by DCB or, in its absence, by INN;
>
> iii) Reference Drug product - innovative product registered at the federal agency in charge of the sanitary surveillance and marketed in the country, for which effectiveness, safety and quality have been scientifically proven to the competent federal agency, upon its registration[98]

The crucial difference in this legislation was the requirement of a generic drug needing to have its 'effectiveness, safety and quality being proven'.[99] This is in contrast to a similar drug which here had no such requirement. Since 1999 this has changed and similar drugs are, with some exceptions, now required to undergo many of the same safety and quality tests which generic drugs have to prior to market authorisation. Resolution 133, launched in May 2003, made it clear that a similar drug has to submit bioavailability data, pharmaceutical equivalence tests and a copy of an ANVISA issued GMP certificate.[100] There are however exceptions to these rules. Similar drugs registered prior to 2003 have been granted a period of adaptation which is currently set to expire in 2014.[101] These exceptions present some obvious cases whereby substandard drugs may be in circulation with the tacit approval of existing drug regulations. The extent to which such similar drugs that are exempt from bioequivalence tests are a major source of substandard drugs is difficult to quantify, but it is noteworthy that both the producers of generic drugs and research-based pharmaceutical companies agree that these similar drugs need to be tightly regulated. Executive Director of the Brazilian Generic Pharmaceutical Association Ver Valente even went so far as to say that producers of generics and Big Pharma have 'a common enemy – those who produce "similar" drugs.'[102]

Summary and key issues

While overall much of Brazil's regulatory framework is akin to similar strong regulation in more developed countries, in practice Brazil has some real problems in its implementation and enforcement of these rules and regulations. As will be explored in Section 3, Brazilian follow-through and inspection rates when it comes to GMP and compliance issues are lacking. There are also real

[98] Law 9787, Article 3, Medicamento Generico, ANVISA, http://www.anvisa.gov.br/hotsite/genericos/legis/leis/9787_e.htm
[99] Ibid.
[100] Resolution RDC 133, 29 May 2003, 'Regulates the Registration of Similar Drugs and other provisions', http://www.anvisa.gov.br/eng/legis/resol/133_03_rdc_e.htm
[101] Vera Valente (Executive Director of the Brazilian Generic Pharmaceutical Association), 'Generics in Latin America: An analysis of the Brazilian experience', *Journal of Generic Medicines*, Vol 4, No 1, pp. 30-6, October 2006, p. 32.
[102] *Knowledge Wharton*, Health Economics, 'Generic Drugs in Brazil Are a Hard Pill for Big Pharma to Swallow', March1 2006, Wharton Business School, University of Pennsylvania, http://knowledge.wharton.upenn.edu/article.cfm?articleid=1338

concerns over ANVISA's pharmacovigilance program and its capacity to effectively monitor a pharmaceutical market with the size and growing demand of Brazil. In the same vein, recent regulatory changes by ANVISA risks diluting some of the pre-registration and registration requirements of generic drugs. These new regulations – issued in March 2009 – would lower some of the quality controls and requirements of bioequivalence testing.[103] These changes are primarily aimed at allowing public laboratories to begin manufacturing generics.[104]

Many of the problems Brazil has had in relation to its domestic pharmaceutical industry – and in particular that of similar drugs – are also present in Argentina.

Argentina

Compared with China, India and Brazil, Argentina's long-term economic performance has been uneven. Since the 1980s the Argentine economy has been in a state of turbulence and has moved from periods of strong economic growth to one economic crisis after another. The most recent of these crises began in the late 1990s and culminated in the Argentine government's default on foreign debt in December 2001. The resulting economic crash saw GDP levels drop almost 20% compared to pre-crisis levels and at the height of the crisis close to two-thirds of Argentines were defined as living under the poverty threshold.[105] While the economy recovered under the stewardship of President Nestor Kirchner – hitting annual GDP growth rates of close to 8% between 2003 and 2008[106] – even during this period of high growth and, up until 2008, benign international conditions, the Argentine economy has suffered from high inflation and persistent unemployment. Indeed, the current global recession has hit Argentina hard with inflation running at, or around, 15%, unemployment reaching levels as high as 17% in parts of Buenos Aires, and the public finances dangerously overstretched.[107]

The political and social turmoil caused by the wild fluctuations of the economy over the last decade and a half have had a significant impact on the health care system and, more specifically, the pharmaceutical industry.

Argentine health care and the domestic pharmaceutical market

Health care in Argentina is largely decentralised with a substantial part of health provision being delegated to the provincial level.[108] Much care is provided through so-called Social Works (*Obras Sociales*), that is, local and regional health care providers first created through workers' unions.[109]

[103] See *Valor Economico*, March 9 2009, 'Anvisa facilita producao de remedio generico por laboratorio publico'.
[104] Ibid.
[105] CIA, The World Factbook, Argentina, 'Economy – overview', https://www.cia.gov/library/publications/the-world-factbook/geos/ar.html
[106] For Argentine growth figures see TradingEconomics, Global Economics Research, Argentina GDP Growth Rate, http://www.tradingeconomics.com/Economics/GDP-Growth.aspx?Symbol=ARS
[107] *The Economist*, 'The glass empties for the Kirchners', June 18 2009, and 'Argentina's mid term elections', Leader, June 18 2009.
[108] WHO, Pan-American Health Organization, 'Health System Response', http://www.paho.org/English/DD/AIS/cp_032.htm#respuesta
[109] Ibid.

Most health expenditure is publicly funded (54%) and a large chunk of that comes out of direct taxation.[110]

Both the basis for health care delivery and the role of pharmaceutical treatments within the system have changed significantly in recent years. As suggested above, the severe recession of the early 2000s caused the government to change course on several important issues relating to pharmaceutical policy. The scale and suddenness of the economic downturn had an immediate impact on the consumption of health care and medicines: more than 60% of the population lost their health insurance and the number of pharmaceutical units sold plummeted from over 400 million units per year in 1998 to 225 million in 2002.[111] In response to these developments, in 2002 a new national drug policy was introduced including the following: an essential medicines list and public provision program of such drugs (*Remediar*); reference pricing for many medicines covered by the public social security system; and generic prescription was made compulsory.[112] In turn these policy changes – and the economic turmoil which created them – changed the composure of the Argentine pharmaceutical industry.

As a consequence of the crisis, many multinational research-based companies left the country and sold many of their existing assets to local manufacturers.[113] Relatively weak intellectual property protection and a clear government preference towards generics and similar drugs also contributed to this move. Today, the Argentine pharmaceutical industry and domestic production of medicines is dominated by local firms. Measured by market share eight out of the top fifteen companies are local.[114] The top two companies – with 7.4% and 5.1% of market share respectively – are Roemmers and Bago.[115]

Current drug regulations

The regulation of the medicines and pharmaceutical industry is carried out by The National Drug, Food and Medical Technology Administration (ANMAT) which is a decentralised body of the National Public Administration. ANMAT has a wide remit covering medicines, food, household products, medical equipment and diagnostics.[116] Founded in 1992 ANMAT claims to have 'a body of professionals and technicians [who] work with modern technology to effectively meet the approval processes, registration, standardization, monitoring and control products used in medicines, human food, and cosmetics.'[117] While it 'depends on technical and scientific standards and directives' set by the Ministry of Health, the agency is financially independent.[118] ANMAT describes its chief aim as

[110] Ibid.
[111] Nuria Homedes and Antonio Ugalde, 'Improving access to pharmaceuticals in Brazil and Argentina', *Health Policy and Planning*, Volume 21, Number 2, pp. 121-131, p. 127.
[112] IHS Global Insight, 'Argentina's Pharmaceutical Market Changes after Economic Crisis', 2007, http://www.globalinsight.com/SDA/SDADetail6182.htm
[113] Ibid.
[114] Todd D. Clark, *PharmaHandbook: A Guide to the International Pharmaceutical Industry*, VOI Consulting 2007, p. 461.
[115] Ibid.
[116] ANMAT, Informacion Institucional, 'Que es la ANMAT?', http://www.anmat.gov.ar/institucional/institucional.asp
[117] Ibid.
[118] Ibid.

being: '[to] ensure that medicines, food and medical devices available to the population, own effectiveness (achieving the target therapeutic or diagnostic nutrition) security (high risk / benefit) and quality (responsive to the needs and expectations of citizenship).'[119]

As in Brazil, ANMAT classifies drugs in three ways: i) Innovative or Original, ii) Generics, iii) Similars.[120] Innovative drugs are used as the referenced drug for registration of both generics and similars. However, generic drugs must undergo tests of bioequivalence that similars do not need to. Similar drugs have 'the same active ingredient [as an innovative drug], concentration, pharmaceutical form, and dosage and are used for the same indications as the innovative product. They are equivalent to the innovative product but may differ in size, shape, packaging, and period of activity.'[121] Generics, on the other hand, are defined as 'drugs that have been proven to be bioequivalent to the innovative drug.'[122]

Unlike Brazil, which has introduced legislation to phase out copies and introduce bioequivalence testing for all copied drugs, Argentina does not currently have such a legislative intention or programme. In fact, existing ANMAT documents make clear that such legislation does not exist and any further regulation of such a nature would require a change in existing law. In describing its current efforts in the field of bioequivalence testing of similar drugs, ANMAT states:

> ANMAT has begun to implement a Bioequivalence Program, according to current practice and international recommendations. In countries like Argentina, which have a large number of similar products, these studies must be carried out depending on the health risk. **However, it should be clear that this has nothing to do with a generic drug policy: for this, first a law must be passed that deals with bioequivalence, since currently nothing like this is defined in our health law.** On this issue, the implementation of a generic drug policy involves incorporating into the registry a new class of drugs that, according to international definitions (WHO, FDA), would require demonstration of bioequivalence prior to approval.[123] [Bold added]

The lack of action on bioequivalence testing is a real deficiency of the ANMAT and current drug regulations. This deficiency is in turn compounded by the lack of public awareness of the differences between generics and similars. Indeed, as in Brazil, much of the terminology being used by Argentine officials and policymakers about medicines is not mindful of this distinction between generics and similars. Similars are frequently referred to as generics despite the fact that they do not have to undergo similar tests of quality and safety. In 2005 the Regional Representative of the International Community of Women living with HIV/AIDS, Patricia Pérez, criticised the then Minister of Health and the Environment Dr Ginés González García and ANMAT for jumbling these terms together. Ms Pérez wrote:

---

[119] Ibid.
[120] Nuria Homedes, Roberto Lopez Linares and Antonio Ugalde, *Generic Drug Policies*…, p. 3.
[121] Homedes and Ugalde, 'Multisource drug policies in Latin American: survey of 10 countries', Bulletin of the WHO, January 2005 83 (1), p. 66.
[122] Ibid.
[123] ANMAT, BIOEQUIVALENCE POLICY FOR SIMILAR DRUGS, Original in Spanish. Translated by the Stockholm Network; this is not an authorised translation. http://www.anmat.gov.ar/Documentos_Informativos/Consultor_n376_BiodispII.pdf

> We in ICW are in favour of quality drugs, whether these are branded or generic. We are strongly opposed to taking copycat ARVs [antiretrovirals] – no matter how much the Ministry of Health argues that these ARVs (which the Ministry of Health labels "generics" but which are actually copies) bring down costs and optimise the AIDS budget.[124]

Another area in which current ANMAT regulation is lacking is pharmacovigilance. ANMAT does not have either the capacity or the capability to effectively monitor the safety and quality of many pharmaceuticals, particularly in the post-marketing stages. Its system of pharmacovigilance is both technically limited and current pharmacovigilance regulations place too heavy an emphasis on the pharmaceutical industry to conduct monitoring and reporting of ADRs. First created in 1993 the National System of Pharmacovigilance consists of the centralised authorities at ANMAT (divided into two divisions: Departemento Farmacovigilancia and Servicion de Informacíon de Medicamentos) and over sixty regional centres.[125] This system is severely hampered by the fact that ADR reporting is not mandatory for health professionals for most drugs and medicines (a minority of medicines are subject to reporting).[126] Instead, most ADR reporting is expected to come from the pharmaceutical industry with pharmaceutical laboratories and manufacturers charged with detecting and reporting ADRs to ANMAT.[127]

Summary

While it is clear that the economic crisis of the late 1990s had a direct and lasting impact on medicines regulation in Argentina, it is not entirely obvious that the current global recession will have a similar effect. Certainly, the sharpness of the economic downturn will put even more pressure on health care and existing regulatory budgets, but the challenges the Argentine system of drug regulations faces is not only about financial resources. Just as with Brazil, the existence of similar drugs and the confusion of similars with generics pose significant threats to public health and the integrity of the drug regulatory process. As will be illustrated in Section 3, many Argentines are concerned over the quality of their medicines and the confusion over what constitutes a generic drug.

Many similar issues face our final case study: Turkey.

Turkey

Like China, India, Brazil and Argentina, Turkey is also a relative economic newcomer which has over the past two decades transformed itself into a regional economic and political power with GDP growth rates frequently topping 6%.[128] Indeed, Turkey's economic performance has been relatively

[124] International Community of Women living with HIV/AIDS, Patricia Pérez, 'Generics in Argentina: a test still to be passed', 18 January 2005, posted: http://www.icw.org/node/119
[125] Uppsala Reports, *UR 41*, April 2008, WHO, the Uppsala Monitoring Centre, p. 16.
[126] Ibid.
[127] ANMAT, Pharmacoviglinace, Annex 1. Original in Spanish. Translated by the Stockholm Network; this is not an authorised translation. http://www.anmat.gov.ar/Legislacion/Medicamentos/Disposicion_2438-2000.pdf
[128] CIA, The World Factbook, Turkey, 'Economy – overview', https://www.cia.gov/library/publications/the-world-factbook/geos/tu.html

consistent since the introduction of a range of economic reforms in the early 2000s. Since then, the economy has grown steadily at or around 5% of GDP.[129] While the current global economic downturn has had a significant impact on the Turkish economy (with GDP forecast for 2009 to contract by close to 6%), its banking sector has largely survived and the IMF recently lauded the economy's overall strength and development.[130]

Over the last decade Turkey has also introduced significant changes and reforms to its health care system. These reforms have had a significant impact on the domestic pharmaceutical market and the regulation and access to medicines.

Turkey's healthcare system and pharmaceutical market

Prior to 2003 Turkey's system of health care was quite disparate and highly fragmented. Various government agencies and regional bodies operated different programmes of health provision to different strands of the population.[131] Social security agencies provided insurance to salaried workers in the formal sector, civil servants (active and retired), and the self-employed. A separate scheme (the Green Card programme) of direct government payments provided health coverage for the low-income uninsured.[132]

In 2003 the Turkish Government introduced the Health Transformation Programme (HTP), a set of health reforms meant to increase both the effectiveness of the health care provided and the overall efficiency of the system. Key elements of the HTP included: centralising planning and health care authority into the Ministry of Health; providing universal coverage and the administration of this coverage through one government agency; improving overall quality of health care delivery and patient satisfaction.[133] As part of further reforms in 2008, Turkey established a single-payer system of health insurance for all publicly insured patients.

The HTP reforms were a response to a rapidly deteriorating fiscal situation with regard to health care financing. For all social security spending (including health care) the deficit had risen from 1.1% of GDP during the late 1990s and early 2000s to 3.9% by 2005.[134] Apart from the obvious budgetary impact of this increase in the social security deficit, Turkey was also under pressure from the International Monetary Fund to cut health care spending.[135]

[129] Ibid.
[130] Reuters Update, 'IMF chief sees no need to help Turkey', September 20 2009, http://www.reuters.com/article/marketsNews/idUSLK54457520090920
[131] OECD and the International Bank for Reconstruction and Development/The World Bank, *OECD Reviews of Health Systems Turkey*, 2008, p. 11.
[132] Ibid.
[133] Ibid.
[134] Todd D. Clark, *PharmaHandbook…* VOI Consulting, p. 569.
[135] Ibid.

The HTP reforms also instituted a new system of drug purchasing and regulation. In 2004 reference pricing – based on a basket of five countries – was introduced.[136] In line with Turkey's economic growth and rising prosperity consumption and production of medicines and pharmaceutical drugs has increased sharply during the 2000s. As a percentage of the overall health budget pharmaceutical expenditure is quite high at over 30%. The pharmaceutical market almost doubled in value between 2002 and 2006, growing from a value of €3.3bn in 2002 to €5.2bn in 2006.[137] A slim majority of medicines and pharmaceutical drugs consumed are generics. Between 2002 and 2006 the generics market grew from 48% of the total pharmaceutical market to just over 50%.[138] This number is set to increase as generics are likely to gain market share and the government will continue to contain health care spending and, in particular, spending on pharmaceuticals.

The domestic pharmaceutical industry is quite large and Turkey has a sizeable manufacturing capacity with over 80% of medicines and pharmaceuticals consumed being produced locally.[139] There are close to 150 companies within the pharmaceutical sector with almost 90 companies manufacturing finished formulations and a small number of companies producing active ingredients.[140] Out of these, a clear majority are domestic companies, the rest being multinationals.

Current drug regulations

The General Directorate of Pharmaceuticals and Pharmacies (IEGM) is the government agency charged with overseeing market authorisation of medicines and pharmaceuticals.[141] The IEGM is a division of the Ministry of Health (MOH) and, as such, is lodged within the MOH. While the MOH has ultimate responsibility over market authorisation, IEGM is the *de facto* Turkish drug regulatory authority. Interestingly, IEGM also has responsibility (in consultation with other ministries) for the pricing of medicines as well as market approval.[142] Within IEGM there are eleven departments dealing with different aspects of the drug approval, testing and monitoring process. These departments are summarised in the below table together with a brief description of their respective functions

[136] Ministry of Health (Editor Recep Akdağ), *The Progress So Far, Turkey Health Transformation Programme, November 2002-June 2007*, Ministry of Health, Turkey, June 2007, p. 74.
[137] Pharmaceutical Manufacturers Association of Turkey (IEIS – Generics Association), *Generic Drugs in Turkey*, 2006, p. 3, http://www.ieis.org.tr/asp_pages/index.asp?menuk=14&sayfa=305
[138] Ibid. p. 5.
[139] Ibid. p. 4.
[140] Todd D. Clark, *PharmaHandbook…* VOI Consulting, p. 574.
[141] Ibid. p. 571.
[142] Ibid.

Table 4: Summary of Departments within the IEGM[143]

Department	Function
Clinical Drug Research Department	Oversees applications for clinical trials and regulates and enforces the standards relating to GCP.
Cosmetics Department	Performs market surveillance and oversees manufacturing of cosmetics.
Department of Biological Products	Oversees the registration and authorisation processes of blood products and immunological products (vaccines, antiserums and allergens).
Department of Enteral Nutrition Products and Medical Feed	Oversees and allows for the importation of dietary foods for special medical purposes.
Department of Registered Drugs	Handles procedures related to already registered products.
Drug Product Promotion Activity – Consumer Safety Coordination Unit	Informs the public about new drugs and treatments.
Drug Safety Monitoring, Evaluation Department	Performs pharmacovigilance work and monitors ADRs.
Pharmaceuticals Track and Trace System	
PSUR and National Reports Assessment Unit	Monitor and evaluate Periodic Safety Update Reports (PSUR) with regards to product authorisation renewal, changes in market authorisation routine reports etc.
Quality Control Department	Oversees quality, safety and efficacy properties of medicines and pharmaceuticals. Inspects, monitors manufacturing of drugs; carries out annual market surveillance program. Issues GMP certificates.
Standards Department – Pharmacopeia	Sets pharmacopeia standards in accordance with European standards and Turkish laws.

The legislation guiding drug approval is the 'Pharmaceutical and Preparations Law', law number 1262, originally passed in 1928. The relevant piece of regulation guiding the manufacture of pharmaceutical drugs and medicines is 'Regulation on the Manufacturing Practices for Medicinal Products for Human Use'. Article 5 of this Regulation makes clear that 'manufacturing of medicinal products for human use may take place solely on sites given manufacturing site authorization'.[144] And the following Article 6

[143] Ministry of Health of Turkey, General Directorate of Pharmaceuticals and Pharmacy, Outline of Departments and functions: http://www.iegm.gov.tr/Default.aspx?sayfa=departmants&lang=en
[144] Republic of Turkey, Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy, 'Regulation on the manufacturing practices for medicinal products for human use', Ankara 2004, Articles 5-6.

outlines how such manufacturing site authorisation will only be granted after inspections have taken place by MOH staff.[145]

Since 2004-5 (and the launch of the HTP reforms) Turkey has been seeking to harmonise its drug regulations with European standards and there have been a number of changes to market authorisation policies. This is particular with regards to pharmacovigilance. In March 2005 new regulations were introduced to create a more comprehensive pharmacovigilance structure to monitor ADRs; collect, record and assess data; and establish better chains and links of communications between all stakeholders.[146] The Regulation was drawn up explicitly 'for the purpose of achieving harmony with the relevant legislation of the European Union on medicinal products for human use'[147] and outlines how the onus for monitoring is on both the manufacturer of the pharmaceutical product as well as healthcare professionals. (This is in stark contrast to Argentina's system of pharmacovigilance which does not mandate health professionals to do any ADR reporting.)

Summary

The reform initiatives of recent years – including the overhaul of Turkey's health care system and effort to harmonise important parts of its regulatory framework with EU rules and guidelines – have left Turkey with a health and drug regulatory system in a state of change. As with many of the other countries in this survey which have recently instituted big changes to their regulatory structures – see China and Brazil – the crucial issue is whether or not these reform efforts are being effectively implemented.

The purpose of the following pages is to provide a snapshot of what is happening on the ground with drug regulations and to ask whether many of the reform initiatives and changes discussed in the previous country outlines are really having an impact on the supply of counterfeit and substandard drugs.

[145] Ibid.
[146] Ministry of Health Turkey, General Directorate of Pharmaceuticals and Pharmacy, 'Regulation Regarding the Monitoring and Assessment of Medicinal Products for Human Use', http://www.iegm.gov.tr/Default.aspx?sayfa=safety_regu&lang=en&thelawtype=14&thelawId=161
[147] Ibid.

Section 3: Implementing Drug Regulations – Challenges on the Ground

Counterfeit and substandard medicines are a real and growing threat to public health systems around the world. They are of particular concern in poor and developing countries where health and regulatory systems, as well as domestic pharmaceutical manufacturing, are underdeveloped. For example, in 1999 the WHO commissioned a study of 503 samples of 12 pharmaceutical products in Myanmar and Vietnam.[148] Out of this sample 11% failed laboratory quality testing performed by the WHO.[149] Other studies have found similar results. For instance, a 1992 study of a variety of medicines sold in retail shops from across Bangladesh found that 37 out of 137 brands examined were found to be of substandard quality.[150] Other, more recent studies have found a similar number of substandard drugs in circulation in many poor developing countries. A 2008 study of the quality of antimalarial drugs in six African countries found that 35% of samples tests failed either or both semi-quantitative thin-layer chromatography (TLC) and dissolution testing.[151]

As the previous sections have illustrated, substandard and counterfeited drugs are a real and growing problem in all of the sampled countries for this paper. But the problems are not uniform or one and the same in all countries. Neither are the responses to the problem. Yet one thing which is clear from all countries is that implementing policy is as difficult as formulating it.

Seasoned lawmakers and policymakers frequently lament that when it comes to reform, the easy part is passing the legislation. The hard part is implementing change and getting real results on the ground. The purpose of this following section is to explore some of the practical challenges faced by the countries in the previous section's sample of five countries and give a few examples of how their efforts against substandard and counterfeit drugs have progressed. While the following examples are not meant to be viewed as exhaustive empirical surveys of any one country, they do provide snapshots of some of the difficulties and real challenges that exist and persist in these countries.

China

As was noted in Section 2, both counterfeiting and the production of substandard drugs are rife in China. In many instances, China has the dubious distinction of being the world leader in counterfeiting. For example, in 2006 close to half – 47% – of all counterfeited Viagra seizures were made in China.[152] In the United States Pharmaceopeial Association's *Matrix of Drug Quality Reports*

[148] WHO, *Counterfeit and Substandard Drugs in Myanmar and Viet Nam, Report of a study carried out in cooperation with the Governments of Myanmar and Viet Nam*, Geneva 1999, p. v-vi.
[149] Ibid.
[150] Jiben Roy, 'The menace of substandard drugs', *World Health Forum*, Volume 15, 1994, pp. 406-7, p. 406.
[151] Roger Bate et al, 'Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa – A Six Country Study', *PLos ONE*, Volume 3, Issue 5, e2132, May 2008, pp. 1-3, p. 1.
[152] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality Reports Affecting USAID-assisted Countries*, June 2009, p. 18.

Affecting USAID-assisted Countries over 25 serious cases of counterfeit or substandard drugs are listed for China.[153] These range from massive seizures of counterfeit and substandard medicines to the administration of such medicines and the often fatal consequences this has. For instance, in May 2006 11 people died from taking antibiotics in which diethylene glycol had been added.[154] Similarly, in 2006 while being hospitalised and treated for hepatitis, a man died from receiving a counterfeit or substandard injection of Armillarisni A.[155] This injection had been contaminated with diglycol instead of propylene glycol.[156] And, beginning in 2007, hundreds of Chinese cancer patients were paralyzed or suffered severe disabilities from impure leukemia drugs.[157] In this case it was found that the manufacturers (Shanghai Hualian) of the leukemia drug had contaminated this and other oncologics with another cancer drug, vincristine sulphate.[158]

Chinese counterfeited and substandard drugs are also widespread outside of the Chinese mainland and China's immediate neighbours. For example, in 2007 the UK's Medicines Health products Regulatory Agency (MHRA) issued four of its 'Class One' emergency recall notices for three major drugs: Casodex (a medicine for prostate cancer); Plavix (a blood thinner used to prevent blood clots, the presence of which can lead to strokes and heart trouble); and Zyprexa (an antipsychotic used to treat schizophrenia).[159] The contaminated batches of these products were traced back to China and an international counterfeiting drug ring.[160] Similarly, in 2006, faked versions of home-testing diabetes strips were discovered by Johnson & Johnson, the manufacturer of the tests.[161] These tests had spread to the United States, Canada, Greece, India, Pakistan, the Philippines, Turkey and Saudi Arabia. Final court filings reveal that around 1 million of these tests had been manufactured in China.

These are just a few of the many examples of how counterfeit and substandard drugs have been manufactured and spread in and outside of China. While the Chinese drug authorities have taken serious action – including changing regulations, increasing the SFDA's budget and international cooperation on drug safety – counterfeiting and substandard medicines are still rife. The cause for the persistence of drug counterfeiting and producing substandard drugs cannot be drilled down to only one specific factor. Instead, there are a number of different causes. These include: government and local corruption; a general lack of accountability and oversight of key regulations and regulators; a pervasive popular culture and acceptance of counterfeited goods and IPR infringement; as well as the sheer scale of the problem. There are a number of things China can do, but there is no quick fix to this issue.

---

[153] Ibid. p. 15-25.
[154] Ibid. p. 17.
[155] Ibid. p. 21.
[156] Ibid.
[157] Ibid. 21-2.
[158] Ibid.
[159] BBC News, 'How fake drugs got into the NHS', February 3 2009, http://news.bbc.co.uk/1/hi/health/7865569.stm
[160] Ibid.
[161] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality*…, p. 19.

India

As one of the world's biggest exporters of generic drugs, India's problem with substandard and counterfeited drugs affects patients across the globe. As was noted above, it is particularly developing countries (which themselves have a limited capacity to produce their own medicines) that are the most vulnerable to contaminated Indian exports of essential drugs. Indeed, India with its large domestic generic manufacturing base, exports drugs all over the world. But there are serious doubts over the quality of many Indian manufactured products. Only recently, in 2007, were Indian vaccines banned from the WHO's pre-qualified list due to concerns over the existing DRA and a track-record of poor manufacturing practices.[162] While they have since been allowed back onto the WHO programme, Indian vaccines will be subject to parallel review by the Canadian health regulator, Health Canada.[163] Similarly, in a 2007 study of anti-malarials in Kenya where India and China were listed as the origin countries of production, over 40% of the drugs sampled contained either an over or under concentration of the active ingredient.[164] Other studies have also found large concentrations of substandard medicines in, or coming from, India. For instance, in 2004, Médecins Sans Frontières' (MSF) procurement centre in Europe discovered fungal contamination of Indian produced IV fluid bags.[165] MSF also listed one particularly illustrative example of the danger of substandard medicines: the death of 30 Indian children caused by contamination of a cough syrup.[166] In this case, diethylene glycol was used instead of propylene glycol. In fact, a compilation by MSF of substandard medicines shows a disproportionate number of drugs with their origins in India.[167]

The United States Pharmacopeia's Drug Quality Matrix shows similar results. Indian entries are numerous and, like China, there are many serious examples of substandard and counterfeit drugs. For instance, in 2004 the Delhi government carried out a series of inspections on local chemists and drug manufacturing sites.[168] Out of the 618 sites inspected, over 100 chemists and three manufacturing sites were suspended for violating the law.

Out of all the countries sampled in this report India seems to have the greatest problem with counterfeit and substandard drugs. Unlike China, which at least in theory has a regulatory system in place, India does not have a comprehensive system of regulations or a centralised form of authority and enforcement. In a newspaper interview from 2007 a local Delhi pharmacist concisely summed up India's problems. The following is a direct quote from the *Asia Times Online* (one of Asia's most popular news-sites):

---

[162] See *The Economic Times*, 'WHO moots parallel checks on Indian vaccines', 28 July 2009 http://economictimes.indiatimes.com/News/News-By-Industry/Healthcare-Biotech/Pharmaceuticals/WHO-moots-parallel-checks-on-Indian-vaccines/articleshow/4827866.cms and LiveMint.com (online version of *Mint*, an Indian newspaper formed out of a collaboration between HT Media and the *Wall Street Journal*), 'WHO lifts vaccine embargo on India', 20 April 2009 http://www.livemint.com/2009/04/20002755/WHO-lifts-vaccine-embargo-on-I.html

[163] Ibid.

[164] JM Caudron, et al, 'Substandard medicines…',p. 1065-6

[165] Ibid. p. 1067.

[166] Ibid. p. 1067-8.

[167] Ibid.

[168] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality*…, p. 25.

> "The main problem in India is that we lack quality infrastructure to test the quality and purity of drugs," said Akhil Bharadwaj, a New Delhi-based pharmacist. "While our drug pricing is tightly controlled, our drugs' quality remains unmonitored by a registered central agency. Most of our laboratories are ill-equipped and operate in unhygienic conditions. In such a bleak scenario, quality doesn't figure."[169]

Indeed, apart from basic issues of legislation and quality control, India's systems of pharamcovigilance and enforcement mechanisms are sorely lacking. A 2007 estimate found that at the national level India has only 35 inspectors and at the state level 1,000.[170] Divided by the number of medicines outlets each inspector (national and state) would be responsible for 500 medicine outlets.

Brazil

While the prevalence of substandard and counterfeit drugs in Brazil is considerable, it is relatively small compared with that of China, let alone India. A pre-internet revolution estimate by the National Secretariat of Health of the amount of counterfeit drugs in circulation was put at 5-7% of all medicines.[171] The rapid penetration of the internet and selling of counterfeited medicines online has meant that this figure is only increasing. A recent example of counterfeited and substandard drugs being found include a 2008 seizure of illegal medicines and the shutting down of eight pharmacies in the state of Mato Grosso.[172]

The prevalence of low-quality drugs has also been caused by the fact that up until 2003 there was no effective mechanism for quality and safety control of similar drugs. The introduction of legislation that year does ensure that products registered after 2003 will have to undertake the same bioequivalence tests reserved for generics. However, products registered prior to 2003 have received a grace period until the end of 2014. While some products (21 by 2005) and active ingredients have been removed by ANVISA – directly acknowledging the argument that many similars were of substandard quality – final removal of the similar category will not be achieved until the beginning of 2015[173] – the result being that there are still medicines on the market, with regulatory approval, which have not been tested for therapeutic quality or bioequivalence.

Argentina

Argentina also has serious problems with counterfeiting and substandard drugs. In the US Pharmacopiea's Global Drug Quality Matrix, serious cases involving the production of fake cancer drugs were highlighted.[174] In one case no active ingredient was found and in the other the drug had expired but been transferred to a different container.[175] Apart from showing the persistence of counterfeiting drugs, this case also highlights a gap in the regulations of drug repackaging. Specifically,

---

[169] *Asia Times Online*, 'Fake drugs a bitter pill for India', June 7 2008, http://www.atimes.com/atimes/South_Asia/JF07Df01.html
[170] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality*…, p. 26.
[171] Jillian Clare Cohen, 'Public Policies in the Pharmaceutical Sector: A Case Study of Brazil', Human Development Department LCSHD Paper Series No. 54, The World Bank, Latin America and the Caribbean Regional Office, January 2000, p. 18.
[172] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality*…, p. 46.
[173] CIPIH, WHO, Third Meeting of CIPIH, Brasilia, February 1 2005, Session One ANVISA, http://www.who.int/intellectualproperty/events/meeting3/en/index1.html
[174] US Pharmacopeia Drug Quality and Information Program, *Matrix of Drug Quality*…, p. 46.
[175] Ibid.

Argentine legislation allows pharmacists to change the expiration date of a drug as long it is not proven that doing so damaged someone's health.[176]

Highlighting the serious consequences counterfeiting and substandard medicines can have, a 2007 article in *Perspectives in Health*, the magazine of the Pan American Health Organization (the regional office of the WHO) detailed the death of a woman in Patagonia.[177] The woman in question was suffering from anaemia and received a counterfeit injection of an iron supplement. Instead of containing iron sorbitol, the contaminated ampules contained a different iron derivative in a much stronger concentration.[178]

Like Brazil, Argentina's drug laws recognise three different categories of drugs, including similars. While the Brazilian authorities have reformed drug laws with the intent of eliminating similars by 2015 – thereby drawing a clear distinction between the standards of similars and those of generics – Argentina has done no such thing. Instead, similars and generics have been used interchangeably by public officials in their discussions on the need for cheaper medicines. This despite the fact – as explained above – similars do not need to undergo the same type of bioequivalence testing and quality controls which generics must. This lack of quality controls is a serious problem across Latin America. In fact, a 2004 World Bank survey of Latin American regulatory agents and local pharmaceutical experts found that in all countries but Chile and Brazil respondents were concerned over regulators' ability to ensure the quality of medicines: 'Except in the case of Chile and Brazil, survey respondents manifested their frustration with the limited capacity of the regulatory agencies to control the quality of the medicines available in Latin American markets.'[179] This concern over quality is of particular pertinence in Argentina where doctors' concerns over the poor quality of similars lead to opposition to the 2002 proposed government reforms. In fact, the poor quality of similars, and the official language of jumbling together similars with generics, caused a series of protests by physicians against the Generics Law of 2002.[180] Physicians argued that Argentina had no generics as the quality tests of similars were of such a low standard.

Turkey

Turkey too, has serious problems with counterfeit and substandard drugs. According to former Turkish policeman and Interpol operative Cengiz Gümüştüs, Turkey is the fourth largest market for counterfeit medicines in the world in terms of the number of arrests.[181] In fact, the problem of counterfeit drugs is so widespread that the Turkish Government was set to launch a new initiative to track pharmaceuticals during the 2009 summer.[182] All medicines and pharmaceuticals were to be given

[176] 'Deadly Imitations', *Perspectives in Health*, Vol 11, No 1, 2007, http://www.paho.org/English/DD/PIN/Number23_article3.htm
[177] 'Deadly Imitations', *Perspectives in Health*, Vol 11, No 1, 2007, http://www.paho.org/English/DD/PIN/Number23_article3.htm
[178] Ibid.
[179] Nuria Homedes, et al, *Generic Drug Policies...*, p. 9.
[180] Ibid. p. 9-10.
[181] *Hürriyet Daily News*, 'Expert warns on counterfeit medicines', July 1 2009, http://www.hurriyetdailynews.com/n.php?n=expert-warns-on-counterfeit-medicines-2009-07-01
[182] *Today's Zaman*, 'Barcode system to stamp out counterfeit drugs', August 18 2009, http://www.todayszaman.com/tz-web/news-184271-barcode-system-to-stamp-out-counterfeit-drugs.html

a barcode so they could more easily be tracked and counterfeited medicines be detected. However, due to logistical difficulties and wide-spread resistance from pharmacists the scheme has been postponed till the autumn.

While this scheme highlights the pervasiveness of counterfeited pharmaceuticals within the Turkish health care system, the resistance on the part of pharmacists reveals some of the regulatory and structural weaknesses of existing pharmaceutical distribution. For example, the existence of bartering medicines between small-scale pharmacists (which make up the majority of Turkish pharmacists) makes it very difficult to track and monitor the selling and dispensation of particular medicines. This makes pharmacovigilance monitoring and follow-up exceedingly difficult. Batches which are found to have been faulty or tampered with cannot easily be tracked as their whereabouts can have changed numerous times. Similarly, many medicines and pharmaceutical drugs can be purchased without prescriptions even though this is technically illegal.[183]

[183] Ibid.

Final Thoughts and Policy Recommendations

Counterfeited and substandard medicines are a real and growing threat to public health. This paper has attempted to show, firstly, just how serious a threat this is and, secondly, to discuss how the regulations of the production, sale and use of medicines can have an impact on the availability of these dangerous drugs. The paper began by examining the very nature of medical and pharmaceutical regulations: Why are they necessary? What are the concepts and ideas drug regulations are based on? And what are some of the essential best practices? It then moved on to examining how drug regulations have been designed in a number of countries which have experienced problems with substandard and counterfeited drugs. By examining each country separately it was found that because they all faced different sets of challenges, drug regulators and policymakers had responded to them differently. In some cases this had led to positive results; in other instances the results were less encouraging. The paper's final section provided some concrete examples of the lethal effects counterfeiting and substandard drugs can have on public health and how bad, non-existent or un-enforced regulations can play a serious part in this process.

Indeed, the overarching purpose of this paper has been to highlight an often grey area of the access to medicines debate and show just how wide-spread the production of substandard drugs and counterfeiting has become. As this paper has shown, this is a problem that overwhelmingly affects the developing world and emerging markets. The evidence from this paper's sample of China, India, Brazil, Argentina and Turkey shows that while this problem is widespread it also affects countries differently. The specific problems each individual country has to grapple with, depends on the legislative, regulatory, cultural, and socio-economic policies and make-up of that country. As such there are no easy or quick fixes. Some problems can be addressed relatively easily, while others require hard thinking, large resources, and national – or even international – coordination.

The following policy recommendations (summarised in Tables 5 and 6 below) are divided into two categories: general recommendations valid for all countries, and some country-specific recommendations.

Table 5: General Policy Recommendations

- Recognise the problem. Governments in all countries (and across the world) must acknowledge the extent to which the production of substandard drugs and counterfeiting is a real threat to public health and safety. This is the first step towards action.
- There must be a better understanding at the regulatory, policy and public level of the differences between substandard and counterfeited drugs. While the effects of the two are often similar – detrimental and sometimes lethal health outcomes to patients – their causes are not always the same. Counterfeiting is the deliberate production of illegal, unsanctioned and mostly harmful medicines. Substandard drugs, by contrast, can be produced, sold and distributed by completely legitimate and authorised entities who are often unaware of their product being (or becoming) substandard.

Table 6: Country-Specific Policy Recommendations

- **China**: China must do better at implementing its existing regulatory framework. While resources for the SFDA have been increased and there is improvement in national and international coordination, Chinese regulators and policymakers must make enforcement a greater priority.
- **India**: Indian drug regulations are highly disparate, inefficient and not well-enforced. Regulations should be streamlined and a clear regulatory framework and source of authority should be established. The current split between central and provincial functions does not foster efficiency or effectiveness. The resulting provincial and regional differences of rules, regulations and enforcement are at the heart of India's difficulties with substandard and counterfeited medicines.
- **Brazil**: Like China, Brazil's enforcement mechanisms and authorities need to be strengthened. Legislation introduced in 2003 to effectively outlaw similars by 2015 is a step in the right direction, but the long time frame leaves many potentially dangerous drugs in circulation.
- **Argentina**: Unlike Brazil, Argentina has not addressed the existence of non-bioequivalence tested similars and should do so. ANMAT should also introduce a more comprehensive system of pharmacovigilance which increases the burden of reporting onto health professionals.
- **Turkey**: Regulations of pharmacists and pharmacovigilance must be improved and implemented more effectively on the ground.

Together these recommendations provide a first step for guiding policymakers towards a more efficient process for mitigating the risks and effects of substandard and counterfeited medicines.

Appendix

The following table provides a comparison of the Drug Regulatory Authorities of the five countries studied in this paper. The individual regulatory systems are compared in four key categories and capabilities are ranked as: High, Medium or Low. A High capability describes a DRA as having fulfilled a majority of key regulatory responsibilities. A Medium classification defines a system as having achieved some regulatory capabilities but still lacking in important areas. A Low classification describes a system which has not achieved the required capability in a number of areas.

Comparison of Key Regulatory Capabilities of China, India, Brazil, Argentina and Turkey

	Comprehensive Legislative and Regulative Organisation	Pharmacovigilance – Regulation and Implementation	GMP: Code in place and enforced	Overall Quality and Safety Control
China	High[184]	Medium[185]	Medium[186]	Low-Medium[187]
India	Low[188]	Low[189]	Low-Medium[190]	Low[191]
Brazil	Medium-High[192]	Medium[193]	Medium[194]	Medium-High[195]
Argentina	Medium-Low[196]	Low-Medium[197]	Medium[198]	Low-Medium[199]
Turkey	Medium[200]	Medium-Low[201]	Medium[202]	Low-Medium[203]

[184] Comprehensive regulatory body in place. Authority centralised with SFDA which has wide-ranging authority and an increasing amount of resources. Wide-spread counterfeiting and production of substandard drugs caused by the lack of implementation, corruption and overwhelming scale of the problem.
[185] System of pharmacovigilance in place (major changes in 2002 and 2004), although reporting is still believed to be lacking and there is some doubt over the accuracy over official figures on the number of ADRs.
[186] GMP, licensing and inspection processes/regulations in place. Changes to the inspection process in the wake of the trial of former SFDA chief Zheng Xiaoyu emphasised more collective responsibility. These changes also instituted a set of rules to avoid conflicts of interests and the possibility of corruption. Still, corruption persists.
[187] Regulations are in place but enforcement and implementation are lacking.
[188] Pharmaceutical regulations and regulatory powers are divided up between a variety of actors within central and state government. There is overlap between different enforcement and regulatory functions. This lack of clarity hinders the effective running of the regulatory system.
[189] India's system of post-marketing studies and pharmacovigilance is still under development. 2003 reforms instituted a system of national and regional monitoring but given the largely under-regulated nature of pharmaceutical manufacturing and sales, a comprehensive and well-functioning system of pharmacovigilance is some way off.
[190] As regulation of the manufacture and sale of medicines is divided up between central and state government, GMP standards vary both in quality and enforcement from state to state. The high rate of substandard medicines suggests high GMP standards are not followed in all parts of India.
[191] Comprehensive safety and quality regulations are not in place, nor is it clear which line of government is charged with enforcing and implementing existing regulations.
[192] Regulatory system moving towards high international standards with closer regulation of 'similar' medicines and the use of bioequivalence testing for all non-referenced drugs.
[193] It is unclear whether ANVISA has the capacity to effectively implement a comprehensive system of pharmacovigilance.
[194] GMP code in place but there is concern over implementation and resources allocated for inspection and enforcement.
[195] Overall safety and quality standards are good, although there are still concerns over the lack of bioequivalence testing for 'similar' drugs registered prior to 2003.
[196] The regulatory system is lacking in some key areas, most notably the lack of regulation and bioequivalence testing of 'similar' drugs. There are also concerns over the lack of clarity on part of health officials on the quality of these drugs making frequent reference to them as generics.
[197] System of pharmacovigilance is relatively under-developed with the onus of reporting being placed solely on pharmaceutical manufacturers. Health professionals are not obliged to report ADRs.
[198] GMP code in place but worries persist over the lack of bioequivalence testing for 'similar' drugs.
[199] Pharmacovigilance and lack of regulation and testing of 'similar' products remains a concern and lowers the overall safety and quality of Argentina's drug regulatory system.
[200] Pharmaceutical regulations are changing as Turkey seeks to harmonise its existing regulatory framework with EU standards. Turkey is also working to implement an advanced barcode scheme to more easily track and monitor the production and sale of medicines.
[201] Pharmacovigilance monitoring has improved, particularly with new regulations introduced in 2005.

[202] GMP standards are in place and in some cases Turkish pharmaceutical production meets very high standards. But there are problems in the dispensation and sale of pharmaceuticals as many small-scale pharmacists engage in bartering and sale of medicines without a prescription.

[203] While standards and regulations are changing and improving as Turkey harmonises its own standards to those of the EU, the loosely regulated and controlled sale of pharmaceuticals and bartering between pharmacists makes pharmacovigilance and monitoring of medicines used very difficult. This compromises the overall safety of the regulatory system.


4 ml
FU
Injec