



## KEEPING MEDICINES SAFE - EXTENDED

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

By Paul Healy and Dr Meir Pugatch

 STOCKHOLM NETWORK

## Keeping Medicines Safe - Extended

A Further Study of the Regulations Guiding the Approval of Medicines in  
Emerging Markets (Egypt, Peru, Russia and Thailand)

By Paul Healy and Dr Meir Pugatch

Stockholm Network  
35 Britannia Row  
London N1 8QH  
[www.stockholm-network.org](http://www.stockholm-network.org)

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## Executive Summary

Early last year the Stockholm Network published a paper entitled Keeping Medicines Safe which looked at the spread of substandard medicines. The paper formed part of our Patient Safety Series which puts patients' wellbeing and better quality of care at the heart of all our policy recommendations. In the paper, the serious threat to public health posed by substandards was highlighted and the regulations used in the approval, manufacture, sale and use of medicines were examined.

In particular, the paper focused on five countries, Argentina, Brazil, China, India and Turkey, all of which form part of a general grouping described as "emerging markets". The task of this paper is to develop further the findings explored in the previous paper, in particular by broadening the scope of our research to include four additional markets: Egypt, Peru, Russia and Thailand. The importance of these countries relates to the growth in their domestic pharmaceutical markets and in their role in the trade of pharmaceuticals internationally. As a result, they will form an important supplement to what has already been explored in the previous paper. In studying these four additional countries, the purpose of this paper will be to explore the problems that substandards may pose and the effectiveness of regulation designed to prevent such medicines from entering the market.

At present, there is a somewhat blurry distinction between the terms "substandard" and "counterfeit" in regards to pharmaceuticals. The tendency to group substandards and counterfeit medicines collectively is based on a belief among policymakers that a strategy to tackle counterfeits will inevitably prevent substandards from spreading as well. This is because the existence of both substandards and counterfeits can be indicative of the same or similar problems of ineffective drug regulation and enforcement. Therefore, coordinated action is rightly aimed at encouraging more rigorous regulatory control of medicines and enforcement by national DRAs in the developing world. Yet, these are often focused on preventing and detecting counterfeit medicines, which whilst substandard, do not account for all harmful pharmaceuticals that may be in the healthcare system. To complement this, more action is now needed to encourage countries to establish standards that ensure products meet the necessary, internationally accepted criteria of quality, safety and efficacy, which substandard manufacturers would be unable to meet.

The four countries studied in this paper all have flaws in how they regulate against substandard medicines reaching the market. The proof is in the scale of inferior products that are consumed within their healthcare

systems today. The reasons why these countries suffer from high incidences of substandard medicines vary, yet there are a few common themes that present themselves in all four countries:

- Ineffective legal and regulatory frameworks;
- Ongoing gaps between the "text book" legislation and practices on the ground; and
- Lack of transparency, rule of law and even exposure to corruption.

Each country in this study has a great deal of work to do if it wants to rid its public health system of substandard and counterfeit medicines. Specifically, the following policy recommendations should be taken into consideration:

In **Egypt**, recent political developments should push for the implementation of fresh legislation aimed at dealing specifically with those manufacturers which produce inferior pharmaceutical products before instigating reforms to expand healthcare coverage. In addition, there needs to be a substantially increase in the level of enforcement, as well as a greater degree of compliance with international organisations, such as the World Health Organisation, that are taking action against producers of substandards in Egypt.

In **Peru**, there needs to be a greater emphasis on public awareness of the problem of substandard medicines and on enforcing regulations on the manufacturers, in line with internationally-recognised standards, with tough, prohibitive sanctions on those that fail to comply

In **Russia**, new legislation that imposes GMP standards on domestic companies should be implemented rigorously with tough penalties for those who do not comply. On top of this, Russia should look to introduce greater transparency in pharmaceutical decision-making and tougher penalties for manufacturers and producers of substandards and counterfeits.

In **Thailand**, modern legislation is needed to replace the archaic laws currently governing pharmaceuticals. Standards requirements should be introduced for all companies supplying pharmaceuticals in the healthcare system and the relationship between the GPO and the Thai healthcare system needs to be reformed to allow for greater transparency and accountability.

## Introduction

Early last year the Stockholm Network published a paper entitled *Keeping Medicines Safe* which looked at the spread of substandard medicines.<sup>1</sup> The paper formed part of our Patient Safety Series which puts patients' wellbeing and better quality of care at the heart of all our policy recommendations.<sup>2</sup> In the paper, the serious threat to public health posed by substandards was highlighted and the regulations used in the approval, manufacture, sale and use of medicines were examined.

In particular, the paper focused on five countries, Argentina, Brazil, China, India and Turkey, all of which form part of a general grouping described as "emerging markets". These countries were selected because of their growing relevance to the international trade in pharmaceuticals and the expansion of their domestic markets. Indeed, the proliferation of substandards in these countries has a wider pan-European relevance in regard to patient safety, since the globalisation and parallel trade of pharmaceuticals means that substandard products can now travel across borders with greater speed and ease, leading to the possibility of such medicines ending up in the hands of unsuspecting European patients.

The conclusion of the previous paper was that substandards are widespread and also that they affect countries differently. The specific problems each individual country has to grapple will depend on the legislative, regulatory, cultural, and socio-economic policies and make-up of that country. As such, some problems can be addressed relatively easily, while others require hard thinking, large resources, and national – or even international – co-ordination. Finally, the paper offered a number of country-specific policy recommendations.

The task of this paper is to develop further the findings explored in the previous paper, in particular by broadening the scope of our research to include four additional markets: Egypt, Peru, Russia and Thailand. The importance of these countries relates to the growth in their domestic pharmaceutical markets and in their role in the trade of pharmaceuticals internationally. As a result, they will form an important supplement to what has already been explored in the previous paper. In studying these four additional countries, the

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<sup>1</sup> Stockholm Network (February 2010). *Keeping Medicines Safe*. See [http://www.stockholm-network.org/downloads/publications/Keeping\\_Medicines\\_Safe\\_Final\\_Draft\\_2010.pdf](http://www.stockholm-network.org/downloads/publications/Keeping_Medicines_Safe_Final_Draft_2010.pdf)

<sup>2</sup> For more information on the Stockholm Network "Patient Safety Series", please visit <http://www.stockholm-network.org/Conferences-and-Programmes/Health-and-Welfare/Patient-Safety>

purpose of this paper will be to explore the problems that substandards may pose and the effectiveness of regulation designed to prevent such medicines from entering the market.

Building on the findings of the previous study, this paper is divided into three parts. Firstly, it discusses the issue of substandards and the threat that they pose to public health more generally. Secondly, it explores substandards in the four countries outlined above. In doing so, it analyses the healthcare systems of each country and the regulatory and legislative framework which have been put in place to prevent substandards from infiltrating the pharmaceuticals market. Thirdly, the paper looks to offer updated conclusions and policy recommendations as to how countries can keep their medicines safe. Lastly, it concludes with a revised table that compares drug regulation in all the nine countries covered by the *Keeping Medicines Safe* paper series.

## Substandard Medicines

At present, there is a somewhat blurry distinction between the terms “substandard” and “counterfeit” in regards to pharmaceuticals. Whilst these terms are often referred to interchangeably, each can pose distinctively different problems and therefore need to be defined early on in this paper.

Counterfeits are pharmaceuticals “deliberately and fraudulently mislabelled with respect to identity and/or source”<sup>3</sup>, i.e. they are presented as something that they are not. They are not the genuine product in so much as they are not manufactured by the company that holds the relevant intellectual property rights for the pharmaceutical's chemical composition, packaging and labelling. Counterfeit trading in any industry is usually linked with organised crime, under-regulated industries, and sometimes with corruption in business and politics. In this respect, pharmaceuticals are no different, with the caveat that there is not much health threat posed by a fake handbag but taking a fake medicine can prove potentially rather dangerous.<sup>4</sup>

Substandard medicines are defined by the World Health Organisation (WHO) as “products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective”. What this means is that whilst counterfeit medicines are almost certainly substandard, it is not necessarily the case that all substandard medicines are considered to be counterfeit.<sup>5</sup> Indeed, to assume so would ignore those substandards that occur as a result of negligence, human error or insufficient human and financial resources.<sup>6</sup> In fact, there are many pharmaceuticals that have been approved for use by the relevant drug regulatory authorities (DRA), hence considered “legitimate”, which do not meet the necessary standards aimed at ensuring their quality, safety and efficacy in terms of patients' use – like their appropriate conservation, transport, etc.

These substandards are extremely hazardous to the public since they are considered by patients to be genuine and valid for consumption. The risk to the patient is significant, since substandards can have serious adverse health effects and clinical outcomes.<sup>7</sup> By taking medicines that have an incorrect formula of active ingredient or are made with the wrong ingredients entirely, patients could potentially develop allergic

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<sup>3</sup> This definition was developed by the WHO in order to deal with the absence of one that is universally accepted, it can be found on the WHO's own website at <http://www.who.int/medicines/services/counterfeit/overview/en/>

<sup>4</sup> Kelesidis, Theodore et al (2007). “Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence” in *Journal of Antimicrobial Chemotherapy* (2007, 60, 214–236), p. 215.

<sup>5</sup> Kelesidis et al (2007), p. 214.

<sup>6</sup> WHO – Substandard and Counterfeit Medicines. <http://www.who.int/mediacentre/factsheets/2003/fs275/en/>

<sup>7</sup> Kelesidis et al (2007), p. 229.

reactions and other side effects. This is because, aside from simply not working, substandards can be potentially toxic, which would ordinarily be identified during effective regulatory processes. In addition, by only taking some of the correct ingredients, patients may also develop a resistance to particular drugs, which will make it harder for them to be treated effectively in the future.<sup>8</sup> This underlines the importance of DRAs whose role it is to prevent substandards from reaching the market and to remove those that are already there. However, and alarmingly, many substandards are being approved for use by DRAs, particularly outside of the developed world.

The tendency to group substandards and counterfeit medicines collectively is based on a belief among policymakers that a strategy to tackle counterfeits will inevitably prevent substandards from spreading as well. This is because the existence of both substandards and counterfeits can be indicative of the same or similar problems of ineffective drug regulation and enforcement. Today, most substandards and counterfeits originate from those markets that are not well protected, where the lack of adequate drug safety controls allows these drugs to flow unobstructed. Recent estimates suggest that between 10 and 30 % of medicines sold in developing markets are either substandard or counterfeit, although as this figure is difficult to calculate for both types of medicines, the real amount could probably be higher.<sup>9</sup> Therefore, coordinated action is rightly aimed at encouraging more rigorous regulatory control of medicines and enforcement by national DRAs in the developing world. Yet, these are often focused on preventing and detecting counterfeit medicines, which whilst substandard, do not account for all harmful pharmaceuticals that may be in the healthcare system.

To complement this, more action is now needed to encourage countries to establish standards that ensure products meet the necessary, internationally accepted criteria of quality, safety and efficacy, which substandard manufacturers would be unable to meet. For example, pharmacopoeias are a long established reference in pharmaceutical standards and some, such as the United States Pharmacopeia (USP) and the British Pharmacopoeia (BP), are recognised as the international benchmark for thousands of pharmaceuticals. These official listings outline the criteria for manufacturing pharmaceuticals, detailing the level of quality, purity, strength and consistency to which these products should adhere. At present, around 130 countries recognise the standards set in the USP and almost 100 countries recognise the listings in the

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<sup>8</sup> Bate, Roger (2008). *Making a Killing: The Deadly Implications of the Counterfeit Drug Trade*. American Enterprise Institute Press, Washington DC, p. 4.

<sup>9</sup> Pharmaceutical Research and Manufacturers of America (2009). *Special 301 Submission 2009*, p. 8.

BP, meaning that, at the very least, 32% of countries are not conforming to either of these widely-recognised standards.<sup>10</sup>

In addition, a standard that many regulators use to prevent substandards reaching the market is good manufacturing practices (GMP). GMP, as defined by the WHO, demands “that products are consistently produced and controlled to the quality standards appropriate to their intended use”, whilst “diminishing the risks inherent in any pharmaceutical production”.<sup>11</sup> In ensuring this, the WHO helpfully provides assistance as to guidelines and principles for effective GMP. In addition, other important standards set by the WHO include good distribution practices (GDP) and good storage practices (GSP). Many pharmaceutical regulators make such standards a mandatory requirement when supplying to their pharmaceutical markets, yet a 1999 report by the WHO found that more than 40% of low income countries had no laws regarding the manufacturing and distribution practices of pharmaceuticals, nor did they have inspections of facilities carried out by regulatory representatives.<sup>12</sup>

The paper will now analyse the potential threat of substandards and the regulatory and legislative framework designed to tackle such challenges in the following four countries: Egypt, Peru, Russia and Thailand. Counterfeits will also be discussed because, besides being substandard themselves, they offer an indication of a vulnerable environment for substandard manufacturers to ply their trade. The paper will refer, as much as possible, to the legislation and regulations linked to manufacturing, registering and distributing pharmaceuticals. However, it should be noted that in all four markets access to such information can be difficult, which not only highlights a significant problem relating to transparency but also a necessary limitation to the scope of this paper.

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<sup>10</sup> For US Pharmacopeia – About USP, see <http://www.usp.org/aboutUSP/>. Also, for British Pharmacopoeia, see <http://www.pharmacopoeia.co.uk/>

<sup>11</sup> World Health Organisation (2007). *Quality Assurance of Pharmaceuticals, A compendium of guidelines and related materials*, Volume 2, 2nd edition, p. 17.

<sup>12</sup> World Health Organisation (2004). *The World Medicines Situation*, p. 97. See [http://www.searo.who.int/LinkFiles/Reports\\_World\\_Medicines\\_Situation.pdf](http://www.searo.who.int/LinkFiles/Reports_World_Medicines_Situation.pdf)

## Egypt

Egypt has been one of the Middle-East's fastest growing economies. International Monetary Fund (IMF) figures show that the economy has grown annually by 5% over the last ten years and, even in the shadows of a global financial crisis, the economy is still growing by 4.7% and is expected to have picked up further to 5.3% in 2010.<sup>13</sup> Annual inflation has increased over the last few years and in 2009 stood at 16.2% yet this was expected to drop back down to pre-crisis levels over the next few years. Similarly, the last few years has seen a depreciation of the Egyptian pound against the US dollar, but again the situation now seems to be improving.<sup>14</sup> From January 2011, Egypt saw a number of large-scale protests against the current regime of president Hosni Mubarak that resulted in the president agreeing to step down and a referendum on a constitutional amendment, which will pave the way for new parliamentary and presidential elections. As a consequence, the way that Egypt is likely to develop in the future is uncertain and whilst this paper will outline the "current" situation in regards to health policy, it is fully aware that this status quo is probably going to be transformed.

### Egyptian health and pharmaceuticals

Despite an impressive national income, Egypt's health status still remains relatively poor.<sup>15</sup> For years, policymakers have sought to establish a comprehensive healthcare system that would allow for universal coverage funded by monthly premiums paid by all citizens, except the most in need. This was the ambition of a health insurance bill that was previously being drafted, but which struggled to find support at a time of financial cautiousness, with some policymakers even resorting to World Bank loans to develop the health insurance system and speed up reforms.<sup>16</sup>

Instead, a decentralised and segmented healthcare system remains that covers only 52% of the population.<sup>17</sup> Social insurance is mandatory for formal government and company employees, who contribute between

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<sup>13</sup> International Monetary Fund (IMF) World Economic Outlook Database, October 2010. See [http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weorept.aspx?pr.x=60&pr.y=11&sy=1980&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&c=612,682,419,686,611,449,469,453,429,456,433,732,439,463,443,744,446,466,672,474&s=NGDP\\_R\\_PCH&grp=0&a](http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weorept.aspx?pr.x=60&pr.y=11&sy=1980&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&c=612,682,419,686,611,449,469,453,429,456,433,732,439,463,443,744,446,466,672,474&s=NGDP_R_PCH&grp=0&a).

<sup>14</sup> International Monetary Fund (IMF) World Economic Outlook Database, October 2010. Also, XE currency charts: USD/EGP 2010. See <http://www.xe.com/currencycharts/?from=USD&to=EGP>

<sup>15</sup> Gericke, Christian (2004). *Comparison of Health Care Financing Arrangements in Egypt and Cuba: Lessons for Health Reform in Egypt*, (Berlin University of Technology) p. 8. See <http://www.wz.tu-berlin.de/diskussionspapiere/2004/dp03-2004.pdf>.

<sup>16</sup> *The Arabist* - Egypt's healthcare crisis. See <http://www.arabist.net/blog/2010/3/13/egypts-healthcare-crisis.html>. Also, "Health Committee to ask for World Bank loan for healthcare reform" in *Al Masry Al Youm* (14/05/2010). See <http://www.almasryalyoum.com/en/news/health-committee-ask-world-bank-loan-healthcare-reform>.

<sup>17</sup> "Higher growth forecast for Egypt" in *German-Arab Trade (GAT) magazine* – September/October 2010. See <http://aegypten.ahk.de/index.php?id=1274&L=15>

0.5% and 1% of their salary whilst their employers top up with three times more. Overall, however, 61.9% of health spending in Egypt is funded by private means - with 95.1% of all private expenditure spent on out-of-pocket payments.<sup>18</sup> Furthermore, around 63% of these out-of-pocket private payments are spent on pharmaceuticals.<sup>19</sup>

The Egyptian pharmaceutical market has been calculated as being worth between \$1.6 and \$2.2 billion, making it the second biggest regional market, after Turkey.<sup>20</sup> In 2011, the market is expected to grow by 16%, 5% more than the rest of the Middle East and Africa. Total spending on pharmaceuticals is also expected to have grown steadily, from \$2.48 billion in 2009 to an estimated \$4.24 billion in 2010.<sup>21</sup> This growth of the pharmaceutical market has been attributed to greater modernisation of healthcare and increased privatisation over the last ten years.

Currently, 93% of pharmaceuticals sold in Egypt are manufactured locally, yet 85% of active ingredients are imported into the country.<sup>22</sup> Some have suggested that the depreciated Egyptian pound, as well as low generic importation, has thus accounted for relatively high pharmaceutical prices in Egypt as compared to the rest of the region.<sup>23</sup> However, the exportation of Egyptian pharmaceuticals has also grown and in 2009 reached \$600 million, three times more than expected. It is now anticipated that by 2015 the Egyptian pharmaceutical export market could be worth more than \$1 billion.<sup>24</sup>

#### Substandards and counterfeits

The Egyptian government had long been wary of the problem of both substandards and counterfeits in their healthcare system. In 2006, it launched raids that uncovered workshops producing fake copies of Viagra (sildenafil citrate), which were being produced using an unknown powder, coloured blue to match the authentic pills. Other investigations have also found copies of Plavix (clopidogrel bisulfate) that were nothing

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<sup>18</sup> World Health Organisation (WHO) – Global Health Observatory 2007. See <http://apps.who.int/ghodata/#>

<sup>19</sup> Gericke (2004), op cit., p.8

<sup>20</sup> Espicom Business Intelligence (2010). *The Pharmaceutical Market: Egypt*. Also, "Hikma makes move into Egypt" in *Financial Times* (10/08/2007). See <http://www.ft.com/cms/s/0/bf10285a-46d9-11dc-a3be-0000779fd2ac.html>

<sup>21</sup> *German-Arab Trade (GAT) magazine* (September/October 2010) "Pharma Sector in the Region: Higher Growth Forecast for Egypt"

<sup>22</sup> El-Shinnawy, Azza (2009). *Trends of Total Factor Productivity in Egypt's Pharmaceutical Industry: Evidence from the Nonparametric Malmquist Index Approach*, Economic Research Forum, Cairo, p. 1. Also, United States Trade Representative (2009). *2009 National Trade Estimate Report on Foreign Trade Barriers*, United States Trade Representative, Washington DC, p. 166.

<sup>23</sup> Ibid.

<sup>24</sup> GAT (2010), op cit.

more than starch, and scams that saw pills switched for others containing lower concentration, i.e. 50mg for the price of 100mg.<sup>25</sup>

Global concerns with regards to counterfeits in Egypt stem from the fact that 7% of all global cases of counterfeits originate from there.<sup>26</sup> A study into substandards in Nigeria in 2001 also showed that 48% of drugs tested there were substandard and that Egypt was one of the 12 countries that these drugs had originated from.<sup>27</sup>

As a consequence, international pressure is being applied by the WHO International Medical Products Anti-Counterfeiting Task Force (IMPACT), a network of global organisations and authorities aiming to deal with the growing public health crisis of counterfeits.<sup>28</sup> A transnational investigation between IMPACT and INTERPOL led to a series of police raids on Egyptian counterfeiting operations in 2009, seizing ten containers, each holding hundreds of thousands of counterfeits produced in extremely insanitary conditions and bound for the Middle East.<sup>29</sup>

In acknowledging Egypt's problems, the government minister of health Prof Harem El-Gabaly argued for a greater distinction between substandards and counterfeits. In doing so, Prof El-Gabaly questioned the role of international health bodies, such as the WHO, in dealing with matters relating to intellectual property, which he believed should be more appropriately handled by the World Trade Organisation or the World Intellectual Property Organisation. Yet, whilst it is true that tackling substandards and counterfeits should probably involve some different strategies, as this paper has already discussed, Prof El-Gabaly is ignoring two important facts. Firstly, counterfeits are in fact substandard and therefore it is within the WHO's sphere of interest to warrant involvement. Secondly, the proliferation of counterfeits can signal that the Egyptian market is also unable to stem the flow of substandards. The presence of substandards can often be much harder to establish in a healthcare system and so illegal trade in counterfeits, which is a lot easier, can be a good indicator of an environment where substandards may also thrive.

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<sup>25</sup> "The Ministry of Health and Population targets counterfeit drugs in pharmacies" in *Egypt Today* (10 May 2009).

<sup>26</sup> "New counterfeit report highlights worrying trends" in *In Pharma* (07/11/07). See <http://www.in-pharmatechnologist.com/Industry-Drivers/New-counterfeit-report-highlights-worrying-trends>.

<sup>27</sup> J.M. Caudron et al (2008). *Substandard medicines in resource-poor settings: a problem that can no longer be ignored*, in *Tropical Medicine and International Health* (Volume 13, No 8, pp 1062–1072 August 2008) p. 4. See [http://www.msf.org.za/docs/ScientificDocs/TMIH2008\\_Vol13\\_substandards.pdf](http://www.msf.org.za/docs/ScientificDocs/TMIH2008_Vol13_substandards.pdf)

<sup>28</sup> WHO International Medical Products Anti-Counterfeiting Task Force (IMPACT) – About us. See <http://www.who.int/impact/about/en/>

<sup>29</sup> INTERPOL - Arrests and major seizure of counterfeit medicines across Egypt follow international co-operation with INTERPOL and IMPACT stake-holders (29/05/10). See <http://www.interpol.int/Public/news/2009/CounterfeitMedecine20090529.asp>. Also, "Inside the fake Viagra factory" in *Daily Telegraph* (23/08/2005). See <http://www.telegraph.co.uk/news/uknews/3322770/Inside-the-fake-Viagra-factory.html>.

### Regulatory and legislative framework

The Egyptian Drug Authority (EDA), which exists within the Ministry of Health (MoH) is responsible for regulating the safety and quality of pharmaceutical products and it does so through its own three departments: the Central Administration of Pharmaceutical Affairs, the National Organization for Drug Control and Research, and the National Organization for Research and Control of Biologicals.<sup>30</sup> Recently, the Egyptian Pharmacovigilance Center (EPVC) was established within the Central Administration of Pharmaceutical Affairs.<sup>31</sup> It is the role of the EPVC to detect, understand, assess and ultimately prevent adverse drug reactions (ADRs). Whilst in its infancy, the intentions of the EPVC are encouraging with a planned network of operation that is expected to be rolled out in 2011, although current political instability may now cause delays.<sup>32</sup> A public education campaign has also been designed to achieve greater awareness of the threat of substandards, which publically lists registered drugs and also factories, wholesalers and pharmacies not in compliance with quality requirements.<sup>33</sup>

Under Egyptian law pharmaceuticals companies need to be registered in order to have their products sold by Egyptian pharmacies. In that light, recently the government decreed that any pharmacies caught selling unregistered medicines would be prosecuted, with compliance ensured by a team of 1,000 inspectors some of whom are being trained and assisted in how to use the latest methods of detection by major pharmaceutical companies.<sup>34</sup> There are also plans in place that would impose stronger inspection measures on the 3,000 or so drug warehouses that supply the pharmacies. Many of these drug warehouses have hitherto been difficult to regulate, as they often sell directly to customers or to pharmacies without providing the proper documentation that would indicate the source or expiry dates of the medicines supplied. New, tougher inspections on these outfits would provide the government with a greater handling of the flow of substandards and counterfeits.

Yet, many of Egypt's problems in dealing with substandards and counterfeits can stem from the fact that its regulatory system is still guided by a pharmaceutical law that has not been updated since 1955. When the

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<sup>30</sup> Egyptian Drug Authority (EDA) – About. See

[http://www.eda.mohp.gov.eg/About/ENRA\\_Mission.aspx?Main=about&aboutid=4&SubAbout=10](http://www.eda.mohp.gov.eg/About/ENRA_Mission.aspx?Main=about&aboutid=4&SubAbout=10)

<sup>31</sup> "The construction of the Egyptian Pharma co vigilance center (EPVC)". See [http://www.ems.org.eg/akhpar\\_hama/EDA4-8.htm](http://www.ems.org.eg/akhpar_hama/EDA4-8.htm)

<sup>32</sup> Egyptian Pharmacovigilance Center (EPVC). See <http://www.mohp.gov.eg/sec/News/Dr.%20Amr%20Saad.pdf>

<sup>33</sup> Prof. Dr. Hatem El-Gabaly - Workshop on Intellectual Property Enforcement and Combating Trade in Counterfeit Medicines and Medical Devices (12 January 2009). See <http://eda.mohp.gov.eg/Download/Docs/counterfeit.doc>. Also, list can be found at the EDA website: <http://www.eda.mohp.gov.eg>

<sup>34</sup> "Sanofi-Aventis launches 'anti-counterfeit medication' initiative" in AMEinfo.com (21/06/10). See <http://www.ameinfo.com/235874.html>.

law was passed, there were just 3,000 pharmacies and 1,500 registered products in Egypt; now there are 52,000 pharmacies and more than 12,000 registered products.<sup>35</sup> As a result, the law is incapable of dealing with the problems currently facing the pharmaceutical market. For example, current laws could see a person caught trading in substandards and counterfeits hit with a fine of just \$3.46.<sup>36</sup>

### Conclusions

The inability of Egyptian policymakers to pass long-attempted reforms to the healthcare system points to stagnation in the development of modern health services in Egypt. However, the need for reform does seem to remain and it is probable now that a restructuring of the healthcare system can be achieved. This should allow for greater patient coverage and access, which will inevitably result in the continued growth of domestic pharmaceutical consumption. As a result, outstanding issues relating to inadequate drug regulation need to be addressed right now in order to ensure that ruthless substandards manufacturers are not able to capitalise on the growing needs and demands of patients.

In addition, the growth of Egypt as an exporter of pharmaceuticals warrants concern internationally about the regulation of pharmaceuticals and the potential for substandards to spread throughout the region. Egypt's national problems with substandards could very well turn into a global problem if public health threats are exported to countries importing inferior Egyptian products. This explains why international organisations have taken an interest in counterfeits in the Egyptian healthcare system, despite the government's belief that some should not be there.

Recent momentous developments in Egypt now provide an opportunity for reform, with the replacement of a previous political class that seemed to lack the political will and enthusiasm to do much about substandards issues, although it may be some time before Egypt returns to any form of political stability. In truth, what Egypt needs is fresh legislation that deals specifically with the issue of substandards and places tougher restrictions and penalties on the manufacturers of inferior health products.

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<sup>35</sup> GAT (2010), *op cit.*

<sup>36</sup> *Ibid.*

## Peru

Various demographic studies have shown that almost 14 million Peruvians, representing 54% of the total population, live in poverty.<sup>37</sup> Furthermore, recent calculations from the World Bank showed that 15.4% lived on less than \$2.50 a day, a measure of extreme poverty. This figure, however, has been reduced somewhat from 24.2% of people in extreme poverty in 2005.<sup>38</sup> For ten years (1990-2000), the now incarcerated former President Alberto Fujimori focused his economic policy on pro-market reforms. In doing so, Peru saw continual economic growth during the mid-1990s that peaked at 12.9% in 1994.<sup>39</sup> This growth hit a short slump during the 1997 Asian financial crisis, but has since continued to grow steadily under President Alejandro Toledo and now under President Alan García Pérez. Whilst the financial crisis slowed this growth in 2009, the economy is expected to return to over 8% annual growth in 2010, with both inflation and government debt relatively low.<sup>40</sup>

### Peruvian health and pharmaceuticals

Whilst historically many Peruvians have been too poor to afford insurance to cover healthcare costs, a recently agreed Universal Health Insurance (AUS) system – the Spanish acronym for Aseguramiento Universal en Salud - plans to extend cover to everyone in Peru. The new system, signed into law early in 2010, will mandate health insurance for the whole population through tiered co-payments, whilst the poorest citizens will have their contributions subsidised.<sup>41</sup> Currently, the scheme is beginning to be rolled out and is only, as yet, available to those uninsured inhabitants of Lima and the Callao region. This early phase has already added 3.8 million new people to a healthcare system that was previously being accessed by 5.8 million. However, only 1.1 million of those new additions are entitled to subsidy. Moving forward, AUS coverage will be extended to the poorest areas of the country, where the need for subsidised healthcare is likely to be greatest.<sup>42</sup>

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<sup>37</sup> Muroi, Flora (2005). *Drugs and Pharmaceuticals*. US and Foreign Commercial Service and US Department of State, Washington DC.

<sup>38</sup> World Bank (2010). *Did Latin America Learn to Shield its Poor from Economic Shocks?* See [http://siteresources.worldbank.org/INTPOVERTY/Resources/LACs\\_Poor\\_and\\_Economic\\_Shocks.pdf](http://siteresources.worldbank.org/INTPOVERTY/Resources/LACs_Poor_and_Economic_Shocks.pdf)

<sup>39</sup> International Monetary Fund (IMF) World Economic Outlook Database, October 2010. See [http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weoreptc.aspx?pr.x=77&pr.y=2&sy=1980&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&c=293&s=NGDP\\_RPCH%2CPCPI%2CPCPIPCH%2CLUR%2CGGXCNL\\_NGDP%2CGGXWDG\\_NGDP&grp=0&a=](http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weoreptc.aspx?pr.x=77&pr.y=2&sy=1980&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&c=293&s=NGDP_RPCH%2CPCPI%2CPCPIPCH%2CLUR%2CGGXCNL_NGDP%2CGGXWDG_NGDP&grp=0&a=)

<sup>40</sup> International Monetary Fund (IMF) World Economic Outlook Database, October 2010.

<sup>41</sup> "Peru announces free health-care for the poor" in *Irish Sun* (04/04/10).

<sup>42</sup> "Peru begins roll-out of unified universal health-care system" in *La Prensa* (16/07/10). See <http://www.laprensasa.com/2.0/3/309/772706/America-in-English/Peru-begins-roll-out-of-unified-universal-health-care-system.html>. Also, "Universal Health Care For ALL of Peru" in *Hispanically Speaking News* (18/07/10). See <http://www.hispanicallyspeakingnews.com/notitas-de-noticias/details/universal-health-care-for-all-of-peru/>

As a result of this expansion of healthcare coverage, the market for pharmaceuticals in Peru is expected to grow significantly. In 2004, the market was already worth \$543.4 million, of which \$212.3 million accounted for imported products.<sup>43</sup> This is because no substantial domestic research industry exists in Peru and most domestic pharmaceutical manufacturers formulate products using imported active ingredients.<sup>44</sup> As a result of pharmaceutical growth, the number of pharmacies, so-called “boticas”, has unsurprisingly grown significantly over the last ten years.<sup>45</sup> In 2004, 50% of pharmaceuticals in Peru were generics sold under brand names, 33% were generics sold under their scientific international non-proprietary name (INN) and just 17% were original branded medicines.<sup>46</sup>

A sanitary registry is required for imported pharmaceuticals, which must be submitted to the Peruvian customs, although concerns have been raised that this requirement is not enforced as vigorously for parallel traders as it is for innovative pharmaceutical companies.<sup>47</sup>

#### Substandard and counterfeiting problems

Fresh in many Peruvians' minds, as a tragic recent example of the threat that substandards can pose, is the death of four children suffering from leukaemia, after an adverse reaction to a drug they were administered. At first, it had been announced by the minister of health that no negligence on behalf of the manufacturers was committed and that the samples administered had in fact been counterfeits. Yet, some are now disputing this and suggesting that the products were substandard.<sup>48</sup> Whilst this dispute has by no means been proved, either way the case highlights the damage that pure regulation can have upon innocent, and often vulnerable, patients. The public responded to this, and to other similar cases, with peaceful protests by cancer sufferers demanding that the Peruvian regulatory authority enact adequate regulation to cover certain medicines that are currently exempt from quality, safety, and efficacy testing.<sup>49</sup>

The Pharmaceutical Security Institute publishes an annual report that analyses counterfeiting, illegal diversion and theft incidents from around the world. Its 2009 study backs up the Peruvian public's concerns, ranking

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<sup>43</sup> Muroi (2005), op. cit. p.

<sup>44</sup> Ibid.

<sup>45</sup> Ibid.

<sup>46</sup> Alcalde, Gerardo Valladares (2005). *Evaluation of Potential Effects of the Free Trade Agreement Being Negotiated with the United States on Access to Medicines*. Health Ministry of Peru, Lima.

<sup>47</sup> PhRMA 2009, p217

<sup>48</sup> “How Safe Are Your Medicines?” in *The American* (01/10/10). See <http://www.american.com/archive/2010/september/how-safe-are-your-medicines>

<sup>49</sup> Ibid.

Peru as the fifth highest country globally, second in its region, for reported incidents of counterfeiting. It was noted that a cottage industry had developed in Peru, whereby substandards are produced, generics are masked as branded products and where expiration dates are altered.<sup>50</sup>

The WHO and IMPACT estimate that between 10 and 20% of pharmaceuticals in Peru are counterfeit, whilst Peru's National Quality Control Center recently reported that 22.4% of counterfeits found did not contain any active ingredient.<sup>51</sup> A recent study from the *Pan American Journal of Public Health* highlighted how, since 2005, counterfeits had increased annually by an average of 45%, with the market worth \$66 million in 2006 (\$26 million more than in 2002).<sup>52</sup> In Lima alone, the number of illegal pharmacies that were devoted to counterfeits was estimated at 1,800 in 2005, up from 200 in 2002, whilst around 460,000 adulterated and expired medicines were seized by authorities in 2005 alone.<sup>53</sup>

#### Regulatory and legislative framework

The General Directorate of Medicines, Supplies and Drugs (DIGEMED) exists within the Ministry of Health to regulate pharmaceuticals, yet it seems to struggle to control the production, importation, and distribution of substandards.<sup>54</sup> The time taken to register products in Peru is extraordinarily short, with drugs being approved on average within just seven days. However, a recent law passed by the Peruvian Congress is expected to extend this timeline to around six months.<sup>55</sup> In addition, laws have also been passed that overhaul the regulation of pharmaceuticals by setting broad minimum standards of quality for every single product marketed in Peru.<sup>56</sup>

The Peruvian System of Pharmacovigilance was established in 1999 and it conducts a number of functions linked to detecting and preventing ADRs. Between its inception in 1999 and 2009, it has recorded a total of 16,074 ADRs, 65% of which were reported by health professionals and 29% were recorded by pharmaceutical companies.<sup>57</sup>

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<sup>50</sup> Pharmaceutical Security Institute (2010), op. cit. p. 42.

<sup>51</sup> Bate (2008), op. cit., p15. Also, "Counterfeit medicines threaten public health in Peru" in World Health Advocacy. See <http://www.whadvocacy.com/articles/international/186-counterfeit-medicines-threaten-public-health-in-peru>

<sup>52</sup> Ibid. Also, World Health Organisation (WHO) – Counterfeit Medicines (2006).

<sup>53</sup> Ibid. Also, Bate (2008), op. cit., p. 49. Also, International Medical Products Anti-Counterfeiting Taskforce (IMPACT) - Counterfeit Medicines: an update on estimates (2006).

<sup>54</sup> Bate (2008), op. cit. p. 49.

<sup>55</sup> Africa Fighting Malaria (2010). *Drug Registration - a necessary but not sufficient condition for good quality drugs – a preliminary analysis of 12 countries*. See <http://www.aei.org/docLib/bate-putze-productregistration-101001.pdf>

<sup>56</sup> Pharmaceutical Security Institute (2010), op. cit., p. 42.

<sup>57</sup> Serrano Mestanza, Kelly E. (2009), "Pharmacovigilance Peruvian System", Powerpoint presentation. See <http://www.who-umc.org/graphics/22780.pdf>

However, it has also encountered a number of challenges, not least the low rate of reporting. A public awareness campaign that was recently launched, and sponsored by the ministry of health, called “Por tu salud, ponle ojo al medicamento” (For your health, keep an eye on the drug) aims to prevent the public from buying illegal pharmaceuticals and to make them aware of the risk of substandards. The campaign educates consumers about appropriate places to buy pharmaceuticals and the characteristics of illegal and substandard products.<sup>58</sup>

### Conclusions

The growth of the Peruvian economy will soon be met by the development of Peruvian society, with greater prosperity hopefully spreading to the poorest areas of the country. As part of this process of social change, healthcare coverage will soon reach people who have never received any health treatments in their life. There is little doubt that demand for pharmaceuticals will grow as a consequence and so too, probably, will the spread of substandard medicines.

One of Peru’s main problems is that much of the public does not yet seem fully aware of the dangers that substandards can pose to them and the sometimes useless but many times adverse effects that they could have on their healthcare treatment. This mostly stems from issues of poverty and illiteracy. The cottage industry that prevails in many black markets in Peru is indicative of this and proves that stronger regulation and enforcement is needed to ensure that the manufacturers and distributors of pharmaceuticals comply with internationally recognised standards of practice.

Overall, the government seems responsive to this problem but is held back by an inability to engage the public in the process. As a result, further efforts are needed to inform the public about the threat of substandards and the role that the public can play. Yet, it is not all about public involvement. Tougher regulation and enforcement are also needed in order to deter and hinder manufacturers of substandards from prospering, particularly in light of health reforms that will bring a large number of patients into the healthcare system for the very first time.

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<sup>58</sup> Pharmaceutical Security Institute (2010), *op. cit.*, p. 68.

## Russia

It took some time for the Russian economy to recover from the collapse of the Soviet Union and it wasn't until 1997 that post-Cold War economic growth was first achieved. Then a rouble crisis, triggered by financial contagion from Asia and high government debts following the first Chechen war, saw the economy plunged back into recession in 1998. Yet since then, the Russian economy has grown steadily, hitting a peak of 10% in 2000. It wasn't until the most recent global financial crisis that Russia's economy shrank again, by 7.9% in 2009. The economy revived in 2010, growing by 4%, and is expected to continue to grow by between 4 and 4.4% over the next five years.<sup>59</sup>

Russia has also undertaken something of a slow journey in moving from a "Semashko" healthcare system – a system that was characterised by centralised command and control - to a modern system more adapted to the needs of today's patients. Russian life expectancy in the USSR was 67.8, but since then it has dropped to 67.5.<sup>60</sup> In comparison, its neighbour Poland, which left the USSR with life expectancy at 66.5, now eclipses it at 71.5.<sup>61</sup> WHO statistics for total expenditure on health, as a percentage of GDP, show that Russia now ranks 112<sup>th</sup> of 187 countries with just 5.4% of GDP spent on health.<sup>62</sup>

### Russian healthcare and pharmaceuticals

The USSR had all but ended the growth of the domestic pharmaceutical industry in Russia, which developed in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries. Instead, the Soviet system focused on using pharmaceutical discovery to supplement the economic and scientific aims of the Five Year Plans. Despite some important Russian medical findings during the Cold War, the prohibition of patents and trademarks prevented a research industry from developing.<sup>63</sup> Since the demise of the USSR, a pharmaceutical market has been able to expand and, from the rouble crisis onwards, it has grown substantially, with a compound annual growth rate of 19% between 2003 and 2008.<sup>64</sup> Even in the midst of a new financial crisis, market demand for

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<sup>59</sup> International Monetary Fund (IMF) World Economic Outlook Database, October 2010. See [http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weorept.aspx?sy=1989&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&pr1.x=47&pr1.y=7&c=922&s=NGDP\\_R,NGDP\\_RPCH,PCPI,PCPIPCH,LUR,LP,GGR\\_NGDP,GGX\\_NGDP,GGXCNL\\_NGDP,GGX\\_WDG\\_NGDP,BCA,BCA\\_NGDPD&grp=0&a=#download](http://www.imf.org/external/pubs/ft/weo/2010/02/weodata/weorept.aspx?sy=1989&ey=2015&scsm=1&ssd=1&sort=country&ds=.&br=1&pr1.x=47&pr1.y=7&c=922&s=NGDP_R,NGDP_RPCH,PCPI,PCPIPCH,LUR,LP,GGR_NGDP,GGX_NGDP,GGXCNL_NGDP,GGX_WDG_NGDP,BCA,BCA_NGDPD&grp=0&a=#download)

<sup>60</sup> Federal State Statistics Service - Ожидаемая Продолжительность Жизни При Рождения. See [http://www.gks.ru/free\\_doc/2008/demo/osn/05-08.htm](http://www.gks.ru/free_doc/2008/demo/osn/05-08.htm).

<sup>61</sup> Central Statistical Office (GUS) - Life Tables of Poland 1990-2009. See [http://www.stat.gov.pl/gus/5840\\_894\\_ENG\\_HTML.htm](http://www.stat.gov.pl/gus/5840_894_ENG_HTML.htm).

<sup>62</sup> World Health Organisation (WHO) – Global Health Observatory 2007. See <http://apps.who.int/ghodata/#>

<sup>63</sup> Coalition for US-Russia Trade (2008). *The WTO and Russia's Future: The Pharmaceutical Industry's Perspective*. Coalition for US-Russia Trade, Washington DC.

<sup>64</sup> GalbraithWight (2010). *Russian Healthcare System Report*. GalbraithWight, East Sussex.

medicines grew by 11.6% in 2009.<sup>65</sup> Optimism is now high that the ongoing globalisation of the pharmaceutical industry presents Russia with an incentive to increase the role of innovation in its domestic industry, so that Russians can start to become innovators of new medicines.

In theory, the cost of medicines in Russia is borne by both the patient and the state. Vital drugs are itemised in the Essential Drugs List (EDL), which the state reimburses for free, or at a discounted price, to patients entitled to receive them, i.e. those who suffer from serious conditions. However, Russia's ailing state finances demand that very often only the cheapest essential drugs can be afforded. As a consequence, most of the medicines on the EDL are manufactured by domestic Russian companies or are drugs that can be cheaply imported.<sup>66</sup> Those drugs not included on the EDL are purchased by patients themselves. Estimates suggest that patients, in fact, pay for 70% of all drugs purchased in Russia.<sup>67</sup> For most Russians in this situation the only option is to seek out cheap drugs manufactured domestically, 90% of which cost no more than 5 roubles (\$0.15) in producer prices. However, these are often simple and traditional drugs dating back to Soviet times, rather than the more modern, innovative ones available.<sup>68</sup>

#### Substandard and counterfeiting problems

The tendency of both the Russian government and its citizens to search out the cheapest medicines available has allowed the spread of substandards to continue almost unabated. Estimates suggest that substandards and counterfeits account for around 12% of drugs in Russia and the market for selling them is worth around \$300 million per year.<sup>69</sup> A recent opinion poll also showed that roughly 40 per cent of Russian citizens were concerned that they were being exposed to such drugs.<sup>70</sup>

In 2006 a report by *The Lancet*, a leading medical journal, described widespread Russian practices whereby drug manufacturers, who operate legitimate pharmaceutical production businesses by day, would dedicate time at night to "producing extra quantities of a certified drug that does not pass through quality control, or sophisticated copies of well-known drugs are produced, often with reduced levels of expensive active ingredients". It also said that 70% of substandard medicines and counterfeits in Russia were produced domestically, and an estimated 70% of them were copies of foreign medications.<sup>71</sup>

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<sup>65</sup> "Russia pharma: Lilly's Russian relations" in *Economist Intelligence Unit* (06/08/09).

<sup>66</sup> "Russia: The challenge of access to medicines" in *PMC-Экспо*, 2008. See <http://expo.rusmedserv.com/articl2.html>.

<sup>67</sup> *Ibid.*

<sup>68</sup> *Ibid.*

<sup>69</sup> Bate (2008), op.cit. p. 21.

<sup>70</sup> "Russia warns of counterfeit threat" in *Securing Pharma* (29/06/08).

<sup>71</sup> "Russia cracks down on counterfeit drugs" in *The Lancet* (28/10/2006). See [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(06\)69619-0/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(06)69619-0/fulltext).

### Regulatory and legislative framework

The regulation of pharmaceuticals is conducted by the Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor), which is responsible for controlling the safety, quality and efficacy of medicines, as well as licensing and registering products.<sup>72</sup> An important challenge that Roszdravnadzor needs to face head on is the establishment of international GMP standards in domestic pharmaceutical manufacturing. There are presently 400 Russian pharmaceutical companies operating in the country, of which just 40 meet international GMP standards, equating to around 468 manufacturing factories which are not compliant.<sup>73</sup>

In an attempt to address this problem, new legislation was adopted in September 2010. It made a number of provisions aimed at tackling the issue of substandards and counterfeits in Russia. Intended to replace the 12-year-old pharmaceutical law, the new measures introduced mandatory European GMP and GCP standards for all manufacturers by 1<sup>st</sup> January, 2014. Any company that fails to comply by then will have their licenses revoked. This measure was meant to be enforced in 2012. However, late negotiations have allowed companies more time. It has been estimated that the cost of converting to GMP standards will be around \$1 billion, yet reports by Pharmexpert estimate that the process of upgrading could cost more than \$18 billion.<sup>74</sup> The new law also specifies that substandards and counterfeits must be destroyed by the organisation that is licensed for the collection, transportation and disposal of grade I-IV waste.<sup>75</sup>

Russia has also been working recently to increase its collaborations with the developed world. An agreement between Roszdravnadzor and a research-based company saw drug regulators trained by the latter, helping it to establish “good manufacturing” to a common global standard.<sup>76</sup> The US Pharmacopeia has also agreed to work alongside Roszdravnadzor on a programme to reduce the availability of counterfeit and substandard medicines, with the aim of harmonising Russia’s pharmacopoeia standards with those of the world's leading pharmacopoeias.<sup>77</sup>

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<sup>72</sup> Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor) document. See <http://www.roszdravnadzor.ru/i/upload/files/1188395609.65833-4011.pdf>

<sup>73</sup> “New Russian Pharmaceutical Bill Passed on Final Reading” in IHS Global Insight (26/03/10). See <http://www.ihsglobalinsight.com/SDA/SDADetail18459.htm>.

<sup>74</sup> IHS Global Insight 2010.

<sup>75</sup> “Russia adopts rules on destruction of fake, substandard drugs” in *Securing Pharma* (09/09/10).

<sup>76</sup> “Russia pharma...”, op. cit.

<sup>77</sup> “Russia, USA get closer on pharmacopoeial standards” in *Securing Pharma* (14/04/09).

In regards to pharmacovigilance, Russia joined the WHO International Drug Monitoring Program in 2004 and has also since established the Federal Centre for Adverse Drug Reactions Study, which replaces an old Soviet body called the All Union Centre for Study of Side Effects of Drugs.<sup>78</sup> Regional centres support the work of the central body and, by 2009, 51 such regional monitoring centres had been established<sup>79</sup>.

There are a number of factors that encourage this spread of substandards and counterfeits in Russia. The first is the lack of transparency in the Russian regulatory system, which has made it hard at times to detect and prevent practices such as informal payments from threatening the legitimacy of decisions made by the regulatory body. Concerns about the construction of the EDL, and indeed how pharmaceuticals are regulated, stem from issues of transparency in decision-making. In particular, there are also concerns about the lack of open signs of interest in the quality and safety of pharmaceuticals.<sup>80</sup>

The case of Vladimir Bryntsalov, a member of the Russian Duma and a former candidate for the presidency, is indicative of this problem. The billionaire Bryntsalov is the owner of ZAO Bryntsalov, a pharmaceutical company privatised in 1992, which is responsible for 10% of Russia's legitimate pharmaceuticals.<sup>81</sup> Bryntsalov has long been accused of producing both substandards and counterfeits. In particular a dispute with a partnering international diabetics pharmaceutical company from the late 1990s onwards saw Bryntsalov accused of making insulin with substandard raw materials obtained from other suppliers. In fact, in 2001 the Moscow Arbitration Court found in favour of a claim from the Russian Ministry of Health that Bryntsalov had sold them animal insulin, instead of more expensive human gene-engineered insulin, as called for in the contract.<sup>82</sup> Numerous other claims exist of counterfeiting products from international pharmaceutical companies, including the leading antibiotic sold in Russia. Companies, such as a Dutch producer of insulin crystals, terminated their partnerships with Bryntsalov because of concerns that crystals were being used in formulas not yet approved by health regulators.<sup>83</sup> In 2009, Bryntsalov-A were found guilty of counterfeiting 50 brands of medicines, yet the prosecution handed out only token fines of no more than \$1,500.<sup>84</sup>

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<sup>78</sup> "A new pharmacovigilance centre set up in Russia". See <http://www.who-umc.org/DynPage.aspx?id=14298>

<sup>79</sup> "Russia has all the required infrastructure and resources to conduct high-quality, accurate clinical trials.". See <http://www.synrg-pharm.com/article107.htm>

<sup>80</sup> Pharmaceutical Research and Manufacturers of America (PhRMA) *Special 301 submission* (2007), p. 147

<sup>81</sup> Bate (2008), op. cit., p. 21.

<sup>82</sup> "The Trials of a Russian Drug Czar" in *Bloomberg Business Week* (29/01/01). See [http://www.businessweek.com/2001/01\\_05/b3717150.htm](http://www.businessweek.com/2001/01_05/b3717150.htm)

<sup>83</sup> "The Trials of a Russian Drug Czar: Can Moscow rein in Vladimir Bryntsalov?" in *Bloomberg Business Week* (29 January 2001).

See [http://www.businessweek.com/2001/01\\_05/b3717150.htm](http://www.businessweek.com/2001/01_05/b3717150.htm)

<sup>84</sup> "Fake Russian tamiflu comes as little surprise" in IPN Health Blog (17/11/09). See [http://policynetwork.blogs.com/fightingdiseases/counterfeit\\_and\\_substandard\\_medicines/](http://policynetwork.blogs.com/fightingdiseases/counterfeit_and_substandard_medicines/)

Russian law has always treated all falsely-labelled drugs as counterfeits, yet the offence of counterfeiting itself does not carry any administrative or criminal remedies.<sup>85</sup> In the 2004 Law of Medicines that defined pharmaceutical counterfeits, there were no prosecution articles added to criminal or civil legislation. Furthermore, there is also a lack of procedure for gathering evidence and scant acceptance by Russian courts of the need to facilitate court proceedings. Trademark infringement is addressed through legislation, yet it applies only in cases of numerous violations or significant damages and imposes inadequate penalties (\$5000 to \$8000 maximum). The penalty set in the Administrative Violations Code is even lower (\$1400 maximum). Debates have been ongoing in the Russian Parliament which aim to increase criminal and administrative liabilities but nothing has been done so far.<sup>86</sup>

### Conclusions

The size of Russia and its economy should warrant it being a much bigger player in the global pharmaceutical arena than it is currently. Much of the reason why it has not yet been able to produce a substantial domestic industry is because of the lack of progress made under communism. The spectre of the Soviet Union still seems to hang over Russia with former practices and tendencies still hindering further progress.

At present, Russia has both a growing demand for pharmaceuticals and a need for them to be cheap, which makes it susceptible to substandards and counterfeits, particularly among a public that doesn't appear to be fully aware of the dangers they present. To counter this, there needs to be a stable and rigorous regulatory system to protect patients, but instead Russian has a system beset with problems of transparency and accountability. New legislation that imposes GMP standards on domestic companies is certainly a move in the right direction. However, how such obligations are implemented and enforced will be critical. Overall, Russia needs to establish a transparent and predictable regulatory system that is much more in line with the standards in other parts of Europe.

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<sup>85</sup> Pharmaceutical Research and Manufacturers of America (PhRMA) *Special 301 submission* (2009), p. 10.

<sup>86</sup> *Ibid.*, p. 95.

## Thailand

The sustained economic growth in Thailand which took place from the mid-1980s to mid-1990s was halted by an economic crisis that put the Southeast Asian economy into recession. As a consequence, Thailand was forced to agree to a \$17bn loan from the IMF. Since then, and despite this drawback, the economy has continued to grow again at 3.7% of GDP. But Thai spending on healthcare is low, putting it in the lowest quartile of all countries in the world.<sup>87</sup> Some 73.2% is made up of government spending, which accounts for 13.1% of all government spending.

### Thai healthcare and pharmaceuticals

The equal right to access quality health services was guaranteed in the 1997 Thai constitution, yet no subsequent law provided universal healthcare coverage until 2002. Then, a tax-funded health insurance scheme, called the “UC scheme”, was introduced for approximately 47 million people (around 74% of the population), whilst those already covered by public civil service or social health insurance schemes remained as they were.<sup>88</sup>

All three schemes use the National List of Essential Drugs (NLED) as the basis for their benefits packages, which are compiled by the Thai Ministry of Public Health and with the assistance of evaluations by the subcommittee for development of the NLED.<sup>89</sup> The NLED forms part of the National Drug Policy established in 1981 and drugs on the list are priced by establishing a median price for all products in the same therapeutic class, regardless of origin or quality. Whilst there is no official “buy Thai” policy, the government has been accused of having a strong influence over hospital purchasing decisions in favour of local pharmaceutical companies.<sup>90</sup> The list also encourages greater generic use, particularly of those medicines manufactured by the state pharmaceutical company, rather than branded pharmaceuticals. Yet, despite this, branded drugs still play a major role in Thai healthcare, mainly because the NLED represents only 5% of the total drug consumption in Thailand.

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<sup>87</sup> World Health Organisation (WHO) – Global Health Observatory 2007. See <http://apps.who.int/ghodata/#>

<sup>88</sup> Tanhcharoensathien, Viroj. (2007). *Achieving universal coverage in Thailand: What lessons do we learn?* (Health Systems Knowledge Network)

<sup>89</sup> Wibulpolprasert, S. (2008). *The Need for Guidelines and the Use of Economic Evidence in Decision-Making in Thailand: Lessons Learnt from the Development of the National List of Essential Drugs.* (J Med Assoc Thai Vol. 91 Suppl. 2 2008) See <http://www.thaiscience.info/journals/Article/The%20need%20for%20guidelines%20and%20the%20use%20of%20economic%20evidence%20in%20decision-making%20in%20thailand%20lessons%20learnt%20from%20the%20development%20of%20the%20national%20list%20of%20essential%20drugs.pdf>

<sup>90</sup> PhRMA 2007, Op. cit, p. 64.

The pharmaceutical industry in Thailand primarily consists of non-research based manufacturers. Less than 10 Thai companies are involved in the production of raw material that could be used in the production of medicines and almost all of these raw materials are intermediate ingredients, such as alcohol, solvents and sodium chloride. Since domestic production of active ingredients is almost non-existent, most chemical compounds required for transformation into finished drugs - i.e. about 95% of compounds used in the country - are imported.<sup>91</sup>

In 2005, there were 162 firms involved in pharmaceutical manufacturing, 90% of which are private companies. The rest are the two state enterprises, established by the Thai government, called the Government Pharmaceutical Organisation (GPO) and the Armed Forces Pharmaceutical Factory (AFPF).<sup>92</sup> The GPO was established in 1964, under the Ministry of Public Health and is the most important public enterprise in the pharmaceutical field. It is the GPO's role to be the source of cheap drugs to public hospitals. It also exports medicines to other developing countries, such as Malaysia, Myanmar, Nepal, Laos and Cambodia. In 2002, it also agreed to supply anti-retroviral drugs to thirteen African countries. The GPO is exempted from registration and GMP requirements and maintains an exclusive position in supplying government hospitals with products on the NLED. As a result, the GPO may with impunity manufacture any product, even those still under SMP protection.<sup>93</sup>

In 2002, a report by the Thai auditor-general Jaruvan Maintaka reported that the GPO had stolen approximately \$13 million from the government over the previous four years. Her report noted that the GPO had sold about 60% of its medical products to government agencies at above market prices. In some cases, products were marked up 1,000%. The report also noted that, occupied with copying Western medicines, the GPO has had little interest in channelling money toward the innovative division of its drug industry. In 2005, GPO profits were over \$35 million, of which only 2% were reinvested into research and development.<sup>94</sup>

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<sup>91</sup> Kuanpoth, J (2007), *Intellectual Property Rights and Pharmaceuticals: A Thai Perspective on Prices and Technological Capability*, (Thammasat Economic Journal, Vol.25, No.4., December 2007) p. 16.

<sup>92</sup> Ibid. p. 14.

<sup>93</sup> PhRMA pre-2009, p65

<sup>94</sup> Bate, Roger (2007). *Thailand and the Drug Patent Wars*, p. 2.

### Substandard and counterfeiting problems

In 2004, the WHO estimated that 8.5% of all medicines on the market in Thailand were substandard.<sup>95</sup> The PSI ranked Thailand fifth for incidents of counterfeits and warned that the smuggling of medicines was increasing.

In a 1997 study by Shakoor et al samples of malaria drugs (chloroquine) and selected antibacterials from Thailand were analysed. It showed that 40% of samples from Thailand were substandard with respect to British Pharmacopoeia limits, with some amoxicillin drugs showing zero quantities of active ingredient.<sup>96</sup> A further study by Dondorp et al, which looked at antimalarials (artemisinin derivatives and mefloquine) throughout Southeast Asia, found that 53% of drugs analysed that were labelled "artesunate" did not in fact contain any artesunate in them, whilst among the 44 mefloquine samples looked at, 9% contained less than a tenth of the expected amount of active ingredient.<sup>97</sup> Artesunate was also looked at by Newton et al, which showed that of 104 shop-bought samples in Southeast Asia, 38% did not contain artesunate and were counterfeit.<sup>98</sup>

### Regulatory and legislative framework

The Food and Drug Administration (FDA) of Thailand is responsible for regulating pharmaceuticals, a job which is mainly performed by the Drug Control division. Currently medicines are defined as either "modern" or "traditional" drugs, with the latter enjoying less stringent controls and regulations.<sup>99</sup> Long-established attempts have been made by the Thai government to increase the capacity and sophistication of domestic pharmaceutical manufacturers. Both the Sixth National Economic and Social Development Plan (1987–1991) and also the Seventh Plan (1992–1996) included measures to promote and support local drug manufacturers in implementing GMP.<sup>100</sup> However, among the 171 privately owned Thai companies, only a few are compliant with GMP standards.<sup>101</sup> Current regulations do now require new pharmaceutical companies to comply with GMP, as well as the international Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme, whilst some existing companies have been given import

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<sup>95</sup> US Pharmacopeia 2004, p. 23.

<sup>96</sup> O Shakoor et al (1997). *Assessment of the incidence of substandard drugs in developing countries*. (Tropical Medicine and International Health, Volume 2 No 9 PP. 839-845 September 1997). See <http://onlinelibrary.wiley.com/doi/10.1046/j.1365-3156.1997.d01-403.x/pdf>.

<sup>97</sup> Kelesidis 2007, p. 223.

<sup>98</sup> Ibid., p. 225.

<sup>99</sup> Food and Drug Administration – Introduction. See <http://www.fda.moph.go.th/eng/drug/intro.stm>

<sup>100</sup> Food and Drug Administration - Pre-marketing Control. See <http://www.fda.moph.go.th/eng/drug/pre.stm>

<sup>101</sup> "Thailand: Critical Need for New Investment" in *Pharma Focus* (Feb 2007). See <http://www.pharma.focusreports.net/index.php#state=ReportDetail&id=56>

duty exemptions on machinery and exclusions on corporate income tax to encourage updating of existing factories.<sup>102</sup>

Present Thai drug laws are more than forty years old, thus too outdated to deal with the modern growth in substandards and counterfeits.<sup>103</sup> Yet, unlike other countries, Thailand seems reluctant to do much about it. The original drug law, which is still in effect, was passed in 1967 and attempts at updating have been painstaking and time-consuming.<sup>104</sup> When reforms are achieved, it is expected that they will include measures to reclassify medicines, to enforce GMP for all manufacturers and more requirements linked to drug licensing.<sup>105</sup> However, there is often a failure to pursue criminal charges against those that supply substandards and counterfeits and, when charges are brought, the penalties are usually insignificant relative to the profits made. The time that it takes to get this inadequate outcome is also lengthy, as are administrative actions such as revoking the license of a pharmacy found to be selling counterfeit medicines.

One big problem in regards to substandards in Thailand seems to be the GPO and the preferential treatment it receives within the Thai health system. GPO facilities for manufacturing HIV treatments, for example, have failed to pass WHO manufacturing standards on even simple products, such as antibiotics and aspirins. Bioequivalence data to support the quality of GPO-manufactured drugs are also unavailable, suggesting at best that drugs being produced are inferior copies.<sup>106</sup> In 2007, a factory was closed down because it was producing substandard GPO-Vir, a drug produced by the GPO, which has already developed a resistance rate among users of nearly 50 %.<sup>107</sup> An estimated 108,000 of 500,000 people living with HIV/AIDS depend on GPO-Vir and twenty thousand of those treated, almost one fifth, have already developed a resistance. A 2005 study, by Thailand's Mahidol University, found that within a group of 300 patients sampled for the resistant-inducing effects of GPO-Vir, between 39.6 % and 58 % showed resistance to it.<sup>108</sup>

Thailand introduced a programme for ADR as far back as 1980, which was formalised in 1983, making it one of the first developing countries to have a formal plan in place.<sup>109</sup> A safety monitoring programme was

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<sup>102</sup> *Ibid.*

<sup>103</sup> Bate (2008), *op. cit.* p. 54.

<sup>104</sup> Food and Drug Administration – Laws and Regulations. See <http://www.fda.moph.go.th/eng/drug/laws.stm>

<sup>105</sup> *Ibid.*

<sup>106</sup> Bate (2007), *op. cit.* p. 3.

<sup>107</sup> Bate (2008), *op. cit.* p. 7.

<sup>108</sup> Bate (2007), *op. cit.* p. 3.

<sup>109</sup> Dr Weerasuriya, K (200). Presentation on “Global Trends in Pharmacovigilance” at Pharmacovigilance; Partnership for Patient Safety 2-3 July 2008. See <http://www.fda.moph.go.th/fda-net/html/product/apr/%E0%B9%84%E0%B8%9F%E0%B8%A5%E0%B9%8C%E0%B8%9B%E0%B8%A3%E0%B8%B0%E0%B8%8A%E0>

fully implemented in Thailand in 1991 that aimed to assess the safety of new drugs when conditionally introduced in the Thai healthcare system. The aim of the programme was to note and highlight ADRs and to encourage physicians, pharmacists and other health professionals to have more concerns about the safety of new drugs and their usage.<sup>110</sup> Each drug has a monitoring period, after which all ADRs have to be analysed and evaluated. In this process, problems relating to the underreporting of ADRs and the lack of awareness by health professionals have been noted.<sup>111</sup>

### Conclusions

The Thai government is keen to find or produce cheap pharmaceutical products that are available locally. Yet, given the lack of compliance with international organisation in the manufacturing, conservation and distribution of these drugs, this aim has damaging consequences for the public health system. The role of the GPO, which is tasked with producing cheap pharmaceuticals for the healthcare system, needs further evaluation and scrutiny. A more transparent relationship between the GPO and the Thai healthcare system will go some way towards reassuring patients about the medicines that they are consuming.

The long-outdated Thai pharmaceutical law needs to be replaced to reflect the new and modern needs of the healthcare system. In doing so, a greater focus on upholding standards for all companies that supply medicines in Thailand would improve the situation for substandards. The fact that Thailand has one of the longest running ADR programmes in the developing world says more about the historical problems the country has had with substandards than any permanent enthusiasm for trying to eradicate them. There appears to be little awareness among the general public as to the dangers that substandards and counterfeits pose, whilst regulatory authorities and enforcement officials can seem reluctant to make this clear to them.

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<sup>110</sup> Usavakidviree, Vinit (2008). Presentation on "Pharmacovigilance of Drugs in Safety Monitoring Program" at Pharmacovigilance; Partnership for Patient Safety 2-3 July 2008. See <http://www.docstoc.com/docs/4761461/Pharmacovigilance-of-Drugs-in-Safety-Monitoring-Program-Vinit-Usavakidviree>

<sup>111</sup> *Ibid.*

## Conclusion

It should go without saying that all medicines must first and foremost be safe for use, for any person and in any country. Drug regulation is the safeguard against inferior drugs being manufactured, yet if the regulation is inadequate it is almost useless. The four countries studied in this paper all have flaws in how they regulate against substandard and counterfeit medicines reaching the market. The proof is in the scale of inferior products that are consumed within their healthcare systems today.

The reasons why these countries suffer from high incidences of substandard medicines vary, yet there are a few common themes that present themselves in all four countries:

- Ineffective legal and regulatory frameworks – two of the countries in this study have pharmaceutical regulations dictated by laws that are more than forty years old. Such laws do not have the necessary components to ensure that new drugs that enter the market must meet the international criteria of safety, efficacy and quality.
- Ongoing gaps between the "text book" legislation and practices on the ground – a number of countries are able to satisfy international pressures for an "adequate" legal and regulatory framework on paper, yet in practice reforms are rendered irrelevant by customs and attitudes that lend themselves to promoting the cheapest and domestically produce drugs, sometimes regardless of quality, safety and efficacy.
- Lack of transparency, rule of law and even exposure to corruption – in many incidences problems can stem from something bigger than pharmaceuticals. Where there is a lax legal system which is non-transparent and prone to corruption, both in government and business, there will also be decisions and activities made with no responsibility, or care, for their consequences on patients.

Each country in this study has a great deal of work to do if it wants to rid its public health system of substandard and counterfeit medicines.

Specifically, the following policy recommendations should be taken into consideration:

#### Egypt

- Use recent political developments to push for the implementation of fresh legislation that is aimed at dealing specifically with those manufacturers which produce inferior pharmaceutical products before instigating reforms to expand healthcare coverage.
- Substantially increase the level of enforcement, not least with regard to inspections of drug warehouse and pharmacies.
- Secure a greater degree of compliance with international organisations, such as the World Health Organisation, that are taking action against producers of substandards in Egypt.

#### Peru

- Provide much greater emphasis on public awareness of the problem of substandard medicines, particularly for those that are newly included in AUS.
- Introduce stronger regulation of manufacturers and distributors of pharmaceuticals, with greater emphasis on internationally-recognised standards.
- Place a greater emphasis on enforcing regulations on the manufacturers, with tough, prohibitive sanctions on those that fail to comply.

#### Russia

- Ensure legislation imposing GMP standards on domestic companies is implemented rigorously with tough penalties for those who do not comply.
- Introduce greater transparency in pharmaceutical decision-making.
- Introduce tougher penalties for manufacturers and producers of substandards and counterfeits.

#### Thailand

- Enact modern legislation to replace the archaic laws currently governing pharmaceuticals.
- Introduce standards requirements for all companies supplying pharmaceuticals in the healthcare system.
- Reform the relationship between the GPO and the Thai healthcare system to allow for greater transparency and accountability.

## Appendix

The following table provides a comparison of drug regulation of the nine countries so far studied in the *Keeping Medicines Safe* paper series. The individual regulatory systems are compared in four key categories and capabilities are ranked as: High, Medium or Low. A high capability describes regulations as having fulfilled a majority of key 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

	Legislative and Regulatory Framework	Pharmacovigilance	GMP Compliance	Quality and Safety Control
Argentina	Medium-Low	Low-Medium	Medium	Low-Medium
Brazil	Medium-High	Medium	Medium	Medium-High
Egypt	Low-Medium <sup>112</sup>	Low-Medium <sup>113</sup>	Medium <sup>114</sup>	Medium
China	High	Medium	Medium	Low-Medium
India	Low	Low	Low-Medium	Low
Peru	Low-Medium <sup>115</sup>	Low-Medium <sup>116</sup>	Medium <sup>117</sup>	Low-Medium
Russia	Low-Medium <sup>118</sup>	Medium <sup>119</sup>	Low-Medium <sup>120</sup>	Low-Medium
Thailand	Low-Medium <sup>121</sup>	Medium <sup>122</sup>	Low-Medium <sup>123</sup>	Low-Medium <sup>124</sup>
Turkey	Medium	Medium-Low	Medium	Low-Medium

<sup>112</sup> Legislation is outdated and in need of revising.

<sup>113</sup> A new body for pharmacovigilance is expected to improve the situation but it is not yet up and running.

<sup>114</sup> GMP requirements upheld for registered products whilst unregistered products are still an issue, although greater implementation of this is occurring.

<sup>115</sup> Improvements to the law are currently being undertaken to make it more effective, but greater sophistication and regulation is needed.

<sup>116</sup> A long-established system of pharmacovigilance is in place but it suffers from under-funding and lack of public awareness.

<sup>117</sup> GMP and sanitary registration requirements upheld for sale in Peru, although some concerns about enforcement for parallel traders and domestic manufacturers.

<sup>118</sup> Mechanisms favouring cheaper domestic drugs and lack of transparency limits effect of legislation.

<sup>119</sup> Established pharmacovigilance procedures in place with regional monitoring centres that highlight adverse drug reactions.

<sup>120</sup> Significant inefficiencies could be addressed by new legislation, although level of implementation is as yet uncertain.

<sup>121</sup> Outdated, with some reforms likely in the coming years.

<sup>122</sup> Strong tradition of pharmacovigilance, although the implementation and results do not seem to show this.

<sup>123</sup> Strong need for greater domestic compliance.

<sup>124</sup> Domestic traditions and cultures seem to be preventing progress being made on a number of levels.