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EDITORIAL

The Contrasting Medicines Regulatory Environments of China and the Western World

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1 Introduction

China's pharmaceutical exports have steadily grown over the last 10 years, from US$1.8 to 10.7 billion (i.e. a 494 % increase) [1, 2]. Indeed, generic medicines account for 83 % of dispensed prescriptions in the USA and were manufactured primarily in China and India [3]. With the Western world's increasing dependence on Chinese-manufactured generic pharmaceuticals, it is important to consider whether Chinese medicines regulations protect Western consumers from harmful or counterfeit drugs.

2 Comparing China's and the USA's Medicine Regulatory Systems

A comparison between China's medicines regulatory system and the USA's (one of the most stringent Western regulatory systems) gives an insight into the regulation and policing of medicines in these two potentially very different regulatory environments, and enables us to attempt to answer the question, is the Chinese medicines regulatory system of a global standard [4]?

Government medicines regulation and the associated mechanisms in place for bringing new and generic drugs to the market are constructs of the past 75 years. Most of the comprehensive modern Western legislation has stemmed from a small number of instances involving toxic, unregulated drugs, including the sulfanilamide fatalities in 1937 and the thalidomide disaster in the 1960s [5, 6], which led to the development of medicines Acts or similar legislative instruments in much of the developed world [e.g. the Federal Food, Drug, and Cosmetic Act 1938 (USA); Medicines Act 1968 (UK)].

However, in our world of economic unions and free trade agreements, a country's drug regulations are only as good as its weakest import partner. Indeed, in a World Health Organisation (WHO) study in 2002, it was reported that less than 20 % of WHO Member States had a well developed drug regulation system [7]. This worrying statistic manifested itself in the events surrounding contaminated heparin manufactured in 2008 in the USA from a raw ingredient (from pig intestines) extracted in China. There is very little information about how or why the contaminant—an over-sulphated chondroitin—appeared in the medicinal heparin product; however, there is a very strong suspicion that the natural chondroitin sulphate raw material exported from China was 'cut' with an over-sulphated form deliberately, because the over-sulphated form is not naturally occurring (i.e. would not have been present in the pig intestine), is biologically similar and is very much cheaper than natural chondroitin sulphate.

The ensuing actions of the Chinese Food and Drug Administration (CFDA) speak louder than any official statement. In the subsequent 7 years, regulations and laws were introduced by the CFDA at more than double the frequency of the preceding 23 years (calculated from data in [8]). These extensive reforms have enhanced the robustness of the Drug Administration Law of the People's Republic of China 2001. The tenet of this Law is very

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similar to the USA drug legislation, as can be seen, for example, in the drug approval processes for China and the USA [9, 10]. Strengthened and modified by these amendments, the Chinese regulations appear to be sound and comprehensive and, on the face of it, world class.

3 Policing Medicine Regulations

Regardless of how comprehensive a particular country's regulations are, if their policing and enforcement is flawed, the regulations are worthless. There are two main facets of regulation in the drug industry: government regulatory agencies and internal industry policing.

The United States Food and Drug Administration (US FDA) is the world's largest drug regulatory agency [11]. There are three limbs to the Administration's responsibilities: protection of public health, administration and enforcement of laws relating to food and drugs, and provision of a supportive and communicative role for both the industry and the public [12]. The US FDA performs these obligations extremely well with respect to USA manufacturing and production; however, it is recognised that they cannot monitor the international medicines trade—upon which the USA increasingly relies—with the same fine tooth comb.

The US FDA's response to the heparin case was both vigorous and multifaceted. They worked in conjunction with the industry initially to restrict import of contaminated heparin and to issue appropriate warnings. Following this immediate risk mitigation response, they performed a thorough investigation and analysis, prior to implementing new measures to prevent occurrence or a similar event [13].

In conjunction with the US FDA's stringent monitoring of medicines and their marketing, as seen in the recent cases involving GlaxoSmithKline [14], Pfizer [15], and Merck [16], the administration effectively prevents fraudulent or harmful drugs from reaching the market, and in the event they do, has the mechanisms in place to transparently handle the situation to ensure consumer protection.

In contrast, the CFDA appears to function on quite a different platform. Rather than operating primarily to protect citizens and enforce medicines regulations, it might be accused of being the proverbial ambulance at the bottom of the cliff by addressing the repercussions of counterfeits, rather than fixing the root of the problem with the necessary pharmacovigilance.

Interestingly, despite the high number of counterfeit medicines originating from China (196 reports in 2010, compared with 10 from the UK) [1], none of the pharmacovigilance news or alerts issued by the CFDA in 2010 refers to any internal fraudulent or counterfeit medicines [17]. Similarly, of the 42 product recalls issued by the CFDA in the same year, 6 of these relate to medicines; however, only 3 medicines were compulsorily recalled by the CFDA [18]. Such statistics indicate either, at best, a lack of transparency by the CFDA or, at worst, a widespread failure to identify, alert, and deal with the effects of counterfeit medicines. Clearly, this has significant implications for the Western world, which is reliant on medicines manufactured in China to support their health needs.

Importantly, and to China's credit, there has been some acceptance in recent years of the necessity for sound policing of medicines. For example, in 2007, China executed the former head of the CFDA for bribery and corruption [19], and in 2009, counterfeit anti-malarial medicines en route to Nigeria were intercepted; they were labelled 'Made in India' [20], but it was later discovered that they were in fact made in China. As a result of this misdemeanour, the CFDA sentenced six Chinese citizens to death. Most recently, in 2013, Chinese media reported the arrest of 1300 people suspected of producing and selling fraudulent medicines [21]. While these outcomes are extreme (and in our opinion wholly unacceptable), these measures demonstrate an increased degree of policing by the CFDA. In setting penalties at an appropriate level, and enforcing them, China may, over time, be able to focus more of its resources on pre-market surveillance, instead of dealing with problem drugs after they have had fatal effects.

Institutional policing plays a key role in seeking out fraudulent medicines, both at pre-market and post-production stages of their development. By enforcing and ensuring adherence to Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP), pharmaceutical companies can guarantee the drugs going to market are of the highest quality and safety. Additionally, many pharmaceutical companies are engaged in their own market surveillance to identify counterfeit medicines masquerading as their own branded pharmaceuticals [11]. This is, of course, in the company's interest because it prevents market interlopers securing an illicit fragment of their market, and avoids the negative influence of fraudulent and potentially toxic drugs passing off as well-known branded products.

4 Incentives for Self-Regulation of Medicines

The risk of prosecution by the US FDA or other drug regulatory agencies is not the only motivator for pharmaceutical companies to internally regulate. These companies bear a large degree of corporate responsibility, especially in the Western world, to ensure their drugs will not cause harm (i.e. are low risk) and will effectively treat disease

(i.e. are of high benefit); this risk/benefit balance is the driving principle of medicines regulation worldwide. In an environment of strict regulation (e.g. the EU or USA), any misdemeanour is very likely to be discovered and brought to the public's attention. This could have catastrophic effects for the company's corporate image and negatively affect the trust which consumers' place in them. As such, it is in the company's best interests to prevent any such event occurring; this very effectively incentivises rigorous self-regulation.

Furthermore, the vast majority of large Western pharmaceutical manufacturers are publicly listed companies. Any scandal or association of their company with suspect practices will likely affect shareholder confidence and the all-important 'bottom line'. This is exemplified by the Ranbaxy Laboratories Ltd. fraud saga (2004–2005) [22]. The US FDA blocked importation of 30 generic pharmaceuticals from Ranbaxy's Indian plants following safety concerns—there were significant questions about the validity of toxicology reports. Warning letters were issued, which led to Ranbaxy's shares plummeting from 521 Indian Rupees (INR) in the month prior to the import ban, to INR169 (i.e. a 68 % drop in value) the month after the ban [23–25].

5 Are Chinese Pharmaceuticals Produced in a Regulatory Environment Akin to that in the West?

The importance of a self-regulating pharmaceuticals industry cannot be overstated. Global companies with operations in China are very likely indeed to comply with the same stringent quality controls and regulation as their Western counterparts. However, there is a risk that small Chinese drug companies and companies manufacturing and selling pharmaceutical raw materials might not implement such stringent internal policing. Such companies might not be as concerned about their public image or trust, and so might not feel the same pressures to motivate their enthusiasm for self-regulation. In addition, the potential high-reward (i.e. benefit), low-risk environment in which they operate, due to the possibly haphazard CFDA enforcement regimes and their lack of transparency, might well support an ethos that the benefit of reward outweighs the risk of being caught—which may result in the temptation to produce counterfeit goods [1].

Stringent regulatory frameworks across the Western world empower drug regulatory authorities. In turn, the Authorities ensure that pharmaceutical companies adhere strictly to Regulations, vehemently enforcing penalties in the case of breaches. As a result, companies are incentivised to vigorously self-regulate, creating a safe and effective pharmaceutical market.

The growth of the Chinese pharmaceuticals industry is relatively recent and meteoric. Arguably, the creation and adoption of legislation has been stretched to keep pace with the speed of growth of the industry. However, the growth appears to be slowing, if not contracting, and the regulations have evolved and are bedding in. Indeed, medicines regulations now in place are akin to those in the West, and the CFDA is increasingly successfully policing counterfeit and fraudulent medicines. However, there might still be a systemic problem with fraud and a lack of suitable supervision within the Chinese pharmaceutical sector—particularly in small companies and raw product suppliers. Until the CFDA is in a position to effectively police and guarantee adherence to both pre-market and post-manufacturing regulations, and until appropriate penalties are set and enforced, China cannot have a self-regulating pharmaceuticals industry of the quality of that in the Western world, even though they export some US$10.7 billion worth of drugs into the highly regulated Western system every year.

Compliance with Ethical Standards

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