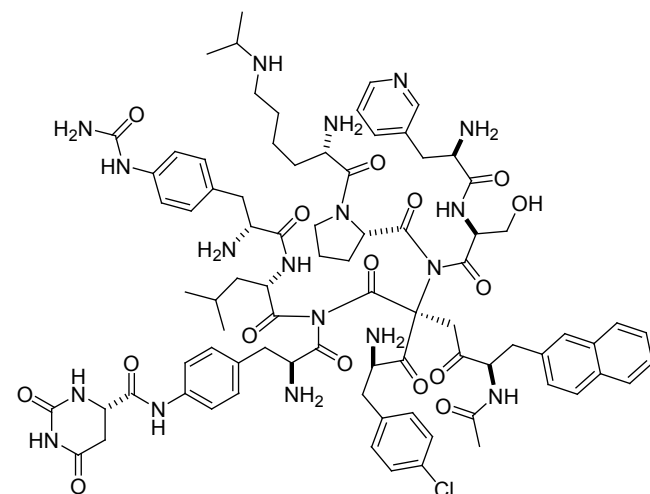


prostate cancer for many years. Surgical castration was the standard method of reducing testosterone from the 1940s until the mid-1980s when the earliest forms of medical castration, luteinizing hormone releasing hormone (LHRH) agonists, were introduced.

Degarelix is the only GnRH receptor antagonist approved by the FDA for the treatment of hormonally-sensitive advanced prostate cancer. The drug is given 240 mg as two injections of 120 mg each. Degarelix achieves medical castration differently than LHRH agonists, specifically by binding reversibly to GnRH receptors on cells in the pituitary gland, quickly reducing the release of gonadotropins and consequently testosterone. The drug was maintained of 80 mg administered as a single injection every 28 days.

In the clinical trial, PSA levels were also monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of degarelix, 85% after one month, 95% after three months, and remained suppressed throughout the one year of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline is related to a clinical benefit.



#### Endnotes

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## Innovative Prescription Medicines Support the Goals of Chinese Healthcare Reform

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### Introduction

The Chinese government is committed to a multi-year healthcare reform "to establish a healthcare system covering urban and rural residents, and to provide safe, effective, convenient, and affordable medical service." This was stated by President Hu Jintao at the 17th China Communist Party Congress in 2007 and then emphasized again a year later in the draft plan for healthcare reform released in October 2008.

In this discussion, while healthcare costs and drug prices are featured prominently, the quality of medicine and the optimal use of medicine, whether innovative or generic, seem to have been neglected. Pharmaceuticals is an essential and valuable component of any healthcare system and often the most cost effective therapy to manage a disease.

This paper highlights key challenges facing China in optimal use of medicines and suggests that in order to realize the value from medicines and to achieve the government's stated goal of providing "safe, effective, convenient, and affordable" medical service to Chinese patients, optimal use of high quality medicines has to be assured. It concludes with recommendations on public policy actions that can be taken to make progress toward achieving this goal.

### Challenges in the Optimal Use of Medicines in China

The World Health Organization (WHO) defines optimal use of medicine as "patients receive[ing] medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"<sup>1</sup>. R&D-based companies devote enormous effort to discover optimal treatment therapies and promote high quality standards.

Despite the benefits of optimal use of medicines, misuse and irrational use of medicine are problems worldwide. According to the WHO, over half of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take them correctly<sup>2</sup>. China is no exception, and faces some specific challenges.

### Inconsistent medicine quality

WHO estimates that 10% of drugs sold worldwide are counterfeit or substandard (often with little or no active pharmaceutical ingredient); this figure runs to 30% in poorer countries, especially in Southeast Asia<sup>3</sup>. In China, high incidence of counterfeit and substandard medicines undermine treatment and pose a potential risk to patient health, as in 2008 when quality problems of human immunoglobulin and TCM injections caused many deaths<sup>4</sup>.

Severe price competition among the large number of pharmaceutical manufacturers in China led many to cut corners on quality standards<sup>5</sup>.

According to a recent study, common problems in quality control include a lack of complete understanding of the medicine produced and a lack of comprehensive quality control<sup>6</sup>. Professors from China Union Medical College reminded the public of the importance of drug quality: “Low-priced generics benefits more people, but if we do not strengthen quality control, there will be many substandard and counterfeit medicines... In addition to drug price, we should consider drug quality as well.”<sup>7</sup>

**Abuse of antibiotics**

Abuse of antibiotics is commonly acknowledged in China. Professor Xiao Yonghong from Peking University Health Science Center said, “China issued Guidelines on Clinical Prescription of Antibiotics in 2004 with clear restrictions on abuse of antibiotics. However, the guideline is often not strictly followed.” WHO notes that antibiotics in Chinese hospitals have been prescribed in as many as 80% of all patient visits, compared with the international average of 30%<sup>8</sup>. In a comparison research conducted by IMS Health, the number of antibiotics prescribed per capita was significantly higher in China than in other countries included (Table 1).

Country	Standardized antibiotic counting units
Australia	0.05
Brazil	0.01
<b>China</b>	<b>10.48</b>
France	0.05
Germany	0.02
India	0.01
Italy	0.04
Japan	0.04
South Korea	0.05
Spain	0.05
United Kingdom	0.04
United States	0.06

Overuse of antibiotics represents a serious threat to patient’s health. A survey conducted by the State-run China Central Television (CCTV) in 2006 found that the abuse of antibiotics has caused deafness in around 300,000 children under seven years old, and represents approximately 30%-40% of all the deaf children in China.

Reducing over-prescribing will also reduce waste in healthcare resources, with the economic impact of antibiotics abuse estimated at RMB117 billion in 2005 (Table 2)<sup>9</sup>. Controlling over-prescribing would greatly reduce pressures on both Chinese patients and China’s healthcare funding. Thus, it lessens pressure for the government to drive medicine prices down, which then reduces the incentive for domestic manufacturers to deviate from GMP standards and enhances their motivation to invest in innovation.

Causes	Cost (RMB billions)
Over prescription and irrational use on patients	55
Hospitalization and treatment caused by infection of drug resistant bacteria	29
Adverse effects caused by antibiotics-abuse	8
Abuse of animals	7
Indirect costs caused by productivity loss	18
Total	117

**Low patient compliance**

Low patient compliance is another common challenge in China, especially for chronic disease medications. A Peking University Hospital survey of over 3,000 diabetics showed 82.3% had issues of irrational use of medicine, and primarily of under-use<sup>10</sup>.

Main reasons for low compliance include patients’ lack of awareness as well as limits on prescriptions. A survey of 320 hypertensive patients in Beijing found a compliance rate of 30.6%<sup>11</sup>. The reasons identified include lack of knowledge and guidance, and lack of or insufficient medical insurance. Also, due to the 7-day limit on each prescription, patients are reluctant to see physicians every week to get their refills.

Under-dosage caused by low compliance is not good for patients’ treatments and may lead to the progression of disease, causing higher medical cost in the future.

**Limited pharmacovigilance /adverse drug reaction reporting**

Adverse drug reaction (ADR) is a crucial problem globally and in China. WHO estimates that every year 2.5 million Chinese patients are hospitalized due to ADR, among whom 190,000 lose their lives<sup>12</sup>.

The Chinese government has made consistent efforts to mitigate the ADR problem, which costs RMB4 billion annually<sup>13</sup>. ADR monitoring guidelines were first introduced in 2004; they outline when and how various parties should report ADR cases. Encouragingly, some large Chinese drug companies have established internal reporting systems and actively seek ADR feedback on their products from hospitals<sup>14</sup>. In general, however, ADR reporting in China is still developing. In 2007, China recorded 540,000 reports, but the per capita number is only ~1/4 of the U.S. level. The SFDA found that reports are mainly from hospitals and that local manufacturers seldom report proactively<sup>15</sup>. “Even though all reports are on a voluntary basis, we noticed that drug manufacturers and distributors are not as forthcoming as medical institutions in reporting ADR cases to the SFDA,” said an SFDA spokesman in 2008.

In western countries, pharmaceutical companies are very active in self-monitoring and ADR reporting with over 50% of ADRs reported from pharmaceutical companies.

**Optimal Use of High Quality Medicine**

All medicines, whether innovative or generic, whether chemicals, biologics, or plant-based, contribute value to the Chinese government’s goal of providing “safe, effective, convenient, and affordable” medical service to Chinese patients. Assuring the quality of medicine, both innovative and generic, which are by far the largest segment of usage in China<sup>16</sup>, and the optimal prescription of medicines are the foundation to meeting the WHO’s definition of optimal use.

**Safe**

China has an established GMP standard, which contributed to improving medicine quality when it was launched in 1999. Despite this fact, Chinese research indicates that domestic medicine manufacturing quality is still highly variable due to the difference in materials used and the quality standards applied. In a research study conducted by Peking Union Medical College, various sterile ceftriaxone sodium products studied showed significant differences in quality metrics such as concentration and dissolution<sup>17</sup>. A research conducted

in 2006 by Shanghai Institute of Pharmaceutical Industry showed that three branded itraconazole capsules have significant differences in impurity and solubility, both measures of quality<sup>18</sup>.

**Effective**

Innovative medicine and quality generics together with TCM are part of the comprehensive therapy for Chinese patients. The use of innovative medicines and vaccines enables more effective prevention and treatment of diseases. These should be viewed in the context of the overall treatments and overall health program

**Convenient**

Incremental improvements on medicine, such as better delivery mechanisms, can make therapy more convenient to patients and hospitals. Developing heat-stable formulations, for example, means drugs do not need to be refrigerated, thus improving distribution reach to rural clinics. Developing child dosage and better flavor opens the treatment options to children. Improving drug concentration and dissolution so fewer pills need to be taken to achieve similar benefits greatly improve patients’ convenience in taking therapy. These improvements can also greatly improve patients’ compliance, which in turn better treat the disease and reduce future complications

**Affordable**

Given the huge healthcare demand and relatively limited resources and budgets, China needs to manage its increasing overall healthcare cost. International experience suggest that making optimal therapy available to patients and minimizing wastage of medicines are important cost saving methods.

Treating patients with optimal therapy can stop or reduce disease progression and reduce the overall costs of healthcare. Innovative medicines developed by the R&D-based pharmaceutical industry provide a ready pipeline of much less expensive future generic products. As is the case in many other markets, most, if not all, generic drugs are former innovative drugs. For example, under the Hatch-Waxman framework in the United States, innovative drugs are offered strong patent production until they go off patent, when much more affordable generic versions are allowed to come onto the market. As a result, 65% of all prescriptions dispensed in the United States today are affordable generics<sup>19</sup>, while innovators focus on developing new compounds. In China, similarly, a lion’s share of the market is taken up by local generic firms with solid

growth<sup>20</sup>. A healthy R&D-based pharmaceutical industry is important to ensure that improved generics will continue to be available in the future.

Targeting optimal use can also prevent unnecessary costs caused by over-use and waste of medicines – an issue common in China and a cause of significant waste of healthcare funds. In 2005, Chinese academics estimated that the abuse and over prescription of antibiotics alone cost China ~RMB100 billion<sup>21</sup>. That money could have been utilized more efficiently elsewhere in the healthcare system.

#### Case study: China hepatitis B (HBV)

*A WHO survey indicates that China has 130 million of the world's 350 million HBV carriers. HBV has brought heavy social and economic burden to China. 20 million will possibly die of HBV related disease and over 30 million are suffering from chronic active hepatitis. Research indicated that each of China's over 30 million chronic active HBV population loses 11.7 years of health life (DALY, disability adjusted life year), and the loss almost doubles to 19.2 years if the disease progresses to cirrhosis<sup>22</sup>.*

*HBV causes ~RMB26 billion of direct medical cost annually in China. A Social Insurance Research Institution research indicated that progression of chronic hepatitis B and its complications are associated with increasing healthcare costs<sup>23</sup>. Thus, a tive prevention and early optimal treatment is important.*

*In the past 20 years, Chinese citizens have benefited from access to vaccines and combined therapy including innovative and generic medicines. In 1989, HBV vaccine technology was transferred by PhRMA member Merck (MSD) to Beijing Tiantan and Shenzhen Taikang – these two companies together account for over 70% of China's current HBV vaccine supply<sup>24</sup>. In 1992 the government started to include HBV vaccine in the children's planned immunization program. Research in Shandong in over 3500 children showed that their HBsAg+ infection rate declined after HBV vaccination became mandatory, from 3.88% in 1990 to 0.27% in 2000<sup>25</sup>. As HBsAg+ rate declined nationally, the vaccine has effectively prevented 30 million people from HBV infection (prevalence declined from 9.75% in 1992 to 7.18 in 2002).*

*Chinese HBV patients can benefit from drug therapy that are optimal to their own situation, and may include a combination of innovative medicine, generics and TCM:*

\* *Lamivudine was introduced by GSK into China in 1998 as the first available nucleoside HBV medicine; now it continues to be suitable for many patients as a relatively economical anti-viral treatment<sup>26</sup>*

- \* *Improved antiviral treatments from multiple companies have been introduced into China*
- \* *Innovations in long-acting interferon, also an antiviral, provide improved patient convenience, with conventional interferon continue to be on the market*
- \* *TCM medicines are widely used alone or in combination with antivirals as complementary liver protecting treatment*

#### IDEAS CHINA CAN ADOPT TO IMPROVE QUALITY USE OF MEDICINES

Based on the global pharmaceutical industry's experience in many countries, the following public policy actions may improve China's quality use of medicine:

1. Further encourage domestic companies to improve manufacturing quality. In addition to further enforcement of compliance with the SFDA GMP standards and encouraging manufacturers to improve process management, looking to international practice and discussing the use of additional manufacturing and clinical quality metrics may also help improve GMP in China.
2. Encourage incremental innovation – especially in areas such as delivery mechanism and dosage – to spur development and improve patient compliance. In China, however, it is still relatively difficult to patent, or otherwise to gain credit for, incremental innovation. Encouraging and rewarding such advances could greatly increase the incentive for companies to invest in incremental innovation.
3. Better promote and provide training on international treatment and prescription guidelines to achieve optimal prescribing. For example, WHO's simple six-step guide to good prescribing and WHO's twelve core interventions to promote more rational use of medicines can be further promoted and encouraged. Other common international treatment guidelines can also be considered for adoption.
4. Improve physician training, especially in the clinics. As China pushes for the rapid expansion of urban community and rural clinics, it will be critical that doctors and staff have adequate training and knowledge to prescribe medicines properly.
5. Explore the use of evidence-based medicine to support optimal prescription. Evidence-based medicine (EBM) is the use of best available evidence to support good decision-making by patients and physicians. It integrates current available evidence, clinical expertise and patient understanding and values. Consumers,

patients, physicians and other healthcare professionals should have access to the range of evidence on all treatment options and health management.

6. Encourage post marketing surveillance and adverse drug reaction reporting. Many pharmaceutical research and biotechnology companies have employed global drug safety physicians who, supported by drug safety scientists, are responsible for a particular product's continuous safety surveillance.
7. Separate prescribing and dispensing. Although it is a difficult issue to address, separation between prescribing and dispensing by doctors is important to eliminate distorted prescribing practices and to better align therapy to clinical needs.

There is value in innovation, quality, and the optimal use of medicine for Chinese patients and China's healthcare system. In healthcare as in many other industries, there are a wealth of international experiences which can be tapped and contributed by academia, by NGOs, by companies and by the industries to support China in this endeavour to improve healthcare.

#### Authors' note:

*The research referenced in this paper was compiled for Pharmaceutical Research and Manufacturers of America (PhRMA). For the complete PhRMA "Innovative Prescription Medicines Support the Goals of Chinese Healthcare Reform," please see [www.phrma.org](http://www.phrma.org) or [www.lek.com/China\\_publications](http://www.lek.com/China_publications).*

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