Potential Health & Safety Impacts from Pharmaceuticals and Supplements Containing Chinese-Sourced Raw Ingredients

Prepared for

U.S. China Economic and Security Review Commission

NSD Bio Group, LLC
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Preface

In recent years there has been increasingly deep concern regarding the potential health and public safety impacts of the widespread and unregulated use of Chinese-sourced ingredients that are imported and incorporated into America's pharmaceutical products, dietary, and nutritional supplements. Issues driving interest in these areas are numerous and varied.

Against the backdrop of past health and safety concerns caused by tainted, or otherwise unsafe raw materials discovered in imported products from China – to include, among others, heparin (a blood thinner widely used by kidney-dialysis and post-surgical patients to prevent blood clots), and wheat gluten (corrupted with the chemical melamine) – this report will address concerns relating to potential threats to consumer health, and whether appropriate American regulatory agencies, particularly the U.S. Food and Drug Administration, and the Department of Health and Human Services have the appropriate resources, policies, and procedures required to respond adequately and effectively.

This report attempts to shed light and insight on particular issues addressing potential implications of a critical component of a complex supply chain, which contributes to U.S. national health security as China continues to strengthen its position as the world's largest supply source of raw materials for pharmaceuticals and supplements. As first reported in 1998 by the U.S. Government Accounting Office, the U.S. imports an estimated 80% of the raw ingredients contained in both products manufactured, sold and consumed in this country. In light of recent passionate debate on unprecedented major reform of the U.S. national health care system during the time of this report, one fundamental remains – extreme confidence in the quality, safety and effectiveness of the medicines used is essential for any improvements (either incrementally or substantial) of the nation's health security, and cannot and should not be compromised to any degree. Analyses contained in this report reflect past and continuing trends of expected outcomes of U.S. corporate strategies based on competitive cost pricing, increased margins, and market growth drivers.

The U.S. China Economic and Security Review Commission (Commission) has requested NSD Bio Group, LLC to prepare an objective, independent report addressing potential health and safety impacts of Chinese-sourced ingredients used in the production and supply of pharmaceutical products, dietary and nutritional supplements to the US marketplace.

This report both draws reference from and adds to specific papers, reports, public hearings, and testimonies to Congress – and in particular, the House Committee on Energy and Commerce and the Commission on this and other import-related matters – as part of the ongoing public debate on U.S. – China trade and product safety issues.

Executive Summary

Against the backdrop of recent health and safety concerns caused by tainted, or otherwise unsafe raw materials discovered in imported products from China, this report attempts to address similar concerns on the potential array of health risks to American consumers from imports of specific raw materials supplied by China used in the U.S. manufacture of pharmaceutical and supplement products. It is well documented that China is a major producer and exporter of FDA-regulated products and therefore presents a range of issues for concern. As evidenced in many past instances, the FDA has encountered compliance problems with other imported items from China, such as cough syrup, toothpaste (contaminated with diethylene glycol – a poisonous ingredient used in antifreeze), pet food (melamine), lead and cadmium in ceramic ware used to store and ship food, staphylococcal contamination of canned mushrooms, and more recently, residential drywall and high cadmium (in place of lead) concentrations found in children's jewelry, both reported by the U.S. Consumer Product Safety Commission, as documented examples. While improvements have been made in oversight procedures and enforcement by Chinese authorities, much still remains to be done to attain international standards and widespread consumer confidence.

In spite of the widely reported tainted heparin-associated incidents of 2008, the U.S. remains one of five major importers of heparin sodium, of which China exported a total of 30 tons (~27,215 kg) in the first quarter of 2009. China has upgraded its enforcement of production quality control measures towards heparin manufacturers, which as the writing of this report, numbered 28 in total, with the top five companies responsible for over 85% of the Chinese heparin export market. Heparin and salts ranked 5th in terms of top API products exported to the U.S. from 2006 to 2008 with an estimated value of close to $21 M and ~22.4K kg. From prior research, it was estimated that in the U.S. alone, two tons of heparin per month was required, 70% sourced from China. One immediate domestic response towards improving import and product safety for the much needed heparin, as part of continuing efforts on securing the supply chain, was a revision of heparin sodium and heparin calcium monographs for new testing and analyses of selected imported raw materials.

There are relatively few regulations related to pharmaceutical exports from China in comparison to industrialized economies with significant global influence. In particular, the regulations on "Pharmaceutical Processing for Export" as currently written are brief, and could be easily interpreted as putting an enormous burden on the destination country or region external to China with respect to quality standards and safety requirements. Up until relatively recently, the Chinese government has emphasized their efforts on the monitoring of drug safety issues inside rather than outside of China. Therefore China's State Food and Drug Administration's (SFDA) surveillance on exported pharmaceuticals were limited due to financial and technical hurdles. Taking into consideration recent drug safety incidents impacting only the Chinese drug consumer, one can easily argue that past regulatory and enforcement efforts were insufficient and inadequate.

As one of many consequences of the wide chasm between China's regulatory and inspection system of pharmaceuticals and other economies' regulatory regimes, Japan, the second largest market for nutritional supplements in the world behind the United States, with a market size for nutritional supplements and health foods over $10 B annually, has adopted rigorous measures in its import controls and regulatory requirements to reduce significantly the chances of tainted, counterfeit, or otherwise unsafe Chinese-produced ingredients in medicines and supplement products. These measures have been implemented in part because Japan has experienced a number of health and safety incidents involving imported Chinese supplements (and related raw materials) in recent years.

The agreement between SFDA and the U.S. Department of Health and Human Services (HHS) signed in December 2007 was the foundation to establish a bilateral mechanism to help ensure designated imported products to the US meet standards for safety and effectiveness. SFDA is currently working toward a system that will enable it to certify that both the manufacturers and their products meet HHS/FDA requirements.

China has evolved into the world's largest supplier of bulk drug or APIs (Active Pharmaceutical Ingredients) required for pharmaceutical products and certain supplements. Despite the current economic downturn, this expansion will continue. China has surpassed the U.S. to become the largest bulk drug manufacturing and exporter in the world, and as a result, China's raw materials impact on the global pharmaceutical market continues to grow. For example, China is the world's No. 1 producer of Acetominophen - a widely used over-the-counter (OTC) analgesic (pain reliever) and antipyretic (fever reducer), commonly used for the relief of fever, headaches, and other minor aches and pains; and is a major ingredient in numerous cold and flu remedies such as Contac, Benadryl, Excedrin, Sudafed, Theraflu, and Vicks among others. China is also a major producer of Vitamin C: China produces over 100,000 tons of Vitamin C, and exports 90% on an annual basis. From 2006 - 2008 Vitamin C was the top API product exported to the U.S. valued in an amount exceeding $72 M and ~21.4M kg. Acetominophen was the11th highest API export to the U.S. market with an estimated value of just over $12.4M and ~3.42M kg.

China has undoubtedly emerged as America's No. 1 pharmaceutical trade partner, as reflected by China's 16.24% share of the market for pharmaceutical ingredients imported into the United States (as of data for 2008). In comparison, the United States held an 11.85% share of the market for pharmaceutical ingredients imported into China for the same period, making the United States the 2nd largest such exporter, resulting in an estimated 4.39% trade imbalance. To put this in perspective, the top 5 of the leading 25 Chinese API Exporters to U.S. during 2006 – 2008 shipped roughly 49.1 million kilograms of API related products worth an estimated ~$167.9 million. Given the increased activity of outsourcing to China by American pharmaceutical companies of their research & development, discovery, and product development functions in the name of cost-benefit considerations, this trend is expected to continue.

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Overview of China's Bulk Drug Manufacturing Industry

China is the World's Largest Bulk Supplier

China's bulk drug or API (Active Pharmaceutical Ingredient) industry has been the backbone of the country's healthcare industry for many decades. With over 20% annual growth, China's bulk drug industry continued to expand at a fast pace in 2008, despite the worldwide economic downturn.

According to the recent statistics data released by the China Chamber of Commerce for Import & Export of Medicines & Health Products (CCCMHPIE) in April 2009,[1] China has surpassed the United States and has become the largest bulk drug manufacturing and exporting country in the world. In 2008, China's bulk drug sales revenue reached 175.6 B RMB ($25.67 B), a 22.6% year-over-year increase. The country's bulk drug exports stood at $17.58 B, a 29.59% growth over the previous year.

China's bulk drug exports have grown by 20% annually since 2001. According to National Bureau of Statistics of China, China produced a total of 2.08 million tons of raw materials for drugs in 2007. [2] For many years, China has been exporting more than half of its bulk drug products to nearly 200 countries or regions across Europe, North America and Asia. As a result, China-sourced raw ingredients have a growing impact on the global pharmaceutical market.

Official statistics reported that China is now able to produce over 1,500 bulk drugs.[3]
Notable achievements of China's API exports are summarized below:

- China is the world's No. 1 manufacturer of penicillin salts, Vitamin C and Acetaminophen.
- China-produced antibiotics, vitamins, hormones, antipyretic analgesics, amino acids, and alkaloids have secured a considerable market share on the global market.
- China-developed artemisinin products have been widely used across the globe to fight against malarial disease.

However, it is acknowledged that China still lags significantly behind in innovative drug development, compared with developed or other developing countries such as U.S. and India. So far, only two China-developed bulk drug exports, Artemisinin and Sodium Dimercaptosucinate, are recognized as innovative drugs by the international community. [4] In 2006 it was reported that 95% of China-produced pharmaceutical products were non-patented generic drugs, and the number of proprietary drugs developed thus far suggests China is still in the growth phase for innovative drug development. [5]

Today, China is home to more than 4,000 Chinese GMP-certified pharmaceutical manufacturers; one-fourth of them involved in API production. [1] Chinese Contract Manufacturing Organizations (CMOs) are playing an increasingly important role in fueling China's API industry. Several industry leaders such as

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[1] CCCMHPIE. Current Status and Development Trend of China's Pharmaceutical Raw Material Industry. Released at 2009 International Exhibition of Pharmaceutical Raw Materials, China. Apr.17, 2009. Available at http://ybsh.mhpie.com.cn/cccmhpie/hydt/html/?1370.html. (in Chinese)
[2] Xiong, Jiabing. API Industry (in China) to Expand rapidly. *Private Economic News.* Aug. 20, 2008 (in Chinese)
[3] State Council of PRC. White Paper of Drug Safety Supervision Situation in China. July 18, 2008. Available at http://www.sda.gov.cn/WS01/CL0027/31372.html (in Chinese)
[4] Qiu, Zhen. SWOT Analysis of API Industry in China. *Chinese Journal of Pharmaceutical Technology Economics and Management. Vol. 2, No. 1, pp. 37-42.* (in Chinese)
[5] http://www.genengnews.com/articles/chitem.aspx?aid=1875&chid=4

Zhejiang Medicine Co., Ltd., Zhejiang NHU Co., Ltd., Shijiazhuang Pharmaceutical Group, Northeast Pharmaceutical General Factory, Shandong Xihua Pharmaceutical Co., Ltd., Zhejiang Hisun Pharmaceutical Co., Ltd., has established a good international reputation as well as solid business relationships with their clients worldwide.

Chinese manufacturers strive to improve the quality of their products in accordance with international standards. Chinese manufacturers have obtained 158 Certificate of Suitability (COS) certifications from Europe by 2008.[1] Chinese drug manufacturers have so far generated over 600 Drug Master Files (DMFs) from U.S. Food and Drug Administration (FDA).

The major categories of Chinese API exports include antibiotics, vitamins, organic acids, amino acids and intermediates, which are displayed in two graphical representations as shown in Figures 1A, 1B.[6]

FIGURE 1A: CHINESE API EXPORTS COMPOSITION 2008

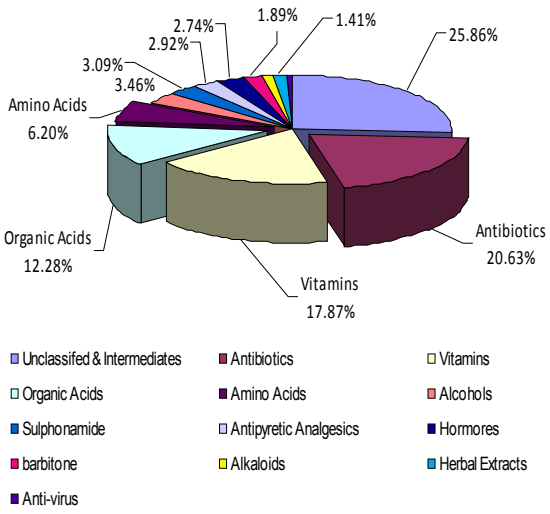
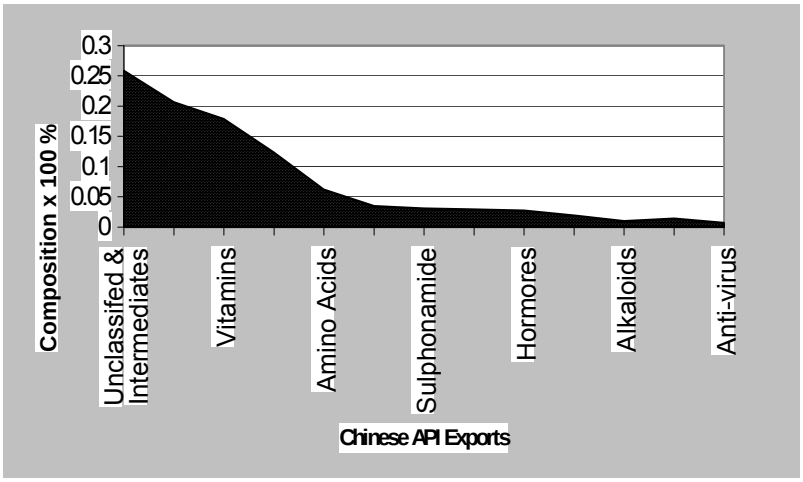


FIGURE 1B: CHINESE API EXPORTS COMPOSITION 2008



[6] Wu, Huifang - China API Imports and Exports Analysis by Categories in 2008. Collected and analyzed May 18, 2009. Available at www.healthoo.com for subscribed members only. (in Chinese)

Penicillin salts:

According to CCCMPHIE[7], China exported 9,855 tons (~$157 M) of penicillin industry salt in 2008, with an average price of $15.97 per kilogram. However by quantity, penicillin salts exports decreased by 27.70% in 2008, compared with 2007. Forty percent of excess production capacity attributed to the decrease of penicillin exports. It is anticipated that Penicillin will be replaced by related downstream products such as 6-APA, amoxicillin, GCLE and ampicillin in the near future.

China exports penicillin salts to five countries: India (84.32%), Iran, Japan, United Arab Emirates, and U.S. The leading penicillin producers are Huaxing, Shijiazhuang Pharma Zhongrun Co., Harbin Pharma Group, North China Pharma Group, Hebei Zhongrun, and Lukang Pharma, Sichuan Pharma.

- Vitamin C:

  According to CCCMPHIE, as the biggest Vitamin C manufacturer in the world, China produces over 100,000 tons of vitamin C and exports 90% abroad each year. The average exports price for Vitamin C was $8-10 per kilogram in 2008, but the price has dropped in 2009. Leading Vitamin C manufacturers in China are Shijiazhuang Pharma, Northeast Pharma, North China Pharma, Aland (Jiangsu) Nutraceutical Co., Ltd.).

- Acetaminophen:

  According to the statistics released by China Customs, China exported 42,388 tons of acetaminophen worth $172.28 M in 2008, an 8.68% decrease in quantity but a 23.75% increase in value, compared with 2007. The average price was $4.04 per kilogram. Major destinations of this product include Asia, Africa, Europe, and America. Anqiu Lu-an Pharma is the industry leader among over 100 Chinese acetaminophen producers and exporters.[8]

- Heparin

  Chinese heparin producers experienced a hard time following the fatal heparin-associated incidents reported in U.S. in early 2008. However, according to CCCMPHIE[9], this situation has changed in 2009, as Chinese authorities and heparin manufacturers are enforcing tougher quality control procedures in production. Heparin exports in the first quarter of 2009 increased 155% and 34%, compared to the first quarter and the fourth quarter of 2008, respectively. The price of heparin also doubled (to $4,354 per kilogram) in the first quarter of 2009, compared with the same period of 2008.

  China exported a total of 30 tons of heparin sodium to 27 countries in the first quarter of 2009. The big importers of China-produced heparin are U.S., France, Germany, Austria and Italy, who were responsible for 86% purchase of Chinese heparin exports.

  Currently, there are 28 heparin producers/exporters in China. The following top five companies have dominated over 80% of Chinese heparin exports:

  - Shenzhen Hepalink Bio-Tech Co., Ltd.
  - Nanjing Jianyou Biochemical Pharmaceutical Co., Ltd.
  - Changzhou Qianhong Bio-pharma Co., Ltd.
  - Yantai Dongcheng Biochemicals Co., Ltd.

[7] CCCMPHIE. Analysis of Chinese API Imports & Exports 2008. Mar. 17, 2009. Available at: http://www.cccmhpie.org.cn (in Chinese)
[8] Chinese Acetaminophen Exports Facing Crisis. *China Pharmaceutical News.* May 4, 2009. (in Chinese)
[9] CCCMPHIE. Heparin Sodium Exports Soars in Q1 2009. May 25, 2009. Available at: http://www.cccmhpie.org.cn (in Chinese)

- Zhejiang Huilong Foreign Trade Co., Ltd.

Top 25 Chinese API Exporters by Revenue

In 2008, a total of 13 Chinese exporters achieved over $100 M exporting revenue (Table 1), according to China Customs data. Interestingly, vitamin exporters took the lead and dominated all the top 6 spots in 2008.[10]

TABLE 1: TOP 25 CHINESE API EXPORTERS IN 2008

Ranking	Exporters	Amount (USD in Million)
1	Zhejiang Medicine Co., Ltd.	292.70
2	Zhejiang NHU Co., Ltd.	264.28
3	Zhejiang Medicines & Health Products I/E Co., Ltd.	252.03
4	CSPC Weisheng Pharmaceutical (Shijiazhuang) Co., Ltd.	217.68
5	Northeast Pharmaceutical General Factory	207.49
6	Aland (Jiangsu) Nutraceutical Co., Ltd.	186.37
7	Sinochem Ningbo I/E Ltd.	168.60
8	Heibei Welcome Pharmaceutical Co., Ltd.	165.27
9	RZBC Imports & Exports Co., Ltd.	127.38
10	Zhuhai United Laboratory Co., Ltd.	116.32
11	Shandong Xinhua Pharmaceutical Co., Ltd.	105.69
12	Anhui BBCA Biochemical Co., Ltd.	104.17
13	Shandong TTCA Co., Ltd.	100.38
14	Harbin Pharmaceutical Group	82.50
15	Ningxia Qiyuan Pharmaceutical Co., Ltd.	64.65
16	Shenzhen Hepalink Bio-Tech Co., Ltd	63.47
17	Aurobindo (Datong) Biopharmaceutical Co., Ltd.	62.56
18	CSPC Hebei Zhongrun Pharmaceutical Co., Ltd.	59.91
19	Fujiang Fukang Pharmaceutical Co., Ltd.	59.25
20	Zhejiang Huahai Pharmaceuticals Co., Ltd.	59.01
21	China Meheco Corp.	55.12
22	Zhejiang Jiuzhou Pharmaceutical Co., Ltd.	52.55
23	Hebei Wangquan Kaidi Imports & Exports Co., Ltd.	51.99
24	Zhejiang Hisun Pharmaceutical Co. Ltd.	50.26
25	Hubei Guangji Pharmaceutical Co.,Ltd.	49.77

[10] Wu, Huifang. 2008 Ranking of Chinese API Exporters. May 15, 2009. Available at www.healthoo.com for subscribed members only. (in Chinese)

Top 25 Chinese Pharmaceutical Manufacturers by Revenue

According to the SFDA Southern Pharmaceutical Economic Institute, the top 25 Chinese pharmaceutical manufacturers in 2008 are listed in Table 2.

TABLE 2: TOP 25 CHINESE PHARMA & HEALTHCARE MANUFACTURERS IN 2008 BY EXPORTS

Ranking	Manufacturer
1	Harbin Pharma Group
2	Shijiazhuang Pharma Group
3	Shanghai Pharma Group
4	Tianjin Pharma Group
5	Yangtze River Pharma Group
6	Jilin Xiouzheng Pharma Group
7	Guangzhou Pharma Group
8	North China Pharma Group
9	Tianjin Jinyao Pharma Group
10	Bayer Schering Pharma Co.
11	China Tongrentang Group
12	Xi'an Jassen Pharma Co.
13	Buchang Pharma
14	Beijing Pharma Group
15	Northeast China Pharma
16	Zhejiang Medicine Co.
17	Zhejiang Huadong Medicine Co.
18	Taiji Group
19	Qilu Pharma
20	Shanghai Roche Pharma Co.
21	Beijing Novartis Pharma
22	Jiangxi JiminKexin Group
23	Zhejiang NHU Co., Ltd.
24	Zhejiang Hisun Pharmaceutical Co. Ltd.
25	China National Biotec Group

Regulatory Agencies and Policies to Ensure Food and Drug Safety Surveillance

For many years, the Chinese government has been striving to improve and implement the country's food and drug safety supervision system, technical supporting system and legal system. Based on our research, we believe that China has established a solid infrastructure to ensure the safety of food and drugs, although flaws, bureaucracy, and corruptions still exist within the system. Significant progress has been observed since 2007, when the State Food and Drug Administration (SFDA) vowed to improve food and drug safety.

However, due to financial and technical hurdles, the Chinese government agencies emphasize their focus on monitoring food and drug safety issues inside rather than outside China. Our research reveals that the SFDA's surveillance on exported Chinese pharmaceuticals remains quite limited.

Terminology discrepancies between China and U.S.:

In China, drugs are defined as "a special kind of commodity used to prevent, treat and diagnose diseases." They include traditional Chinese herbal medicines, small-molecular synthetic pharmaceuticals, crude drugs, drug formulations, antibiotics, biochemical drugs, radioactive medicines, sera, vaccines, blood preparations and diagnostic medicines.[3] Pharmaceutical excipients and packing materials are also regulated as a special category of drugs by the State Food and Drug Administration (SFDA).

Traditional Chinese herbal medicines, vitamins, calcium tablets are regulated as drugs by the SFDA in China. By contrast, in U.S., Chinese herbal medicines are not recognized as therapeutics, while vitamins are categorized as dietary supplements.

Regulatory Agencies and Responsibilities

SFDA and Affiliated Agencies

SFDA is a government agency under Ministry Of Health (MOH), responsible for the supervision on the safety management of food, health food, drug and cosmetics and is the competent authority of drug regulation.

A. History and Commissioners

In 1998, China's State Council officially formed the State Drug Administration (SDA) on the basis of the former State Drug Administration Bureau under the Ministry of Health (MOH). Five years later in 2003, SDA was restructured to the SFDA, which was under the direct supervision of the State Council.

In March 2008, the Ministry of Health (MOH) became the direct supervising authority of SFDA. Mr. Mingli Shao, the Commissioner of SFDA was appointed as one of the Vice Ministers of MOH during that time. Mr. Mingli Shao took his office as the Commissioner of SFDA in June 2005. Prior to that, he was the Vice Commissioner of SFDA

In May 2005, the former SFDA Commissioner, Xiaoyu Zheng, was arrested in a corruption probe initiated by China's nationwide "Anti-Commercial Bribery Campaign". He was later convicted of taking bribes and dereliction of duty and sentenced to death in July 2007. Zheng's execution marks the first time China has imposed a death sentence on an official of his rank since 2000.

Zheng had been the head of the SFDA from 1998 to 2005. His corrupt practices are believed to have led to many deaths associated with substandard or counterfeit drugs or drug ingredients at home and abroad. Zheng had been convicted of personally approving unproven and unsafe medicines after taking bribes from eight pharmaceutical companies totaling more than 6.49 M RMB ($850,000), which resulted in at least a hundred patient deaths (directly and indirectly) in China. It was also discovered during his eight

year reign as the head of SFDA, Zheng personally ordered the approvals of more than 150,000 new medicines, an average of an astonishing 134 times that of U.S. FDA, which only approves 140 or so new medicines annually. Most of those 150,000 medicines approved, were products of the eight pharmaceutical companies that bribed Zheng, and a single unsafe medication of Anhui Hua Yuan Biopharmaceutical Co.

B. Organization

SFDA supervises nearly 2,700 food and drug administration agencies at various levels, which include 31 provincial-level agencies (Provinces also include autonomous regions and municipalities directly under the Central Government), 339 city-level agencies, and over 2300 county-level agencies. SFDA also oversees 1,000 affiliated organizations across China.

SFDA employs a total of over 46,000 people across China. The agency had 14,384 inspectors (including 28 GLP Inspectors, 315 GCP Inspectors, 2,640 GMP Inspectors, and 11,401 GSP Inspectors) by the end of 2007.[11]

SFDA has established the following major state-level drug safety monitoring agencies:

- National Institute for Control of Pharmaceutical and Biological Products (http://www.nicpbp.org.cn)
- Chinese Pharmacopoeia Commission (http://www.chp.org.cn)
- Center for Drug Evaluation (http://www.cde.org.cn)
- Drugs Certification Center (http://www.ccd.org.cn)
- Center for Health Food Evaluation, also known as National Traditional Chinese Medicine Protection and Evaluation Commission (http://www.zybh.gov.cn)
- Center for Drug Reevaluation & National Center for Adverse Drug Reaction Monitoring (http://www.cdr.gov.cn)
- Center of Medical Device Evaluation, SFDA

C. Responsibilities

1. To organize relevant authorities to draft laws and regulations on the safety management of food, health food and cosmetics; organize relevant authorities to formulate comprehensive supervision policy, work plan and supervise its implementation.

2. To exercise comprehensive supervision on the safety management of food, health food and cosmetics in accordance with laws; organize and coordinate supervision work on safety of food, health food and cosmetics carried out by relevant authorities.

3. To organize and carry out investigations and impose punishment on serious safety accidents of food, health food and cosmetics; as delegated by the State Council, to organize, coordinate and conduct specific law-enforcement campaigns over safety of food, health food and cosmetics nationwide; organize, coordinate and collaborate with relevant authorities in carrying out emergency rescue work on serious safety accidents of food, health food and cosmetics.

4. To comprehensively coordinate the testing and evaluation for the safety of food, health food and cosmetics; formulate provisions on releasing of supervision information for safety of food, health food and cosmetics in conjunction with relevant authorities and monitor their implementation; disseminate safety information of food, health food and cosmetics from relevant authorities and release it to the public regularly.

5. To draft law and administrative regulations on drug administration and supervise their enforcement; carry out protection system for certain traditional Chinese medicinal preparations and administrative protection system for pharmaceuticals in accordance with law or regulations.

[11] SFDA Annual Statistic Report 2007. Sep. 17, 2008. Available at URL: http://www.sda.gov.cn/WS01/CL0108/32801.html (in Chinese)

6. To draft law and regulations on administration of medical devices and supervise their enforcement; take charge of registration and regulation of medical devices; draft relevant national standards, draw up and revise professional standards of medical devices, manufacturing practice and supervise their implementation.

7. To be in charge of drug registration; generate, revise and promulgate national standard of drugs; draw up criteria for marketing authorization of health food; review and approve health food; set up classification system for prescription drugs and OTC drugs; establish and improve ADR monitoring system; be responsible for drug reevaluation, review drugs to be withdrawn and formulate national essential medicines list.

8. To draft and revise good practices for drug research, manufacturing, distribution and use, and supervise their implementation.

9. To control the quality of drugs and medical devices in manufacturers, distributors and medical institutions; release national quality bulletin on drugs and medical devices on a regular basis; investigate and punish illegal activities of producing and selling counterfeit and substandard drugs and medical devices in accordance with law.

10. To regulate radioactive pharmaceuticals, narcotics, toxics, psychotropics, and other controlled drugs and devices in accordance with law.

11. To draw up and improve qualification system for licensed pharmacist; supervise and direct the registration of licensed pharmacist.

12. To direct national drug regulation and comprehensive supervision on the safety management of food, health food and cosmetics.

13. To carry out exchanges and cooperation in drug regulation, relevant safety management of food, health food and cosmetics with foreign governments and international organizations.

Adverse Drug Reaction Monitoring System

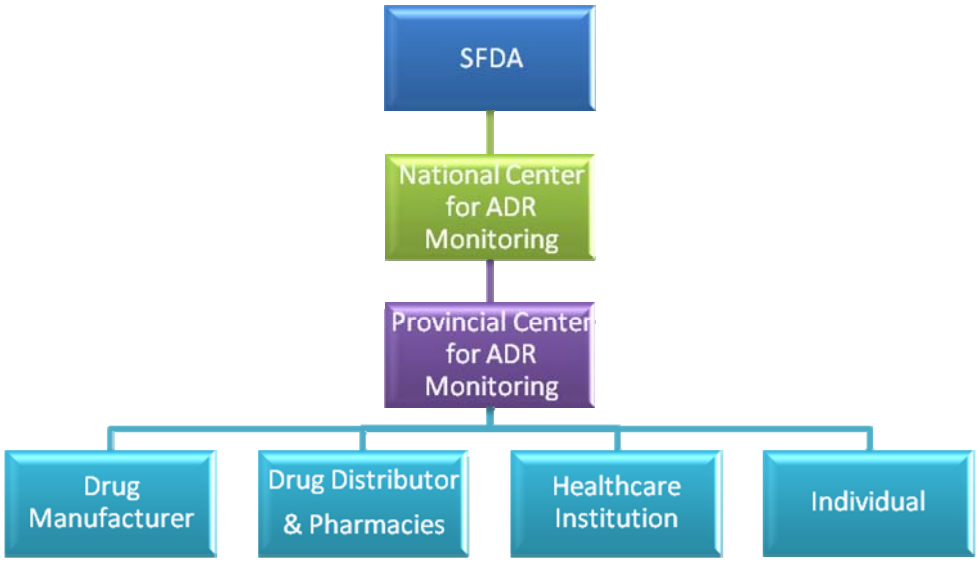
China's National Center for Adverse Drug Reaction (ADR) Monitoring was established in 1989. In 1998, China officially joined the WHO Collaborating Centre for International Drug Monitoring. In November 1999, SFDA issued a trial version of "Regulations on Adverse Drug Reaction Reporting and Monitoring", which was revised and finalized in March 2004.

To date, China has established a three-level (as shown in Chart 1) adverse drug reaction (ADR) reporting and monitoring network. 34 provincial-level ADR monitoring centers (including all provincial ADR centers, a national military hospital ADR center, and Xinjiang Construction Military Troop ADR center), have been established. Under provincial ADR centers, over 200 local ADR monitoring centers or stations have been founded. A nationwide electronic and on-line instant ADR reporting information network has also been formed.

Procedurally, the formal Chinese monitoring system requires pharmaceutical industry and healthcare professionals to report most ADR reports quarterly. However, new, uncommon, serious or group ADRs are required to be reported within a shorter period. Reports will be made to local centers, which then analyze and transmit them to a national ADR center operated by SFDA. The national authority is then empowered to authorize further studies, publish formal warning announcements or prohibit use of a product.[12]

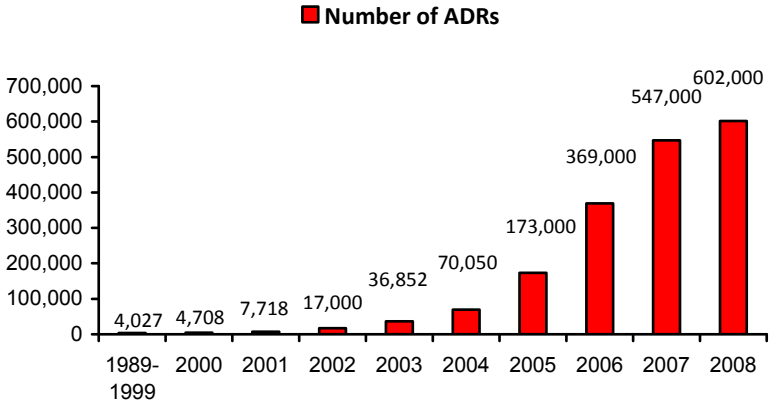
[12] Zhou, Y. et. al. An Overview of Adverse Drug Reaction Monitoring in China. *Int J Pharm Med 2006; 20(2): 79-85*

CHART 1: ADR REPORTING SYSTEM IN CHINA



Total ADR reports in China have been increased year over year (Chart 2) and reached 602,000 in 2008, which is equivalent to 460 ADR reports per one million of population. This figure is very close to that of developed countries.

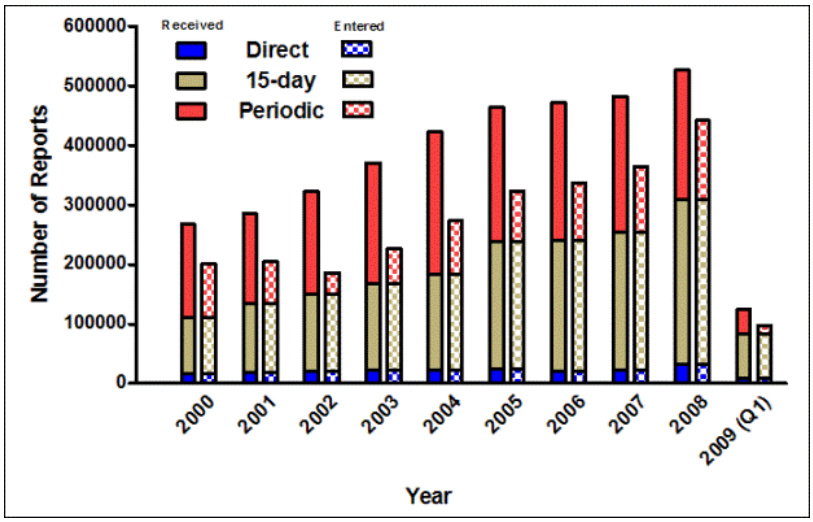
CHART 2: NUMBER OF ADR REPORTS IN CHINA[13]



A comparison of ADR reports the SFDA received, with the number of ADE (Adverse Drug Event) reports received by the U.S. FDA, accounting for China's population (4.33 times of U.S.), it is positioned that the FDA received considerably more ADE reports than China per annum.

[13] Source: SFDA publicly released information.

CHART 3: NUMBER OF ADE REPORTS IN U.S.[14]



Noticeably, among the 602,000 ADR reports in 2008, 85.7% were from hospitals, 10.4% from drug manufacturers or distributors, and 3.8% from individual patients.[15] The percentage of ADR reports generated voluntarily by drug manufacturers is considerably low, compared with U.S. and other industrialized countries. In an effort to encourage and enforce Chinese drug manufacturers to report ADR cases voluntarily, SFDA announced on November 6, 2008 that it is considering amending the 2004 version of ADR Reporting and Monitoring Regulations, which shall emphasize the responsibilities and liabilities for drug manufacturers to voluntarily report adverse drug events.

- Center for Drug Reevaluation, SFDA

  Responsibilities:

  a. Draft, issue and revise the "National Basic Drug Directory"
  b. Draft, issue and revise the "National Over-the-counter (OTC) Drug Directory"
  c. Drug re-evaluation and elimination.
  d. Provide technical advice to the National ADR Monitoring Center

- National Center for ADR Monitoring

  Responsibilities:

  a. Perform nationwide ADR monitoring
  b. Collect, evaluate, provide feedbacks, and report ADR cases
  c. Organize research on ADR monitoring methods

[14] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm
[15] Source: National Center for ADR Monitoring. Jan. 20, 2009.

d. Build and maintain national ADR information database
e. Provide technical advice to provincial-level ADR monitoring centers
f. Release ADR Information Bulletins
g. Publish ADR information journals (such as Chinese Journal of Pharmacovigilance)
h. Participate in international ADR information exchange

- ADR Information Bulletins

  Since the first issue of "ADR Bulletin" was issued in November 2001, SFDA has released a total of 22 issues of ADR Bulletins by June 2009, which are associated with ADRs of 50 pharmaceutical products in China, -- mostly antibiotics, anti-virus agents, and traditional Chinese herbal medicines (TCMs). Among them, the 15th Issue of ADR Bulletin only listed internationally reported ADRs outside China.

Drug Control Institutes

Under the supervision of SFDA, there is one national-level and 33 provincial-level drug (quality) control institutes performing lab-based analysis and quality control of pharmaceutical products in China. Some provincial-level institutes (see Table 3) are designated as "Port Drug Control Institutes", which are authorized to perform analyses on, and registration of imported drugs. Chinese exported pharmaceutical products (raw material drugs and finished drugs) must pass examination of provincial drug control institutes, and meet the requirements of the foreign clients accordingly.

TABLE 3: PORT DRUG CONTROL INSTITUTES IN CHINA

National Institute for Control of Pharmaceutical and Biological Products (NICPBP)	
Beijing Institute for Drug Control	Dalian Institute for Drug Control
Tianjin Institute for Drug Control	Jiangsu Institute for Drug Control
Shanghai Institute for Drug Control	Fujian Institute for Drug Control
Zhejiang Institute for Drug Control	Qingdao Institute for Drug Control
Xiamen Institute for Drug Control	Guangdong Institute for Drug Control
Wuhan Institute for Drug Control	Chongqing Institute for Drug Control
Hainan Institute for Drug Control	Shanxi Institute for Drug Control
Chengdu Institute for Drug Control	Guangxi Institute for Drug Control

In July 2009 the National Center for Drug Safety Evaluation and Monitoring affiliated to NICPBP, received a one-week Good Laboratory Practice (GLP) inspection conducted by U.S. FDA and received positive feedback from FDA.

Chinese Pharmacopoeia

Pharmacopoeia of PRC (Chinese Pharmacopoeia) is a legal document that lists drug quality standards for all specification of drugs that have been approved in China. The first edition of Chinese Pharmacopoeia was published by MOH in 1953. Since then, a total of eight editions of Chinese Pharmacopoeia have been published (1953 Edition, 1963 Edition, 1977 Edition, 1985 Edition, 1990 Edition, 1995 Edition, 2000 Edition, 2005 Edition). Since the 1985 Edition, Chinese Pharmacopoeia has been available in two languages: both Chinese and English.

The 2005 edition of Chinese Pharmacopoeia consists of three volumes, including 3,214 monographs of drugs.

- Volume I contains monographs of Chinese materials extract, Chinese traditional patent medicines, single ingredient of Chinese crude drug preparations etc.;

- Volume II contains monographs of chemical drugs, antibiotics, biochemical preparations, radiopharmaceuticals and pharmaceutical excipients;

- Volume III contains information on biological products.

The Chinese Pharmacopoeia Commission has started to prepare for the Ninth Edition, or the 2010 Edition of Chinese Pharmacopoeia since December 2007, which is scheduled to complete by October 2010. The new pharmacopoeia is anticipated to particularly raise the quality standards of TCMs, and emphasize the controllability and safety of some high-risk drug products, such as biological preparations and vaccines. The new pharmacopoeia will also collect quality standards of a greater number of pharmaceutical excipients.

Regulatory Policies

Drug Administration Law

In September 1984, China's National People's Congress (NPC) officially approved the country's first "Drug Administration Law", which for the first time in China's history, stipulated the legal liabilities and responsibilities involved in pharmaceutical research, production and distribution. The Law also specified the legal liabilities and responsibilities of producing or selling counterfeit or substandard drugs.

In February 2001, NPC amended the Drug Administration Law, which increased the legal liabilities of producing or selling counterfeit or substandard drugs, and raised the standards of Good Manufacturing Practice (GMP) and Good Supply Practice (GSP). The Central Government further released a detailed "Regulations for Implementation of the Drug Administration Law" in August 2002 to enforce the Law. The full content of both the Law and its implementation regulations is available at the SFDA's English website: http://eng.sfda.gov.cn/eng.

These laws and regulations provide legal guidelines to strengthen drug administration, ensure drug quality and safety, and protect Chinese citizens' legitimate rights and interests when using pharmaceutical products.

Counterfeit Drug and Substandard Drug

According to Articles 48 and 49 of the Drug Administrative Law, production and distribution of counterfeit and substandard drugs are prohibited.

- Counterfeit drug is defined as, "A drug is a counterfeit drug in any of the following cases":
  (1) the ingredients in the drug are different from those specified by the national drug standards; or
  (2) a non-drug substance is simulated as a drug or one drug is simulated as another
  The Law also specified that "A drug shall be treated as a counterfeit drug in any of the following cases:"
  (1) its use is prohibited by the regulations of the drug regulatory department under the State Council;
  (2) it is produced or imported without approval, or marketed without being tested, as required by this Law;
  (3) it is deteriorated;
  (4) it is contaminated;
  (5) it is produced by using drug substances without approval number as required by this Law; or
  (6) the indications or functions indicated are beyond the specified scope.

- Substandard drug is defined, as "A drug with content not up to the national drug standards is a substandard drug.
  The Law further specified that: "A drug shall be treated as a substandard drug in any of the following cases":
  (1) date of expiration is not indicated or is altered;

(2) batch number is not indicated or is altered;
(3) it is beyond the date of expiration;
(4) no approval is obtained for the immediate packaging material or container;
(5) colorants, preservatives, spices, flavorings or other excipients are added without authorization; or
(6) other cases where the drug standard are non conforming

Pharmaceutical Exports Regulations

Based on our research, there are relatively few regulations related to pharmaceutical exports from China.

I. Drug Administration Law (hereinafter refers to the Law):

In Article 44, the Law stipulates that "The State Council shall have the power to restrict or prohibit the exportation of drugs which are in short supply within the country."

In Article 45, the Law stipulates that "Anyone who wishes to import or export narcotic drugs and psychotropic substances that fall within the scope specified by the State shall produce the Import License or Export License issued by the drug regulatory department under the State Council."

II. Regulations on Pharmaceutical Processing for Export (trial version): released by SFDA on July 29, 2003

This brief Regulation contains 10 articles. It defines "Pharmaceutical Processing for Export" as "Pursuant to the laws, a domestic pharmaceutical manufacturer is entrusted by an overseas pharmaceutical company to produce or package pharmaceutical products, and export all these products to a designated country or region (outside China), by using domestic or imported crude drug substances, excipients, packing materials and using the formulations, production procedures, quality standards and packing labels provided by the overseas company."

In Article 3, the Regulation specifies that "The Pharmaceutical Processing for Export Contract signed by both parties shall comply with the Chinese laws and regulations, and shall not violate any other human being's rights and interests. The entrusted (Chinese) manufacturer shall strictly follow the production procedures and quality standards as stipulated in the contract. The (overseas) entrust party shall take full responsibility for the product quality."

In Article 4 and 5, the Regulation requires the Chinese pharmaceutical manufacturer to submit an application to a provincial-level food and drug administration agency with necessary documentation. The corresponding provincial-level drug administration agency shall inspect the application and issue an official approval if the application meets all requirements.

Finally, in Article 10, the Regulation excludes any biological products for disease prevention purposes (e.g. vaccines) from such kind of cross-border contract production.

China-U.S. Agreement to Strengthen Drug Safety of Chinese Exports

In December 2007, SFDA and the U.S. Department of Health and Human Services (HHS) signed a Memorandum of Agreement (MOA) to enhance the safety of drugs, excipients and medical devices exported to the U.S. from China. The MOA was signed in Beijing by HHS Secretary Mike Leavitt and SFDA Commissioner Mingli Shao, and remains valid until 2012.

Under the MOA, China and the U.S. are establishing a bilateral mechanism to help ensure some designated imported products to meet standards for safety and effectiveness by building quality into the process from the start. SFDA will require firms that manufacture certain products intended for export to the U.S. to register with SFDA. SFDA will also work toward a system that will enable it to certify that firms that manufacture products, and the products themselves, meet HHS/FDA requirements.

The agreement covers the following designated drugs and medical devices that are manufactured in China for export to the U.S.:[16]

a. SFDA-Designated Drugs:
    i. Recombinant Human Insulin
    ii. Lysine Fat and Lysine Salt
    iii. Cefoperazone and its salts
    iv. Paclitaxel injection
    v. Penicillin and its finished dosage form
    vi. Diagnostic kit for blood screening, specifically, for HIV/AIDS and Hepatitis B & C
b. SFDA-Designated Medical Devices:
    i. Intraocular Lenses
    ii. Cardiac pacemakers
c. HHS/FDA-Designated Drugs:
    i. Gentamicin sulfate (Antibiotics)
    ii. Atorvastatin and its salts (Lipitor)
    iii. Sildenafil and its salts (Viagra)
    iv. Dietary supplements intended for erectile dysfunction or sexual enhancement
    v. Human Growth Hormone
    vi. Oseltamivir and its salts (Tamiflu)
    vii. Cephalosporins manufactured in facilities that also manufacture non-cephalosporin drugs
    viii. Glycerin (Pharmaceutical formulation)
d. HHS/FDA-Designated Medical Devices:
    i. Glucose test strips
    ii. Condoms

Recent Efforts to Enhance Drug Safety

- On October 19, 2006, China launched a nationwide drug safety technology campaign, as a result of several drug-related incidents in 2006, such as the Xinfu substandard drug adverse event and the Qiqihar No. 2 Pharma Counterfeit drug incident. SFDA, in conjunction with the Ministry of Science and Technology and the State Administration of Traditional Chinese Medicine, initiated the campaign, which focused on providing technological support for every step of the drug from manufacturing to patient. Other plans considered for improving drug safety overall were to improve post-marketing surveillance, develop monitoring and supervision of traditional Chinese medicine, implement pre-clinical trial safety checks, and develop standards for drug use and distribution.
- On January 15, 2007, SFDA announced that all the medicines approved between 2002 and 2003 will have to undergo a re-registration and re-approval. A drug production approval is valid for 5 years.

[16] HHS-SFDA. Agreement between the Department of Health and Human Services of the United States of America and the State Food and Drug Administration of the People's Republic of China on the Safety of Drugs and Medical Devices. Dec. 11, 2007. Available at: http://globalhealth.gov/news/agreements/ia121107a.html.

- On July 10, 2007, the former corruptive SFDA Commissioner, Xiaoyu Zheng, was executed. Several associated high-ranking SFDA officials were also placed with charges and under arrest. SFDA also began to re-examine all the approved drugs
- On September 8, 2007, SFDA announced that Chinese government would invest a total of 8.8 B RMB ($1.16 B) in the next four years to improve food and drug safety supervision facilities. The intended investment would be allocated to several key projects, including the following:
  - reconstruction and updating the National Institute for Control of Pharmaceutical and Biological Products
  - purchasing bio-test equipments for 16 port drug control institutes
  - improvement of national ADR monitoring system
  - construction of new facilities for the food and drug administration agencies in some areas experiencing financial difficulties.
- On March 16, 2008, SFDA announced that since July 2006, the agency had cancelled 1,604 drug approvals, while 7,999 drug applications were voluntarily withdrawn by the applicants. SFDA had revoked 157 GMP certificates, shut down 27 pharmaceutical manufacturers, and ordered 370 pharmaceutical manufacturers to suspend production to improve production and quality control systems. Meanwhile, SFDA had revoked 1,210 GSP certificates, and shut down over 6,000 pharmaceutical distributing companies.
- In May 2009, SFDA partnered with a dozen of Chinese government agencies to establish a joint-meeting system, in an attempt to crackdown production and distribution of counterfeit drugs both inside and outside China. These agencies included the Ministry of Health, Ministry of Industry and Information, Ministry of Public Security, Ministry of Supervision, Ministry of Finance, Ministry of Commerce, and China Customs. The establishment of this joint meeting initiated a one-year special campaign to fight against fake drugs. More regulations to fight against bogus drugs will be released in the future.

- In May 26, 2009, the Supreme People's Court of PRC and the Supreme People's Procuratorate of PRC co-issued the "Explanations on several legal questions when handling criminal cases related to production, selling of counterfeit and substandard drug products". These "Explanations" provides guidelines on the standards on how to justify the appropriate crime for production and sales of fake drugs, which are significant "enough to seriously endanger human health".

U.S. is China's No. 1 Pharmaceutical Trade Partner

Trends of Raw Material Exports from China to U.S.

Each year, U.S. pharmaceutical manufacturers import 75%-80% of the essential raw ingredients for production of finished drug products that supply the U.S. domestic market. China-sourced and India-sourced bulk drugs have accounted for 40% of these imported bulk ingredients in the U.S. market.[17]

Among the destinations of Chinese pharmaceutical exports, U.S. has taken the lead for many years, followed by India, Germany, Japan, and Netherlands. These top five countries accounted for 46.4% of Chinese API exports in 2008. On the other hand, the top five pharmaceutical importing partners of China are Germany, U.S., Japan, France and Swiss. Tables 4 and 5 show raw material exports and imports data provided by China Customs, respectively.

TABLE 4: China's Pharmaceutical Raw Material Exports in 2008[18]

Ranking	Country	Exports (Million $)	Share	Annual Growth
1	**U.S.**	**2,246.66**	**16.24%**	**48.63%**
2	India	1,672.59	12.09%	26.74%
3	Germany	962.96	6.96%	39.06%
4	Japan	759.93	5.49%	25.50%
5	Netherlands	638.29	4.61%	28.99%
6	South Korea	510.77	3.69%	20.84%
7	Brazil	426.55	3.08%	67.02%
8	Spain	365.53	2.64%	31.08%
9	Italy	356.19	2.58%	28.93%
10	Belgium	346.06	2.50%	23.89%
11	Hong Kong	295.73	2.14%	20.81%
12	Indonesia	278.28	2.01%	34.75%
13	Thailand	279.20	2.02%	41.94%
14	Israel	234.02	1.69%	57.27%
15	France	196.03	1.42%	20.38%
16	U.K.	197.79	1.43%	23.05%
17	Vietnam	201.67	1.46%	33.59%
18	Taiwan	184.13	1.33%	13.57%
19	Singapore	191.77	1.39%	31.04%
20	Pakistan	166.47	1.20%	22.31%

[17] Zhu, Yushu. FDA's Hassle and China's Challenge. (China) Pharmaceutical Economic News. Jan. 7, 2008 (in Chinese)

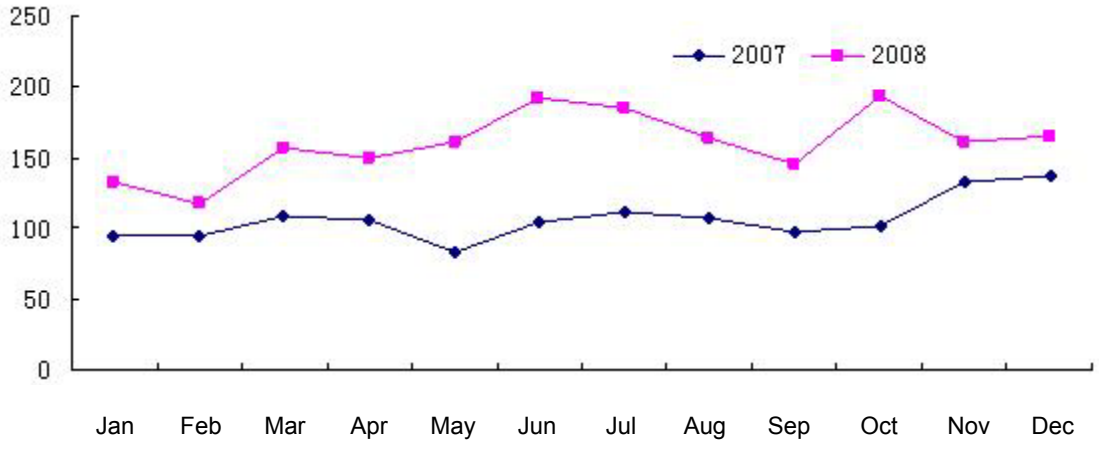
[18] Wu, Huifang. China Pharmaceutical Imports and Exports Summary in 2008. Collected and analyzed on May 8, 2009. Available at www.healthoo.com for subscribed members only. (in Chinese)

TABLE 5: China's Pharmaceutical Imports in 2008[18]

Ranking	Country	Imports (Million $)	Share	Annual Growth
1	Germany	1,133.24	14.47%	50.31%
2	**U.S.**	**928.34**	**11.85%**	**17.07%**
3	Japan	780.30	9.96%	7.72%
4	France	695.17	8.87%	50.56%
5	Swiss	485.03	6.19%	40.59%
6	Belgium	483.05	6.17%	68.84%
7	U.K.	397.82	5.08%	25.39%
8	Italy	369.36	4.72%	63.34%
9	Ireland	312.46	3.99%	38.14%
10	India	247.10	3.15%	-6.91%
11	Hong Kong	253.46	3.24%	17.56%
12	South Korea	202.61	2.59%	-6.41%
13	Taiwan	215.78	2.75%	28.16%
14	Sweden	220.92	2.82%	64.90%
15	Denmark	189.62	2.42%	33.71%
16	Malaysia	142.98	1.83%	24.10%
17	Netherlands	139.10	1.78%	18.94%
18	Spain	123.05	1.57%	54.14%
19	Austria	72.34	0.92%	33.19%
20	Singapore	75.21	0.96%	96.96%

Undoubtedly, U.S. has been and will be China's largest pharmaceutical trade partner for a long time, as China is aimed to become the world's largest pharmaceutical outsourcing hub, with a focus on North American and European markets. Figure 2 shows Chinese API exports to U.S. in 2007 and 2008.

FIGURE 2: 2007-2008 Chinese API exports to U.S. (Million $)[19]



[19] Wu, Huifang. Analysis of Chinese API exports in 2008. Collected and analyzed on May 13, 2009. Available at www.healthoo.com for subscribed members only. (in Chinese)

Latest data released by CCMHPIE showed that in the first five months of 2009, Chinese API exports to U.S. slightly declined by 6.5%, compared to the same period of 2008. Between January and May 2009, China exported $946 M of API products to U.S., accounting for 14.7% of total Chinese pharmaceutical exports. [20] U.S. is still the number-one country of destination for Chinese API exports in 2009.

DMF Filing of Chinese Raw Materials

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. DMFs are typically filed for supplying bulk drugs or active pharmaceutical ingredient (API). There are four types of DMFs:

Type II: Drug Substance, Drug Substance Intermediate, and Material Used in their Preparation, or Drug Product
Type III: Packaging Material
Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in their Preparation
Type V: Other – Sterile manufacturing plants, biotech contract facilities, clinical, toxicology

Since the early 1980s, Chinese API manufacturers have been actively seeking entrance to the U.S. market starting by registering DMFs with FDA. On December 31, 1980, Shanxi Pharmaceutical Industry Corp registered China's first DMF for its product, meprobamate. Based on our research on the U.S. FDA DMF database, the number of DMFs filed by Chinese manufacturers each year exceeded 100 in the past three years (see Table 6). By the first quarter of 2009, the total number of active DMFs filed by Chinese manufacturers reached 628, which included that of 588 Type II, 31 Type III, and 9 Type IV.[21]

TABLE 6: ANNUAL DMF NUMBERS FILED BY CHINESE API MANUFACTURERS

YEAR	TYPE II	TYPE III	TYPE IV	TYPE V	TOTAL
2009 (Q1)	16	5	0	0	**21**
2008	114	13	0	0	**127**
2007	123	6	2	0	**131**
2006	101	5	0	0	**106**
2005	80	1	1	0	**82**
2004	30	1	1	0	**32**

[20] CCMHPIE. China's Pharmaceutical Imports and Exports Continues to Expand between Jan. and May 2009. Collected and analyzed on July 2, 2009. Available at: http://www.cccmhpie.org.cn (in Chinese)
[21] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm#download

Table 7 lists the Chinese manufacturers with the greatest number of DMFs, as of the end of 1st quarter 2009.

TABLE 7: CHINESE MANFUACTURERS WITH MOST TYPE II ACTIVE DMF

Manufacturer	Number of DMFs
Zhejiang Hisun pharmaceutical Co. Ltd.	35
Zhejiang Huahai pharmaceutical Co. Ltd.	20
Chemwerth Inc.	17
ALP Pharm Beijing Co. Ltd.	16
Tai Heng Industry Co. Ltd.	10
Shandong New Time pharmaceutical Co. Ltd.	9
Polymed Therapeutics Inc.	8
Qilu Antibiotics Pharmaceutical Co. Ltd.	8
Zhejiang Jiuzhou Pharmaceutical Co. Ltd.	8
Chongqing Daxin Pharmaceutical Co. Ltd.	7
Tianjin Tianyao Pharmaceuticals Co. Ltd.	7
Chongqing Carelife Pharmaceutical Co. Ltd.	6
Qilu Tianhe Pharmaceutical Co. Ltd.	6
World Jiangsu Industry Co. Ltd.	6
Zhejiang Hisoar Pharmaceutical Co. Ltd. Chuannan Branch	6
Hubei Biocause Pharmaceutical Co. Ltd.	5
Jiangsu Hengrui Medicine Co. Ltd.	5
Shanghai Sunve Pharmaceutical Co. Ltd.	5
Zhejiang Hisoar Pharmaceutical Co. Ltd.	5
Zhejiang Supor Pharmaceuticals Co. Ltd.	5
Anqiu Luan Pharmaceutical Co. Ltd.	4
Axitec Co. Ltd.	4
Changzhou Pharmaceutical Factory	4
Chifeng Arker Pharmaceutical Technology Co. Ltd.	4
HEC Pharm Co.	4
Qilu Pharmaceutical Co. Ltd.	4
Shanghai Desano Chemical Pharmaceutical Co. Ltd.	4
Yangzhou Pharmaceutical Co. Ltd.	4
Zhejiang Neo Dankong Pharmaceutical Co. Ltd.	4

As of this writing, only one drug preparation product produced in China had been officially approved to enter the U.S. market. In June 2007, Zhejiang Huahai Pharmaceutical Co. became the first Chinese pharmaceutical manufacturer to receive FDA approval for a finished drug product (nevirapine). The company will be able to export its medicine to the U.S. after May 2012, when the U.S. patent held by Boehringer Ingelheim for the AIDS drug nevirapine expires.[22]

[22] 'U.S. Opens the Door to Chinese Pills' by Nicholas Zamiska, October 9, 2007 The Wall Street Journal

By comparison, China's big competitor, India, has held a total of 2,178 active DMFs by the end of the first quarter of 2009. Undoubtedly, India Pharmas have been taken the lead in DMF filings among all the foreign countries that seek entrance to the U.S. market.

Major Chinese API Exports to U.S.

After an analysis on the three-year (2006, 2007 and 2008) raw statistic data obtained from the China Customs, we summarized the top 50 API exports that China exported to U.S. during the period from January 1, 2006 to December 31, 2008. The ranking is based on exports revenue in US dollars. To clarify, API exports hereinafter refer to APIs, pharmaceutical intermediates and excipients.

TABLE 8: TOP 50 API PRODUCTS EXPORTED FROM CHINA TO U.S. (2006-2008)

Rank	Exports	Revenue (US$)	Quantity (kg)
1	Vitamin C and its derivatives	72,018,334	21,389,654
2	Vitamin E and its derivatives	49,664,853	9,127,062
3	Citric Acid	47,154,453	64,099,908
4	Tetracycline derivatives and salts	27,857,861	2,551,365
5	Heparin and salts	20,865,388	22,429
6	Vitamin B1 and its derivatives	19,462,504	1,328,905
7	Vitamin B6 and its derivatives	17,826,168	1,165,432
8	Vanillin(4-Hydroxy-3-methoxybenzaldehyde)	17,692,793	1,441,946
9	Vitamin A and its derivatives	16,469,392	1,266,660
10	Lincomycin and derivatives and their salts	12,851,888	89,678
11	Acetaminophen	12,405,396	3,423,406
12	Ibuprofen	11,026,973	1,279,585
13	Vitamin B2 and its derivatives	9,257,351	439,450
14	Vitamin B12 and its derivatives	8,608,481	149,270
15	Sulfadimidine	8,406,868	578,800
16	Lysine ester and salts	8,093,258	9,061,440
17	D or DL pantothenic acid and their derivatives	7,278,043	1,197,450
18	6-Aaminopenicillanic acid (6-APA)	6,118,825	291,800
19	Cortisone, hydrocortisone, etc.	6,098,617	15,318
20	Acetosalicylic acid (Aspirin)	5,904,119	2,267,214
21	Citric Acid salts and esters	5,871,963	6,637,592
22	Menthol	5,838,635	344,040
23	Gentamicin and derivatives and their salts	4,836,844	25,055
24	Inositol	4,458,520	628,855
25	Propylene glycol	3,572,280	1,713,866
26	Streptomycin and derivatives and their salts	2,620,208	131,528
27	Tetracycline salts	2,564,451	209,975
28	β-naphthol (2-naphthol)	2,551,260	1,415,616
29	Estrogen and progestogen	2,174,416	13,476
30	Sulfadiazine	2,146,306	535,025
31	Choline and salts	2,123,417	2,671,326
32	7-aminocephalosporanic acid (7-ADCA)	1,055,233	24,975

33	ProVitamins	1,010,761	46,881
34	Lecithin	844,535	185,233
35	Sulfamethoxazole	759,322	80,125
36	Pseudoenphedrine and salts	621,679	19,775
37	Mannitol	486,513	234,790
38	Erythromycin and derivatives and their salts	442,988	3,525
39	Lysine	399,535	427,400
40	Furazolidone	362,224	11,900
41	Nucleic acid and salts	358,362	16,519
42	Sorbitol	304,241	674,746
43	Dexamethasone	220,000	500
44	Theophylline, aminophylline and derivatives and their salts	159,280	11,325
45	alprazolam, camazepam and their salts	158,999	56,000
46	Ampicillin salts	158,360	7,440
47	Amoxicillin	135,700	5,700
48	Procaine	94,918	16,200
49	Kanamycin and derivatives and their salts	86,044	1,461
50	Ampicillin preparations	85,150	14,960

U.S. Market Penetration by Chinese-Sourced Ingredients

Many drugs are produced by genetic engineering methodologies such as recombinant DNA technology or liposomal drug delivery systems. Pharmaceutical preparations promoted to medical, dental professions are called “ethical” drugs, also known as prescription drugs. The top six classes of prescription drugs are: central nervous system and sense organs, cardiovascular; digestive and genitourinary; neoplasms (tumorigenic), endocrine and metabolic diseases; parasitic and infectious diseases, and respiratory. These classes of finished-form drugs commanded the highest profit margins (30% of sales was standard), but also demanded high R&D and marketing expenses – 15% and 20% of sales, respectively. Those preparations sold openly to the public are commonly described as “over-the-counter” (OTC) drugs.

OTC drugs or non-prescription drugs are sold directly to consumers without a prescription, and in general had high advertising and low research expenditures, and few are relatively new products. This situation typifies the past and current U.S.-China interdependence relationship driven by the pursuit of U.S. companies to boost output while lowering production and labor expenses. This report’s research analyses supports prior reports and trends that the U.S. relies quite heavily on Chinese suppliers for a number of imports of raw ingredients used in consumer OTC healthcare treatments, though a significant degree are also incorporated into U.S. drug prescription formulations.

For example, China is the global leader in the manufacturing of Acetaminophen - a widely used over-the-counter (OTC) analgesic (pain reliever) and antipyretic (fever reducer), commonly used for the relief of fever, headaches, and other minor aches and pains. Found in more than 100 OTC preparations, it is a major ingredient in numerous cold and flu remedies such as Tylenol, Contac, Benadryl, Excedrin, Sudafed, Theraflu; and also contained in prescribed Vicodin and Percocet (oxycodone with acetaminophen); Tylox capsules contains oxycodone HCL and acetaminophen; Oxycodone which is the primary ingredient of OxyContin, the 9th leading drug in sales for 2008 (~$2.5 Billion)[23]a time-release formula of oxycodone often compounded (or combined) with other ingredients such as acetaminophen. Acetaminophen was the11th highest API export to the U.S. market with an estimated value of just over $12.4M and ~3.42M kg in the period 2006-2008. During the period 2006 to 2008, Acetaminophen

[23] http://www.drugs.com, ‘Top 200 Drugs for 2008 by Sales

imported from China comprised ~50.3% (as shown in Figure 4) of all imported acetaminophen in the U.S. market.

Ibuprofen, the 12th leading API export to U.S. market (in revenue) is found in such products such as Vicoprofen, Advil (~$295.1 Million with a 14.9% market share, 2008 sales), Aleve (~$172.9 Million with a 8.31% market share, 2008 sales), Motrin 1B (~$78.9 Million with a 3.79% market share, 2008 sales), among others.[24] During 2006 to 2008, Ibuprofen imported from China comprised ~60.6% (as shown in Figure 4) of all imported ibuprofen product in the U.S. market.

Menthol, the 22nd leading API export to U.S. market (by revenue) is found in many ordinary consumer products in any neighborhood supermarket or drug store, such as Listerine mouthwash, Vicks VapoRub, Ben-Gay, Icy Hot topical applications, throat lozenges (or cough drops) such as Cepacol, Chloraseptic, Halls, Ricola, and Robitussin, and other products for common aches and colds. During 2006 to 2008, Menthol imported from China comprised ~11.4% (as shown in Figure 4) of all imported Menthol in the U.S. market.

Antibiotics a class of natural and synthetic medications used to treat bacterial of fungal infectious diseases, is also composed of Chinese raw materials. Tetracyclines are broad-spectrum antibiotics, which are protein synthesis inhibitors, which stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins. The most commonly prescribed tetracycline antibiotics are: tetracycline, doxycycline, minocycline, and oxytetracycline. Tetracycline derivative salts was the 4th major API export from China to the U.S.(in revenue), and made ~94.1% (as shown in Figure 4) of all imported Tetracycline derivative salts product in the U.S. market. Ampicillin, an antibiotic in the penicillin group of drugs, which targets the bacterial cell wall of the microbe, is also known by the trade name - Omnipen, to patients. Streptomycin derivative salts are also a top export to the U.S. market ranked 26th (in revenue), and commonly used to treat tuberculosis and infections caused by other bacteria. In the period 2006 to 2008, Streptomycin derivatives and salts imported from China comprised ~74% (as shown in Figure 4) of all imported streptomycin product in the U.S. market. Ampicillin salts and Ampicillin preparations are ranked 46th and 50th (in revenue) respectively of major Chinese API exports to the U.S. market. From 2006 to 2008, Ampicillin salts imported from China totaled roughly ~2.4% (as shown in Figure 4) of all imported ampicillin and salts product in the U.S. market. Penicillins had the largest market share (35%) of top Antibiotic brands in 2008. [25] It is believed that the Penicillin exports will continue to increase in the future.

For additional perspective on the degree of consumption of imported Chinese ingredients contained in many pharmaceutical products sold and consumed in the U.S., we selected a sample of raw materials, referencing import data (U.S. Census Bureau, Foreign Trade Division) of reported leading export API products from China during 2006 to 2008 (Table 8).

FIGURES 3A, 3B, 3C reports the estimated percentages by weight (KG) of Total U.S. imports in each year, comparing import data from both India and the European Union (EU) - excluding United Kingdom, respectively. As India is frequently acknowledged as an emerging exporter of drug-related ingredients and bulk chemicals to the U.S., we believed it was appropriate to include in our estimation analyses. Inclusion of the EU bloc provides additional insight on importation and consumption trends of certain ingredients for the U.S. market in relation to China.

[24] Market Share Reporter – 2009, 'Top Pain Relievers (Internal/Tablet), 2008'
[25] "Top Antibiotic Brands, 2008." Prescription Pad – November, J.P. Morgan, November 1, 2008, p. 25 from IMS America; Market Share Reporter 2010. Gale 2010

FIGURE 3A: Estimated percentage of U.S. market share held by API products imported from China, India, and the EU (out of total API imports by weight) in [2006].

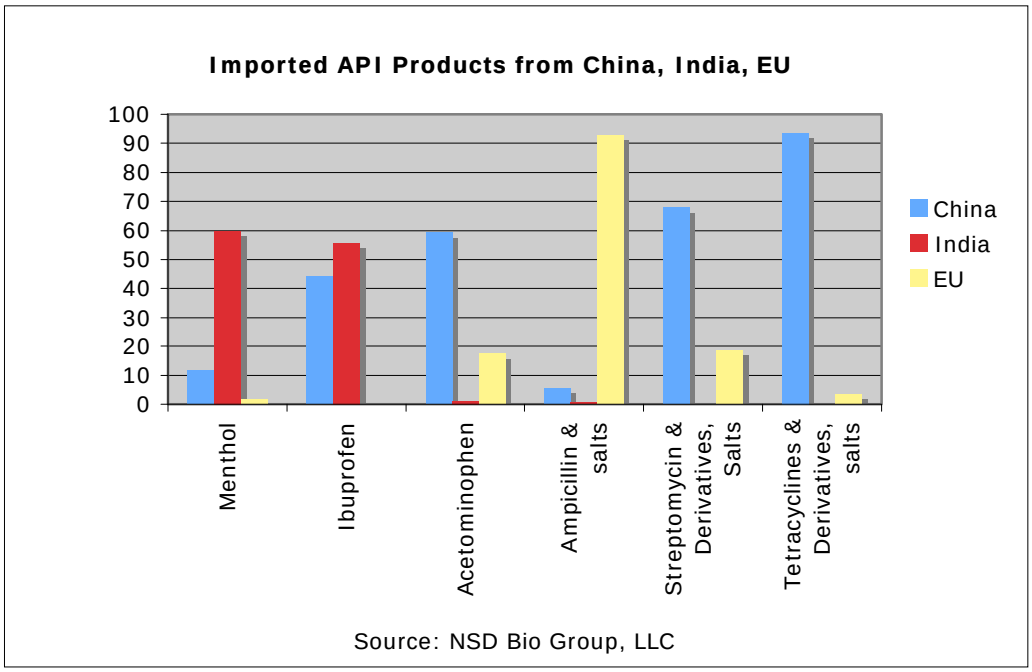


FIGURE 3B: Estimated percentage of U.S. market share held by API products imported from China, India, and the EU (out of total API imports by weight) in [2007].

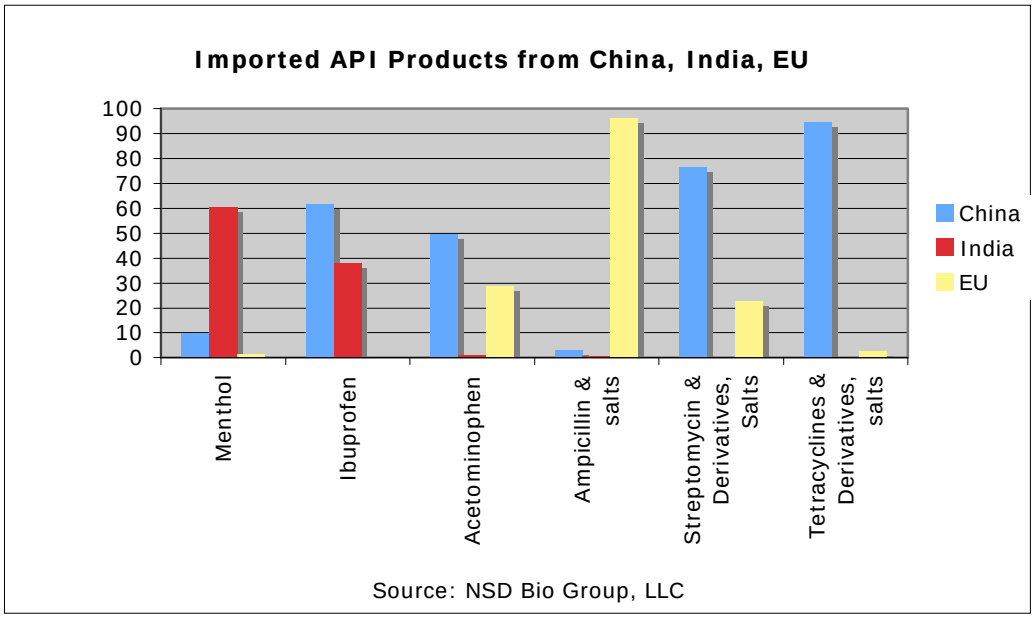


FIGURE 3C: Estimated percentage of U.S. market share held by API products imported from China, India, and the EU (out of total API imports by weight) in [2008].

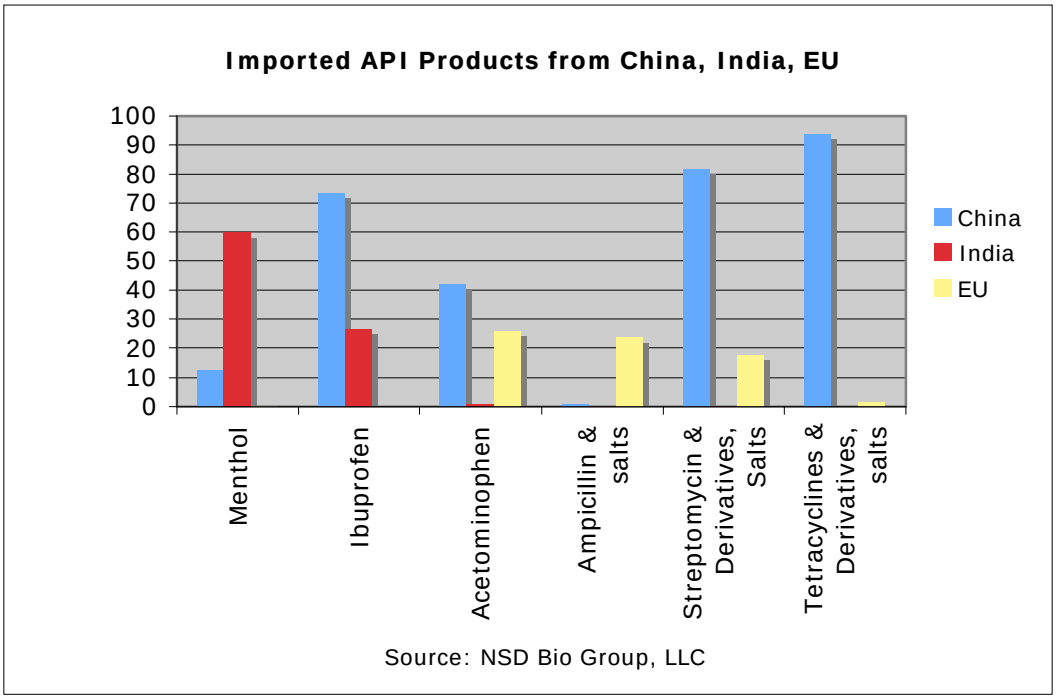
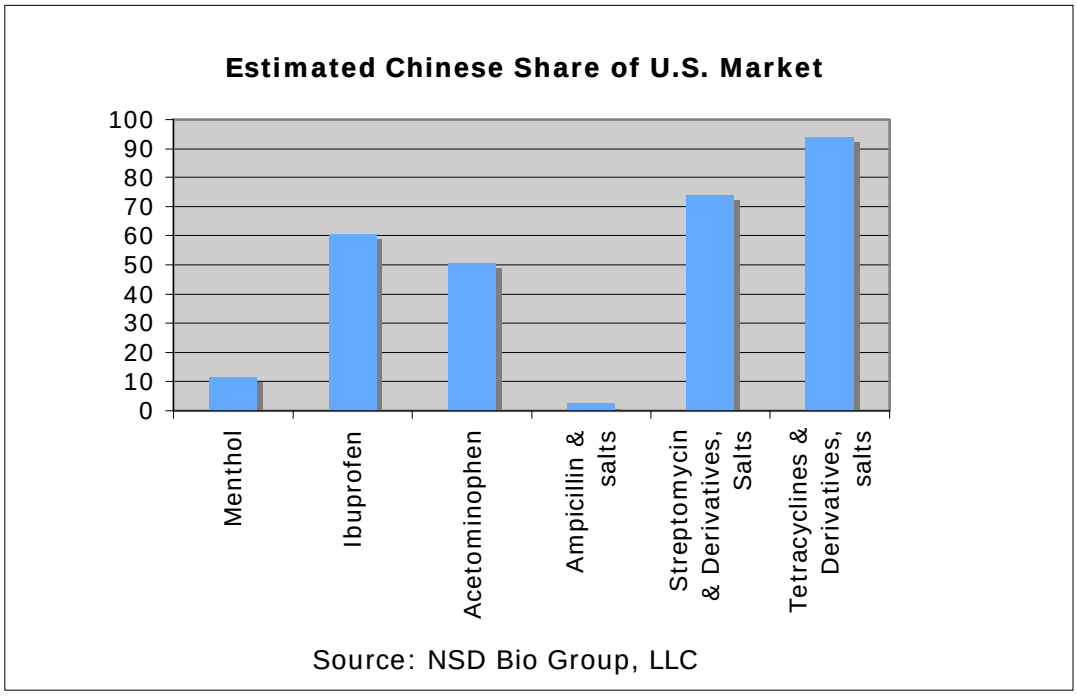


FIGURE 4 represents China's estimated market share by weight (KG) of selected raw ingredients imported by the U.S. during 2006 to 2008; Projected percentages were computed by utilizing U.S. import data (U.S. Census Bureau, Foreign Trade Division):



Major Chinese API Exporters/Manufacturers to U.S.

Also based on our research on the three-year data we obtained from China Customs, we summarize the top 25 Chinese pharmaceutical manufacturers by exports revenue in US dollars in Table 9.

TABLE 9: TOP 25 CHINESE API EXPORTERS/MANFUACTURERS (2006-2008)

	Company Name (in English and Chinese)	Revenue (US$)	Quantity (kg)
1	Zhejiang Medicine Co., Ltd. 浙江医药股份有限公司	46,724,830	2,724,034
2	Zhejiang NHU Co., Ltd. 浙江新和成股份有限公司	44,705,259	7,237,415
3	Northeast Pharmaceutical General Factory 东北制药总厂	33,630,370	8,699,270
4	Shandong Xinhua Pharmaceutical Co., Ltd. 山东新华制药股份有限公司	23,591,958	4,057,940
5	Anhui BBCA Biochemical Co., Ltd. 安徽丰原生物化学股份有限公司	19,196,892	26,388,744
6	CSPC Weisheng Pharmaceutical (Shijiazhuang) Co., Ltd. 维生药业(石家庄)有限公司	18,449,897	5,748,300
7	Aland (Jiangsu) Nutraceutical Co., Ltd. 江苏江山制药有限公司	14,084,043	4,004,800
8	Yixing Union Biochemical Co., Ltd. 宜兴协联生物化学有限公司	13,612,615	18,801,354
10	Yantai Dongcheng Biochemicals Co., Ltd. 烟台东诚生化有限公司	12,836,475	229,130
11	Zhejiang Tianxin Pharmaceutical Co., Ltd. 浙江天新医药化工有限公司	12,688,969	871,725
12	NCPC Heibei Welcome Pharmaceutical Co., Ltd. 河北维尔康制药有限公司	12,151,172	3,539,525
13	Zhejiang Shenghua Biok Biology Co.,Ltd. 浙江升华拜克生物股份有限公司	9,679,616	928,825
14	Hubei Guangji Pharmaceutical Co., Ltd. 湖北广济药业股份有限公司	8,457,799	407,200
15	Zhejiang Xinfu Pharmaceutical Co., Ltd. 浙江鑫富生化股份有限公司	8,170,526	1,289,000
16	Leshan Sanjiu Long March Pharmaceutical Co., Ltd. 乐山三九长征药业股份有限公司	7,787,345	722,539
17	Zhejiang Hisun Pharmaceutical Co., Ltd. 浙江海正化工股份有限公司	7,496,250	1,400,000
18	Shijiangzhuang Pharmaceutical Group I/E Co., Ltd. 石家庄制药集团进出口贸易有限公司	7,404,666	1,124,750
19	Zhejiang Kangle Pharmaceutical Co., Ltd. 浙江康乐药业有限公司	7,009,581	1,895,700
20	Zhejiang NHU I/E Co., Ltd. 浙江新和成进出口有限公司	6,943,838	247,527
21	Shanghai Sunve Pharmaceutical Co., Ltd. 上海三维制药有限公司	6,621,823	259,225
22	Ningbo Green-Health Pharmaceutical Co., Ltd. 宁波绿之健药业有限公司	5,858,069	91,726
23	Qianjiang Yongan Pharmaceutical Co., Ltd. 潜江永安药业有限公司	5,831,143	2,579,575

24	Shijiangzhuang Honghua Pharmaceutical Co., Ltd. 石家庄宏华药业有限公司	5,354,931	680,000
25	Fujian Fukang Pharmaceutical Co., Ltd. 福建省福抗药业股份有限公司	5,305,043	157,790

A brief profile of 5 major Chinese API manufacturers:

Zhejiang Medicine Co., Ltd.

Address: 268 Dengyun Road, Gongshu District, Hangzhou, Zhejiang Province, P. R. China 310011

Website: http://www.china-zmc.com

Overview:

Zhejiang Medicine Co., Ltd. (ZMC) was formed in May 1997 on the basis of the former Zhejiang Xinchang Pharmaceutical Co., Ltd. Zhejiang Xianju Pharmaceutical Co., Ltd., and Zhejiang Medical and Pharmaceutical Co., Ltd. ZMC went public on the Shanghai Stock Exchange Market (stock code: 600216) in August 1998. As of this reporting, ZMC has 2.5 B RMB of total assets, and is one of the leading pharmaceutical companies in China. The company ranked the 16th place by sales revenue in 2008 among the top 100 Chinese pharma manufacturers.

ZMC employs more than 4,000 people, and controls a few subsidiaries including Xinchang Pharma Factory, Vitamin C Factory, Zhejiang Medicine Trading Co.Ltd, Zhejiang Health Creation Biotech R&D Center.

Revenue & Profit:[26]

Year	Total Revenue		Net Profit	
	RMB million	US$ million	RMB million	US$ million
2008	3,761.03	550.06	972.63	142.25
2007	2,208.83	323.05	56.60	8.28
2006	2,196.50	321.24	60.62	8.87

Products:

ZMC produces large scale of vitamins and antibiotics such as Vitamin E, vancomycins, etc. 85% of ZMC's vitamin products are exported overseas. The API and pharma intermediates that ZMC produces and exports include:

- Vitamin E, Vitamin A, Vitamin D3 oil, multi-vitamins, vitamin intermediates.
- Teicoplanin
- Kitasamycin
- Sirolimus
- Miglitol
- Vancomycin HCL lyophilized
- Levoflfloxacin
- KF506 Tacarolimus
- Valglibose

[26] Source: Annual Financial Reports 2006-2008 officially released by ZMC

Exports to U.S.:

As the top Chinese pharma exporter, ZMC exported $46.72 M of API products to U.S. between 2006 and 2008, including the following:

- Vitamin E and derivatives
- Vitamin A and derivatives
- Other vitamins
- Vancomycin and other antibiotics

Quality System Certification:

- All production facilities received Chinese GMP certification
- Vancomycin production facility passed FDA inspection in December 2007.
- Lumefantrine facility passed Australia TGA inspection in July 2005.

U.S. Importers:

- E.M. Sergeant Pulp & Chemical Co., Inc.
- AGY-ENDO Corp. (based in Canada)
- AIDP Inc.

International Partners:

Novartis: ZMC signed a $25.89 M contract with Novartis in 2005 to supply Novartis lumefantrine to produce artemether between August 2005 and September 2006. Additionally, the two parties signed another $29.66 M lumefantrine contract in 2007.

Merck: ZMC is a domestic strategic partner of Merck.

Zhejiang NHU Co., Ltd.

Address: No. 4 JiangBei Road, Chengguan Town, Xinchang County, Zhejiang, P. R. China 312500

Website: http://www.cnhu.com

Overview:

Zhejiang NHU Co., Ltd. (NHU) was founded in November 1988 based on a restructuring of the former Xinchang Chemical Co., Ltd. In June 2004, NHU went public on the small-to-medium-sized enterprise section of the Shenzhen Stock Exchange Market, under the stock code of 002001.

By 2008, NHU had 3.72 B RMB of total assets and 3,400 employees. It controls several subsidiaries including Zhejiang Xindong Chemical Co., Ltd., Zhejiang NHU Imports & Exports Co., Ltd., Xinchang NHU Vitamin Co., Ltd., Xinchang Deli Petrochemical Equipment Co., Ltd., Zhejiang Asen Pharmaceutical Co., Ltd. and Anhui NHU Wannan Pharmaceutical Co., Ltd.

In an effort to promote and market NHU's products into U.S., NHU set up an affiliated company, China Vitamins LLC, in New Jersey, U.S., in 1998. China Vitamins LLC has been actively importing NHU's products to the U.S. market since that time.

Revenue & Profit:[27]

Year	Total Revenue		Net Profit	
	RMB million	US$ million	RMB million	US$ million
2008	3,313.96	484.67	1,374.51	201.03
2007	1,747.88	255.63	77.07	11.27
2006	1,589.09	232.41	28.95	4.23

Products:

Pharmaceutical Intermediates	**Bulk Pharmaceuticals**
Methylene Acetone	β-thymidine
Natural Methyheptenone	Vitamin E Nicotinate
Enynic Alcohol	Vitamin E Oil (crude oil)
Tocopherol	Vitamin E Oil (fine product)
Isophytol	Vitamin A Crystallization
Ethoxymethylenemalonic Diethyl Ester	Vitamin A Oil

Exports to U.S.:

As the No. 2 Chinese Pharma exporter, NHU exported a total of US$44.71 M worth of API products to U.S. between 2006 and 2008, including the following:

- Vitamin A
- Vitamin E
- Linalool
- Other quinines

Quality System Certification:

- All production facilities received Chinese GMP certification
- Passed ISO 9001 inspection in 1999.

U.S. Importers:

- ADM ALLIANCE NUTRITION OF PUERTO RICO LLC

[27] Source: Annual Financial Reports 2006-2008 officially released by NHC.

- BERIE INC.
- CHEMTEX USA INC.
- CHR OLESEN CO.INC.

Northeast Pharmaceutical General Factory (NPGF)

Address: 37 Zhong-gong-bei Street, Tiexi District, Shenyang, Liaoning Province, P. R. China 110026

Website: http://www.negpf.com.cn

Overview:

Established in 1946, Northeast Pharmaceutical General Factory (NPGF) is a large-scale pharmaceutical manufacturer in China and one of the oldest pharmaceutical manufacturers based in Northern China. It is the core subsidiary of Northeast Pharmaceutical Group Co., Ltd. (NPGC), a public listed company on the Shenzhen Stock Exchange Market (stock code: 000597). In 2008, NPGC ranked 15th among the top 100 Chinese pharmaceutical manufacturers. Its total assets reached 4.10 B RMB by 2008.

NPGF specializes in producing chemical synthetic medicines and biological fermented medicines. The Factory employs over 6,000 people and is capable of manufacturing over 30,000 tons of bulk pharmaceuticals annually.

Revenue and Profit:[28]

Year	Total Revenue		Net Profit	
	RMB million	US$ million	RMB million	US$ million
2008	4,609.77	674.19	357.91	52.38
2007	3,706.07	542.42	47.52	6.95
2006	1,918.24	280.75	19.63	2.87

Products:

NPGF primarily produces both bulk and finished series products of vitamin C, phosphonomycin, levocarnitine, cephalosporin, sulfadiazine, berberine, and vitamin B1, among others. Besides China, the factory's products have been sold to over 70 countries, generating over $150 M exporting sales annually.

NPGF ranked first place in vitamin C exports to U.S. during 2006 and 2008. Based on the statistic data retrieved and analyzed from China Customs, from January 2006 to December 2008, the factory exported a total of 8.167 tons (worth $2.672 M) of bulk vitamin C, and 359,020 kilograms of vitamin B1 (worth $5. 051 M) to the U.S.

Accordingly, NPGF has the world's largest single vitamin C production line. Sales of certain products such as sodium phosphonomycin, vitamin B1, sulfadiazine, and levocarnitine, ranked third on a global scale.

Exports to U.S.:

[28] Source: Annual Financial Reports 2006-2008 officially released by NPGC

NPGF exported to a total of $44.71 M of API products to U.S. between 2006 and 2008, including the following:

- Vitamin B1, C, etc.
- Other amino acids
- Sulfadiazine
- Chloramphenicol, its derivatives and salts

Quality System Certification:

- All production facilities have been granted Chinese GMP certifications
- Sulfadiazine and Piracetam granted European COS certificate
- Sucralfate, Amantadine, Rimantadine passed U.S. FDA inspection.
- Levocarnitine passed Japanese certification in July 2009.

U.S. Importers:

- Atlantic Chemicals Trading
- Premium Ingredients, International
- AIDP

International Partners:

- Atlantic Chemicals Trading GMBH
- Premium Ingredients, International
- BASF Corp.
- Kraemer & Martin GMBH

Shandong Xinhua Pharmaceutical Co., Ltd.

Address: Zibo High-tech Development Zone, Zibo, Shandong, P. R. China 255005

Website: http://www.xhzy.com

Overview:

Shandong Xinhua Pharmaceutical Co., Ltd. (Xinhua Pharm) was established in 1993 through restructuring the former state-owned Shandong Xinhua Pharmaceutical Factory, which was initially founded in 1943. Xiahua Pharm is also a public listed company on the Shenzhen Stock Exchange Market (Stock code: 000756) since 1997.

Xinhua Pharm had 2.16 B RMB in total assets and employed nearly 5,000 people by 2008.

Revenue & Profit:[29]

[29] Source: Annual Financial Reports 2006-2008 officially released by Xinhua Pharm.

Year	Total Revenue		Net Profit	
	RMB million	US$ million	RMB million	US$ million
2008	2,096.96	306.91	33.97	4.97
2007	1,886.98	276.18	32.72	4.79
2006	1,667.25	244.02	22.71	3.32

Products:

NAME	DMF/COS/FDA
Acetylsalicylic Acid	DMF/COS/FDA
Refined Acetylsalicylic Acid	DMF/COS
DC-90Acetylsalicylic Acid	DMF.
Analgin	EDMF
	EDMF/COS
Analgin-dc90	DMF
Metamizole Magnesium	DMF
Trimethoprim	DMF
	DMF/COS
Propyphenazone	DMF
	DMF/COS
Caffeine Anhydrous	DMF/COS
Theophylline Anhydrous	DMF/COS/FDA
Calcium Theophylline	DMF
Aminophylline Anhydrous	DMF
Phenazone(Antipyrine)	DMF/COS
Amidopyrine	DMF
Hydrocortisone Base Mic.	DMF/FDA
Hydrocortisone Acetate Mic.	DMF
Ibuprofen	DMF/FDA/COS
Pipemidic Acid Trihydrate	DMF
Pipemidic Acid Anhydrous	DMF
Amidopyrine	DMF
Clidamycin Phosphate	DMF

Exports to U.S.:

Xinhua Pharm exported a total of $23.59 M of API products to U.S. between 2006 and 2008, including the following:

- Aspirin

- Isoprofen
- Cortisone, hydrocortisone, deltacortisone, etc.
- Caffeine and salts
- Crylic acid and its salts

Quality System Certification:

- All production facilities have been granted Chinese GMP certifications
- The table in the Product section has listed all the international certifications that Xinhua has received.

U.S. Importers:

- PEPSI BEVERAGES INTERNATIONAL
- AF PHARMA LLC
- EAST WEST TECHNOLOGIES INC
- ROCHEM INTERNATIONAL INC.

Zhejiang Hisun Pharmaceutical Co., Ltd.

Address: 46 Waisha Road Jiaojiang District, Taizhou City Zhejiang Province, P.R. China 318000

Website: http://www.hisunpharm.com

Overview:

Founded in 1956, Zhejiang Hisun is one of the leading API manufacturers in China with significant overseas contract manufacturing experience with Western firms. The company became a public-listed company (SSX: 600267) on China's Shanghai Stock Exchange Market in 2000, with 449 M RMB ($65 M) registered capital. Hisun currently employs 3,660 people, including 1200 technicians or engineers, 400 researchers, and 1560 production workers.

Products and Exports:

Hisun produces API, chemical intermediates, finished pharmaceuticals, biologics, traditional Chinese medicines, and excipients. 80% of Hisun's API products are exported to 30 countries, with a special focus on Europe and North America. It is estimated that Hisun-made anti-tumor API exports have occupied 60% of the generic API market in U.S. Hisun's lipid lowering statin products, ranks second, internationally in terms of production size, and has a 33.33% market share of the global market.[30]

Hisun started regulatory registration in U.S. and European market in 1989 and received its first FDA approval in 1992. The company has filed 37 active DMF with FDA by Q1 2009. Hisun received and passed a total of 10 times of FDA on-site inspection by 2008.

At the time of analysis, Hisun had 18 API products, having received FDA approval through Abbreviated New Drug Applications, 14 API products, which have received the European CEP certificate (Certificate

[30] Xu, Congyu. Innovation, Internationalization and Social Responsibilities—Secrets of Hisun's Continuous Expansion. Observation and Thinking. Jan. 2009 (in Chinese)

of Suitability to Monograph of European Pharmacopoeia), and 1 API product receiving Australia TGA certification.

FDA (U.S.) Approved (18)

- Acarbose
- Epirubicin HCL (Crystallized)
- Cytarabine
- Doxorubicin HCl
- Fludarabine
- Sulbactam sodium
- Bleomycin Sulfate
- Mitomycin C
- Simvastatin
- Vinorelbine Tartrate
- Floxuridine
- Daunorubicin HCl
- Granisetron HCL
- Adenosine
- Bleomycin A_2/B_2 crude
- Epirubicin HCL (Lyophilized)
- Cladrabine
- Ivermectin

COS (Europe) Approved (14)

- Acarbose
- Lovastatin
- Ivermectin
- Fludarabine phosphate
- Simvastatin
- Epirubicin HCL(Crystallized)
- Vinorelbine Tartrate
- Pravastatin Sodium (Crystallized)
- Doxorubicin HCL
- Mitomycim
- Cytarabine
- Granisetron HCL
- Praziquantel
- Bleomycin Sulfate

Quality System Certification:

Hisun's quality control system is very close to advanced level internationally. The company has passed the following inspections:

- 18 inspections by Chinese SFDA
- 10 inspections by U.S FDA
- 1inspection by EU EDQM
- 1 inspection by U.K MHRA
- inspections by German FHH
- inspections by Australia TGA
- 2 inspections by Japanese PMDA
- 1 inspection by Korea KFDA
- ISO9001: 2000 certification

Revenue & Profit:[31]

Year	Total Revenue		Net Profit	
	RMB million	US$ million	RMB million	US$ million
2008	3,181.98	465.71	199.91	29.26
2007	2,838.77	415.48	149.03	21.82

[31] Source: Official Annual Financial Reports released by Hisun to shareholders.

2006	2,311.51	338.31	83.62	12.24

International Partners:

Hisun has established solid business relationships with many pharmaceutical giants, such as Eli Lilly, Merck, Novartis, Bayer, and Amgen.

Eli Lilly: In June 2003, Eli Lilly announced a $70 M partnership with the WHO; the U.S. Department of Health and Human Services´ Centers for Disease Control and Prevention (CDC); and other entities. The goal of the partnership is to increase the supply and proper use of capreomycin and cycloserine, support efforts to enhance disease surveillance and healthcare worker training, and transfer proprietary Lilly manufacturing technology to countries where the MDR-TB is most prevalent. Lilly therefore signed technology transfer agreements with companies in several developing countries, and Zhejiang Hisun was selected as one of Lilly's global partners. In August 2005, Eli Lilly officially signed an agreement with Hisun to transfer the Capreomycin API manufacturing technology to Hisun. Eli Lilly has injected $4.38 M into the project for a four-year term. Meanwhile, Lilly has invested more than RMB 100 M ($14.27 M) into the project, including improving the technology and expanding production capacity. Lilly will sell Hisun-produced capreomycin APIs and later, preparations, on the global market. Hisun will sell the products in China. The new production base, which should be completed in 2010, will be used to produce between 3 to 5 million doses of lyophilized powder for injection every year.

Recent Case Studies of Drug Safety Incidents

Bogus or substandard medicines have been harming Chinese drug consumers for decades. From the notorious “Jinjiang major fake-drug case” in the early 1980s, to the infamous “Qiqihar No. 2 Pharma fake drugs” and “Xinfu substandard drugs” incidents in 2006, numerous innocent Chinese citizens have been injured or even killed by counterfeit or substandard medications supplied by domestic pharmaceutical companies.

Back in the early 1980s, the “Jinjiang major fake-drug case” represented an organized, large-scale fake drug production and distribution crime enterprise. Up to 46 factories were opened between 1983 and 1985 in a medium-sized town in Jinjiang, Fujian Province, producing fake traditional Chinese herbal medicines in order to realize high profits. These factories used inexpensive edible substances such as white fungus to produce fake herbal medicines. The fake medicines were sold to many provinces in China and generated millions of RMB of illegal profits for the factories.

In the past five years, particularly in 2006, three major drug-quality-related incidents killed dozens and sickened hundreds of patients in China: the Xinfun clindamycin substandard drug adverse event, the Qiqihar counterfeit Armillarisin A injections incident and the Yu Xing Cao Injection adverse event. As a result, China’s drug regulators and responsible manufacturers received overwhelming condemnations from the Chinese public. The entire country questioned Chinese drug authorities through public media, “Why have our human bodies become live test samples for pharmaceutical products? When will fake or inferior drugs disappear in China?” The incidents thereafter instigated serious debate on drug safety enforcement within the Central Chinese government in subsequent years.

The above-mentioned drug safety accidents revealed loopholes in China’s drug safety surveillance and legitimate enforcement and compliance requiremnents. They also revealed many existing gaps in the Chinese healthcare sector, such as abuse of antibiotics, unhealthy competition between pharmaceutical companies, commercial bribery, and corruptions and/or neglect of duty of drug-bidding officials. In addition, these incidents suggested that Chinese pharmaceutical manufacturers have a long way to go to improve their quality assurance system in accordance with international standards.

Chinese drug regulators and authorities continue to face a long and arduous journey to combat against counterfeit or inferior-quality pharmaceutical products. The good news is that Chinese authorities are making efforts to improve the image of “made-in-China” pharmaceutical products, both home and abroad. For example as reported earlier in this report, the SFDA is working with U.S. FDA to establish a more effective and efficient system to enhance the drug safety of Chinese pharmaceuticals.

Xinfu Clindamycin Injections (2006)

Fact: *Death: 11 Injured: 400*

Clindamycin Phosphate Glucose Injection under the brand name of “Xinfu” was manufactured by Anhui Huayuan Biopharmaceutical Co.,Ltd. (Anhui Huayuan). Founded in 1970, the company is located in Fuyang, Anhui Province in South China. Huayuan was a subsidiary of Shanghai Worldbest (Huayuan) Co., Ltd. (Stock code: 600094), a public listed company on the Shanghai Stock Exchange Market.

All three injection production facilities of Anhui Huayuan passed GMP inspection conducted by SFDA in 1999 and 2002. The facilities received production approval to produce Xinfu from the SFDA in 2001 (Approval No. H20010813).

Between July and August 2006, Xinfu injections caused 11 deaths and put hundreds of peoples’ lives in danger in several provinces in China such as Qinghai, Guangxi, Zhejiang, Heilongjiang, and Shandong. The cause of these adverse events identified by the SFDA was a bacterial infection during the production process. Below is a review of this incident.

July 27, 2006: SFDA first received ADR reports from Qinghai Provincial FDA, associated with Clindamycin Injection under the brand name of "Xinfu" produced by Anhui Huayuan. Patients receiving Xinfu injections developed clinical symptoms such as chest distress, palpitation, shivering, stomach pain, diarrhea, nausea, vomiting, allergic shock, and liver and kidney damage. Similar ADR reports were received from other provinces.

July 28, 2006: SFDA sent three investigation teams to Qinghai Province and Anhui Huayuan.

Aug. 1, 2006 Production of Xinfu was suspended.

Aug. 3, 2006 Anhui Huayuan Pharma stopped all production activities.

Aug. 4, 2006 SFDA suspended production of Xinfu products. SFDA also announced and monitored nationwide recall of Xinfu by Anhui Huayuan.

Aug. 11, 2006 SFDA confirmed that the cause of the incident was that the manufacturer violated GMP requirements by failing to follow the correct disinfection procedures. According to the production manual, the injections are required to go through 30 minutes disinfection process under 105^{O}C. However, Xinfu only received 1 to 4 minutes of disinfection under 100-104 ^{O}C.

Aug. 15, 2006 SFDA officially released "Investigation Results of Adverse Drug Events Induced by Anhui Huayuan-produced Xinfu injections". Between June and July 2006, Anhui Huayuan supplied 3.7 million of Xinfu products and 3.19 million units had been distributed to 26 provinces across China. SFDA recalled and suspended 2.3 million of Xinfu injection units by Aug. 14, 2006.

Sep. 31, 2006 The CEO of Anhui Huayuan committed suicide under the pressure of being arrested and bankruptcy.

Oct. 16, 2006 SFDA concluded that Xinfu belonged to the "substandard drug" category, in accordance with China's Drug Administration Law. SFDA sanctions included the following:

- Anhui Provincial Food and Drug Administration (Anhui FDA) was authorized to confiscate all the proceeds from Xinfu sales and imposed a two time fine based on the sales proceeds.
- Anhui FDA was authorized to suspend all production activities of Anhui Huayuan and revoke the GMP certificate of Huayuan and the production approval of Xinfu.
- Anhui FDA was authorized to supervise the destruction of all recall "Xinfu" products.
- Several senior executives of Anhui Huayuan and officials of Anhui Fuyang FDA received "administrative disciplinary penalties".

Discussion:

Xinfu injections caused 11 deaths and put hundreds of Chinese citizens in significant peril to their health. SFDA concluded that Xinfu was a "substandard drug" and the persons responsible for the crime received "administrative penalties", instead of "criminal charges" as expected and warranted. The CEO of Anhui Huayuan committed suicide before being arrested.

Qiqihar Counterfeit Armillarisin A Injections (2006)

***Fact**: Death: 14 Injured: 20-50*

Qiqihar No. 2 Pharmaceutical Co., Ltd. (Qiqihar No. 2 Pharma) was a medium-size pharmaceutical manufacturer in Qiqihar, Heilongjiang Province in Northern China. The company was initially a collective of group-owned companies before merging into the Heilong Group. In September 2005, the company was acquired by Beijing Dongshengyuan Investment Co. for 14.42 M RMB. Qiqihar No. 2 Pharma invested 30 M RMB to meet Chinese GMP requirements and passed GMP inspection in 2002.

Armillarisin A is mainly administered as an injection to treat acute or chronic cholecystitis and chronic and atrophic gastritis. However, in 2006, Armillarisin A Injection produced by Qiqihar No. 2 Pharma caused 11 deaths in Guangdong Province and dozens of adverse drug events in China. The causative factor of the disaster was the choice of a substitute for propylene glycol as excipients for the production of the Armillarisni A Injection. However in September 2005, the manufacturer purchased fake propylene glycol, which was actually toxic diglycol. The poisonous diglycol caused acute kidney failure for patients receiving Armillarisin A.

March 2006 Thanks to its "competitive price", Qiqihar's Armillarisin A Injection defeated other competitors and won the collective drug bidding offered by Guangdong Province-affiliated hospitals, and therefore was the universal Armillarisin A Injection to all the provincial-level hospitals. The Third Affiliated Hospital of Sun Yat-sen University in Guangzhou (capital of Guangdong Province) was the first hospital to purchase Qiqihar No.2 Pharma's Armillarisin A Injection.

April 22-30, 2006 64 patients in the Third Affiliated Hospital of Sun Yat-sen University received Armillarisin A Injection. Several patients with severe hepatitis developed kidney failure. After a specialist team meeting and diagnosis, collected evidence pointed to one of the medications the patients received: Armillarisin A Injection produced by Qiqihar No. 2 Pharma. The hospital therefore reported the serious ADR to the Guangdong FDA and Provincial ADR Monitoring Center. Guangdong FDA notified all hospitals in the province to stop using Armilarisin A Injection. Meanwhile, Guangdong Provincial Drug Control Institute was assigned to conduct analysis on the product samples.

May 3, 2006 Guangdong FDA reported the serious ADRs to the SFDA. The SFDA immediately authorized Heilongjiang FDA to suspend production and distribution of the Armillarisin A Injection in Qiqihar No. 2 Pharma.

May 9, 2006 SFDA issued an urgent nationwide warning on Armillarisin A Injection and an edict for a nationwide suspension using of the product.

May 12, 2006 SFDA issued an urgent notice calling for a nationwide suspension on the distribution of counterfeit Armillarisin A Injection supplied by Qiqihar No. 2 Pharma.

May 14, 2006 Qiqihar Municipal Government released investigation results:

- The cause of the accident was Qiqihar No. 2 Pharma's purchase of a fake pharmaceutical excipient, propylene glycol, used in production of Armillarisin A Injection.
- The fake propylene glycol was actually diglycol, a toxic industrial solvent, whose price is one half of propylene glycol. The alleged chemical dealer, Mr. Guiping Wang, forged many licenses, including his business license, drug registration and manufacturing licenses to sell products to pharmaceutical companies.

- Wang allegedly sold one ton of diglycol, claiming it was "propylene glycol", in the name of the Taixing General Chemical Plant in the eastern Jiangsu Province to a pharmaceutical company in Heilongjiang Province.

- Qiqihar No. 2 Pharma failed to test propylene glycol for the counterfeit "propylene glycol" as required under SFDA regulations before buying the chemical, nor did it crosscheck the licenses provided by Guiping Wang.

- Wang arrested by the police.

May 18, 2006 SFDA officially issued an announcement stating Qiqihar No. 2 Pharma had been producing and marketing “counterfeit drug products”. SFDA therefore authorized the Heilongjiang FDA to revoke the production license and GMP certificate of Qiqihar No. 2 Pharma.

May 22, 2006 Prime Minister Jiabao Wen issued an order to “thoroughly investigate the Qiqihar No. 2 Pharma counterfeit drugs.”

May 24, 2006 SFDA issued an urgent notice (SFDA 2006, No. 9) calling for a nationwide enforcement on drug safety surveillance involved in the drug supply chain, from research, production, distribution and prescription of the drug.

July 19, 2006 Prime Minister Jiabao Wen, chaired a State Council Meeting, which focused on enforcing harsh punishment on the 21 responsible persons associated with the accident.

April 29, 2008 Five key executives at Qiqihar No. 2 Pharma were sentenced 4 to 7 years in prison by Guangzhou Intermediate People’s Court, on charges of “Negligently Causing Serious Accident Crime”.

Chuanhua Zhu	Vice General Manager	7 years in prison
Guifeng Chen	Supervisor of Assay Lab	6 years in prison
Zhongren Niu	Purchaser	5.5 years in prison
Xingping Guo	Vice General Manager	4 years in prison
Jiade Yin	General Manager	4 years in prison

Sep 8, 2008 Guiping Wang, the illegal chemical dealer, was sentenced to life imprisonment and a fine of 400,000 RMB by Jiangsu Provincial Supreme People’s Court.

Discussion:

Qiqihar No.2 Pharma’s counterfeit Armillarisin A Injection was responsible for 14 deaths in Guangdong Province between 2006 and 2008. This incident exposed flaws in China’s drug administration and business licensing administration infrastructure. It shocked the Chinese community as well as the international community that a business man, Mr. Guiping Wang was successfully able to forge basically “everything” -- from his business license, pharmaceutical production license, to the pharmaceutical approval certificate, and was eventually able to sell fake pharmaceutical excipients - diglycol as propylene glycol to the Qiqihar No. 2 Pharma. It was also unbelievable that Qiquhar No. 2 Pharma, an official GMP-pharmaceutical manufacturer certified by the SFDA, could fail to test their purchased excipients according to GMP standards. Quality control supervisors at Qiqihar No. 2 Pharma did a basic test of the fake propylene glycol and were aware that its relative density “did not meet the requirements”. However, they failed to do a further analysis and “passed” the fake excipient forward to production of Armillarisin A Injections.

Perhaps what the Vice General Manager confessed to the Guangzhou Intermediate Court helped explain everything. Xingping Guo, the Vice GM at Qiqihar No. 2, declared that, "we actually **bought** the GMP certificate for 100,000 RMB."[32]

Shanghai Hualian Major Drug Production Quality Accident (2007)

***Fact**: Death: 0 Injured: 130*

Shanghai Hualian Pharmaceutical Factory (Shanghai Hualian) was a Shanghai-based state-owned company with a "solid reputation" and over 60 years of history. The company was acquired by Shanghai Pharmaceutical (Group) Co. Ltd., at one time one of the leading state-owned pharmaceutical enterprises in China. Some of Shanghai Hualian's products had a 50% share of the domestic market. With more than 4,000 employees, Hualian produced over 100 medicines including Methotrexate, Cytarabine, and Vincristine Sulfate, used via intravenous infusion for use in various types of cancer chemotherapy regimens.

During July and August 2007, Shanghai Hualiang's substandard Methotrexate and Cytarabine injections, tainted by Vincristine Sulfate, disabled 130 leukemia patients and sickened nearly 200 patients across China.

July-Aug., 2007	National ADR Monitoring Center received ADR reports from Shanghai, Guangxi, Beijing, Anhui, Hebei, and Henan Province, indicating that some leukemia patients developed peripheral neuropathy such as walking with difficulty, after receiving intrathecal injections of Methotrexate and Cytarabine produced by Shanghai Hualian.
Sep.14, 2007	SFDA and Ministry of Health co-issued a nationwide announcement calling for immediate suspension of any production, sales, and usage of Methotrexate and Cytarabine injections produced by Shanghai Hualian. SFDA also confirmed that small amounts of Vincristine Sulfate were detected in some batches of Methotrexate and Cytarabine injections manufactured by Shanghai Hualian, which had caused the neuropathological adverse events. Shanghai Police were called to investigate.
Dec.13, 2007	SFDA revoked the production license of Shanghai Hualian and confiscated all of the factory's illegal proceeds (80,000 RMB) from the sales of these medicines. SFDA also imposed the highest penalty based on Drug Administration Law, which totaled 1.16 M RMB. The police detained the managers who were found hiding information when the government was investigating their products. Shanghai Municipal Government also requested Shanghai Pharma Group to establish a compensation team to handle compensation issues for the victims.
March 28, 2008	SFDA cancelled all the drug approval numbers issued to Shanghai Hualian.

Discussion:

Shanghai Hualian was a reputable state-owned pharmaceutical manufacturer with 60 years of history. Methotrexate Injection is a cheap medicine priced at 6.07 RMB per dose of injection, and most Chinese manufacturers elect not to produce this product because of the low margins. Therefore, Hualian was assigned to produce methotrexate raw materials and preparations by the government. To reduce the production cost, the company used the same production line for different products, which is acceptable if they adhere the cleaning procedures, as part of their corporate quality control program. However, Hualian exercised gross negligence in the thorough cleaning of production lines. Therefore, Methotrexate and Cytarabine injections were contaminated from the Vincristine Sulfate residue.

[32] Xin Kua Bao (News Express). Qiqihar No. 2 Pharma's GMP Certificate was purchased for 100,000 RMB. August 9, 2007. Available at: http://epaper.xkb.com.cn/view.php?id=113856 (in Chinese)

Dalian Jingang-Andi Counterfeit Rabies Vaccines (2009)

***Fact**: Death: 0 Injured: 0*

Dalian Jingang-Andi Bio-products Co., Ltd. (Jiangang-Andi) was a medium-sized biopharmaceutical company based in Dalian, Changchun Province in Northeastern China. The company had been focusing on developing and producing vaccine products since 2002. Jingang-Andi's rabies vaccines had a solid domestic market share until the company added some illegal substance into the vaccine to "improve the efficiency of the vaccines."

In January 2009, the National Institute for Control of Pharmaceutical and Biological Products (NICPBP) randomly tested rabies vaccine samples produced by Jingang-Andi for monitoring purpose. After a lab analysis, NICPBP scientists identified the content of nucleic acid in the vaccine samples. Although nucleic acid has been confirmed by animal tests that it can serve as an adjuvant to increase the effect of animal vaccines, its effect on human-use vaccines still needs to be further examined and approved through human clinical tests. Whether nucleic acid can be used as an adjuvant to improve human vaccines is still being determined, as first stage clinical trials are being conducted. Jingang-Andi illegally added nucleic acid to its rabies vaccine products. According to China's Drug Administration Law, Jingang-Andi's behavior is considered illegal for producing counterfeit medicines deliberately.

In February 2009, SFDA recalled all 3.389 million doses of rabies vaccines produced by Jingang-Andi in 2008, and revoked the production license and GMP certificate of the company. Dalian FDA imposed a penalty equivalent to three times sales proceeds to the company. The three individuals most responsible for this criminal activity, the General Manager, Vice General Manager, and the Purchaser for the company, were detained by the police.

To note, no adverse drug reports were received related to the counterfeit rabies vaccines.

Other Examples of Tainted, Unsafe Drug Distribution and Use

1. Jiangsu Fake Human Albumin Injections and Rabies Vaccine cases

   In 2008, Jiangsu Province in east China cracked down on 10 major fake-drug cases, including two cases linked to fake human albumin injection and rabies vaccines. Other eight cases were associated with counterfeit eye drops, the distribution of bogus pharmaceuticals through the national postal system, and fake "Gran" (rh-G-CSF),

   During 2007 and 2008, four people in Jiangsu Province were killed and dozens were sickened after receiving bogus human albumin injections and rabies vaccines. These incidences were caused by two separate groups of fake-drug producers and distributors in Nantong and Wuxi City in Jiangsu. Several rural physicians were also involved in selling these fake medicines. Astonishingly, the fake albumin injections were filled with tap water, which contained zero therapeutics (human albumin). Over 10,000 doses of fake human albumin injections were identified and confiscated. The mastermind was given suspended death sentence and her associates were sentenced 14 to 17 years' imprisonment.

2. Hubei-based Large-scale Fake Medicines in 2009

   In May 2009, the Beijing FDA in partnership with Beijing Police, cracked down on a large fake medicine case originated from Hubei Province. 149 people were detained and 10 production and distribution facilities and offices were shut down. 120 types (10 tons) of bogus medicines, mostly traditional Chinese medicine pills, and many production facilities, in addition to ten vehicles were confiscated by the police. The mastermind, Bing Li and Zhiguo Li, was based in Hubei Province. Records showed that these fake medicines had been sold to more than 17,000 people across China. They even posted advertisements and used some official healthcare organizations to advertise their fake medicines.

Brief Overview of Australian Regulatory System

The Department of Health and Aging, Therapeutic Goods Administration implements the Therapeutic Goods Act of 1989 (the "Act") which requires that the standard of manufacture, and quality control of therapeutic goods manufactured outside Australia, be taken into consideration for the registration or listing of those therapeutic goods [33] on the Australian Register of Therapeutic Goods (ARTG), unless the goods are exempt [34]from this requirement by the Act.

A sponsor applying to the Therapeutic Goods Administration (TGA) for registration or listing of a therapeutic good manufactured outside Australia, in the absence of a TGA audit, must provide an acceptable form of evidence to show that the manufacture of the goods is of an acceptable standard. [35] This is referred to as Good Manufacturing Practice (GMP) clearance of overseas manufacturers.

Sponsors of therapeutic goods manufactured outside Australia must obtain GMP Clearance for the overseas manufacturer(s) before the goods are entered on the Australian Register for Therapeutic Goods (ARTG). Sponsors must ensure that current GMP documentary evidence is retained thereafter. It is a standard condition of registration, or listing, to provide this evidence when requested. Failure to supply this information is likely to result in the product's registration/listing being cancelled.

The TGA reserves the right to conduct an audit [36] (inspection) of any overseas manufacturer, irrespective of the documentary GMP evidence submitted to the TGA, even if there is a current GMP Clearance. In addition to the information outlined below, the TGA also reserves the right to request additional documents for the assessment of the GMP Clearance application.

Australia participates in several international arrangements including with various countries, including the United States. The TGA has an agreement with the US FDA that provides for the exchange of information in relation to manufacturers for regulatory purposes. However the TGA does not automatically grant a GMP Clearance to Sponsors of US manufacturers inspected by the US FDA.

GMP Clearance Process for Overseas Manufacturers

To apply for a GMP Clearance of an overseas manufacturer, sponsors must complete an electronic Overseas Manufacturer Clearance Application via the Manufacturers Information System (MIS)[37] for each manufacturing site, and pay the applicable fee. If available in electronic form, the Sponsor may attach the relevant documentary evidence of the manufacturing standard to the MIS application.

An Australian Sponsor must demonstrate that the overseas manufacturers, from which they source medicines and API, comply with the standard equivalent to that expected for Licensed Australian manufacturers. In these instances, the acceptable standards are the Australian Codes of GMP for Medicinal Products or API.

[33] Therapeutic Goods Act 1989 Subsections 25(1)(g), 26(1)(g), 26A(3)
[34] Therapeutic Goods Act 1989 Subsections 25(2D), 26(2C), 26A(7)
[35] Therapeutic Goods Act 1989 Subsections 25(2)(a), 26(2)(a), 26A(4)(a)
[36] The term "**audit**" is used in Australia, whereas overseas regulatory agencies may use the term "**inspection**". These two terms may be used interchangeably.
[37] www.tgasime.health.gov.au

Active Pharmaceutical Ingredients (API)

There are three principal types of API:

i. Non-Sterile;

ii. Sterile; and

iii. Other High Risk API including, for example, those derived from human or animal tissues or recombinant technology.

Some API derived from tissues of animal origin may not be high risk (e.g. fish extracts), probiotics or those derived by classical fermentation technology.

Currently, evidence of compliance with GMP for API manufacture is usually only required for qualified medicines evaluated by the Drug Safety and Evaluation Branch of the TGA. This may also apply to 'active premixes' evaluated by the TGA's Non-Prescription Medicines Branch.

If all steps of manufacture are not carried out at a single site, the manufacturer that conducts the final steps of manufacture, purification, drying, milling and sterilization (if applicable) of the bulk active ingredient is responsible to ensure that key intermediates are also manufactured in accordance with GMP. Separate GMP Certification need not routinely be supplied for the manufacturers of these intermediates. However, the TGA reserves the right to request evidence of GMP compliance for the manufacturers of critical intermediates, if deemed necessary.

Australian Quarantine and Inspection Service (AQIS), Department of Agriculture, Fisheries and Forestry

Human therapeutics and medicines containing biological material of animal or microbial origin

It is the importer's responsibility to identify and to ensure it has complied with, all requirements of any other regulatory and advisory bodies prior to and after importation including the Australian Customs Service, Therapeutic Goods Administration, Department of Health and Ageing, Department of the Environment, Water, Heritage and the Arts, Australian Pesticides & Veterinary Medicines Authority and any State agencies such as Departments of Agriculture and Health and Environmental Protection authorities.

Pharmaceutical excipients are highly processed substances (other than the active pharmaceutical ingredient) that are components of therapeutic products. In Australia, the following substance groups are considered pharmaceutical excipients:

Alcohols	Amino acids	Essences	Esters	Fish oil (other than salmon oil)
Gelatin*	Homeopathics	Pectins	Plant acids	Plant extracts
Plant flours	Plant gums	Plant juices	Plant oils	Plant waxes
Polysorbates*	Resins	Starches	Stearates*	Sugars
Tinctures	Vinegars	Vitamins	Water	Refined wool fats e.g. Lanolin

* Note: Gelatin and polysorbates and stearates derived from animals are not considered AQIS approved pharmaceutical excipients for use in animals. An AQIS Import Permit is required for veterinary therapeutics containing these ingredients and for these ingredients that are imported for use in

manufacture of veterinary therapeutic products. This also applies to gelatin, polysorbates and stearates for use in animal feed, animal feed supplements and animal vaccines.

Dietary supplements and natural medicines containing ingredients of plant origin

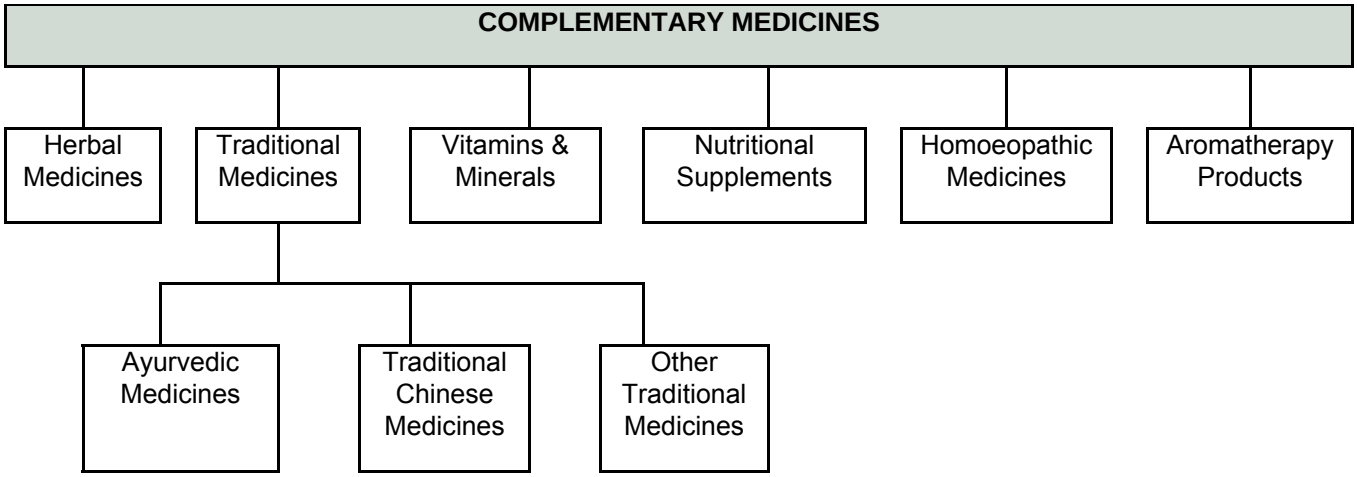
It is the importer's responsibility to identify the component plant ingredients of the product and then search the database of Imported Food Control Act 1992 [ICON], administered by AQIS, for the specific import conditions for each plant ingredient identified.

An Import Permit is required only for those dietary supplements and natural medicines that contain plant material listed on ICON as prohibited and do not comply with the non-commercial conditions above.

Regulation of complementary medicines in Australia[38]

In Australia, medicinal products containing herbs, vitamins, minerals, and nutritional supplements, homoeopathic medicines and certain aromatherapy products are referred to as "complementary medicines". These are regulated as medicines under the Act. Complementary medicines comprise traditional medicines, including traditional Chinese medicines, Ayurvedic medicines and Australian indigenous medicines (see Figure 3).

Figure 3 - Classes of Complementary Medicines



Other terms sometimes used to describe complementary medicines include 'alternative medicines', 'natural medicines' and 'holistic medicines'.

Complementary medicines are generally available for use in self-medication by consumers and can be obtained from retail outlets such as pharmacies, supermarkets and health food stores. While the majority of complementary medicines are indicated for the relief of symptoms of minor, self-limiting conditions, many are indicated for maintaining health and well being, or the promotion or enhancement of health.

[38] Australian Government Department of Health and Ageing, Therapeutic Goods Administration; http://www.tga.gov.au/cm/cmreg-aust.htm

Regulatory framework for medicines in Australia

The Therapeutic Goods Administration (TGA) is responsible for administering the provisions of the Act. The overall objective of the Act is to ensure the quality, safety, efficacy, and timely availability of therapeutic goods, including medicines and medical devices that are supplied in or exported from Australia. While the Act provides a substantially uniform national system of controls over therapeutic goods, other Commonwealth and separate State and Territory legislation may apply to certain therapeutic goods. The Act includes requirements for all therapeutic goods as well as specific requirements for different types of medicines, such as advertising, labeling, and product appearance.

For the purpose of regulating complementary medicines, the Act and the *Therapeutic Goods Regulations 1990* (the "Regulations") respectively define what is a complementary medicine and designate the types of active ingredients that may be used in such medicines.

A complementary medicine is defined as a therapeutic good consisting wholly or principally of one or more designated active ingredients each of which has a clearly established identity and a traditional use. Traditional use means use of the designated active ingredient that is well documented, or otherwise established, according to the accumulated experience of many traditional healthcare practitioners over an extended period; and accords with well-established procedures of preparation, application and dosage.

The TGA maintains the Australian Register of Therapeutic Goods (ARTG), a database that includes details of all therapeutic goods that are imported into, supplied in, or exported from Australia. It is a legal requirement that, unless specifically exempt or excluded, all therapeutic goods are included on the ARTG prior to their supply. Therapeutic goods cannot be included on the ARTG, unless a sponsor for those goods posts an application.

Adverse drug reaction reporting

An adverse reaction reporting system for medicines in Australia is well established. The Australian 'Blue Card' scheme covers all medicines and most health professionals. In addition, sponsors of all medicines included in the ARTG are under an obligation to report adverse reactions to the TGA.

All adverse reaction reports received by the TGA for complementary medicines are reviewed. The review may result in a various outcomes, including further analysis of database reports to investigate potential safety signals, publication of a report in the Australian Adverse Drug Reactions Bulletin or medical journals to raise awareness of the reaction and/or removal of the product from the market.

Brief Summary

Australia has a two-tiered regulatory system for medicines, based on risk

Complementary medicines available for supply in Australia are included on the Australian Register of Therapeutic Goods (ARTG) as listed (low risk) or Registered medicines (higher risk)

Complementary medicines must be manufactured under the same code of Good Manufacturing Practice (GMP) as other medicines

Listed complementary medicines may only contain ingredients permitted by the TGA for use in low risk medicines

Listed medicines are restricted to indication and claims relating to health maintenance, health enhancement or non-serious, self-limiting conditions. Generally, they may not refer to a serious form of a disease disorder or condition or indicate they are for treatment or prevention.

Registered complementary medicines are assessed individually for quality, safety and efficacy. Although Listed medicines are not assessed individually for efficacy, sponsors must certify to the TGA they hold evidence to support all indications and claims made for their products. This evidence may be audited by the TGA.

Exported medicines are regulated to ensure that they are of a similar standard to those supplied in Australia.

Post-market regulatory activities, including reporting of adverse reactions, audits of manufacturers and laboratory testing is an important element of ensuring the quality, safety and effectiveness of medicines regulated by the TGA.

Brief Overview of Japanese Regulatory System

Master File System for Drug Substances

Master File (MF) System

Master file (hereinafter referred to as “MF”) system for drug substances, etc. allows Japanese or foreign manufacturers of drug substances etc. to voluntarily register the data concerning the quality/manufacturing methods of their drug substances, etc. used for manufacture of drugs (pharmaceutical products) to the review authority. This is similar to the FDA Drug Master File mechanism in the U.S.

The registered data is quoted as the necessary information for an approval review of the drug (pharmaceutical product) in which the drug substance is used. Japanese or foreign drug manufacturers can register in MF by submitting the required forms to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) in accordance with the procedures described in the Enforcement Regulations for the Pharmaceutical Affairs Law (hereinafter referred to as “Regulations”).

Foreign manufacturers of drug substances, etc. can also apply for MF registration. In order to apply for MF registration, it is necessary for a foreign manufacturer to obtain a foreign manufacturer accreditation because the accreditation category, the accreditation number, and the date of accreditation of the foreign manufacturing site must be entered in the MF registration application form.

Candidates for MF Registration

1) Drug substances, intermediates, and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.) However, the drug substances, intermediates and pharmaceutical product materials used in OTC drugs (excluding OTC drugs with new active ingredients) are not appropriate for registration in MF, as it is considered that their quality and safety are already established even in the existing specifications and test methods; and

2) New excipients and new pre-mix excipients with a different composition ratio from the existing ones; and

3) Materials for medical devices; and

4) Containers/packaging materials.

GMP Compliance Inspection concerning Pharmaceuticals (including API) of Foreign Manufacturers (Overview Guidance for Foreign Manufacturers)

GMP Compliance Inspection concerning Pharmaceuticals of Foreign Manufacturers is an inspection on the compliance of manufacturing control and quality control methods at the relevant manufacturing sites with Japanese GMP ("Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs", Ordinance of Ministry of Health, Labour and Welfare, No. 179, 2004), conducted by the PMDA. GMP compliance is a requirement for marketing approval.

GMP Compliance Inspections include 1) Inspections that are conducted at the point of application for new marketing approval or of application for partial changes of approved information, and 2) Inspections that are conducted every five years following the obtainment of marketing approval. In the case of ethical drugs, packaging, labeling and storage facilities and external testing laboratories are included in the scope of GMP Inspection, in addition to the manufacturing sites of drug products, API (Active Pharmaceutical Ingredients) and intermediates. In the case of application for partial change approval, GMP Compliance Inspection is not required if the partial change is addition, change, or deletion etc. of administration and dosage, or indication that will not affect the methods for manufacturing control or quality control. While drug products for over-the-counter drugs are included in the scope of GMP compliance inspection, API for over-the-counter drugs are excluded from the inspection (however API of over-the-counter for new marketing approval are in the scope of GMP compliance inspection).

Scope of Drugs subject to GMP Compliance Inspection

Drugs and API (the products shows below a. ~ g. and API for over-the-counter drugs do not require GMP compliance Inspection.)

a. Drugs which are intended to be used for the extermination or prevention of rats, flies, mosquitoes, fleas and other similar creatures, which are not used directly on human bodies.

b. Drugs, which are intended mainly for disinfection and sanitization, which are not used directly on human bodies.

c. Drugs, which are API intended to be mainly used for the manufacturing of drugs indicated in a. or b.

d. Drugs that are manufactured at manufacturing sites that only conduct processes of powdering and/or cutting crude drugs.

e. Drugs that are manufactured and/or marketed by pharmacies.

f. Gases used for medical purposes, 1) nitrous oxide, 2) oxygen, 3) nitrogen, 4) carbon dioxide, 5) compound of nitrous oxide and oxygen.

g. In addition to a. through f., drugs designated by the Minister of Health, Labour and Welfare as causing mild action to human bodies are included in the Japanese Pharmacopoeia.

Facilities subject to Inspection

All manufacturing sites (including external testing laboratories) listed in the marketing approval application or authorization.

Flow of GMP Compliance Inspection

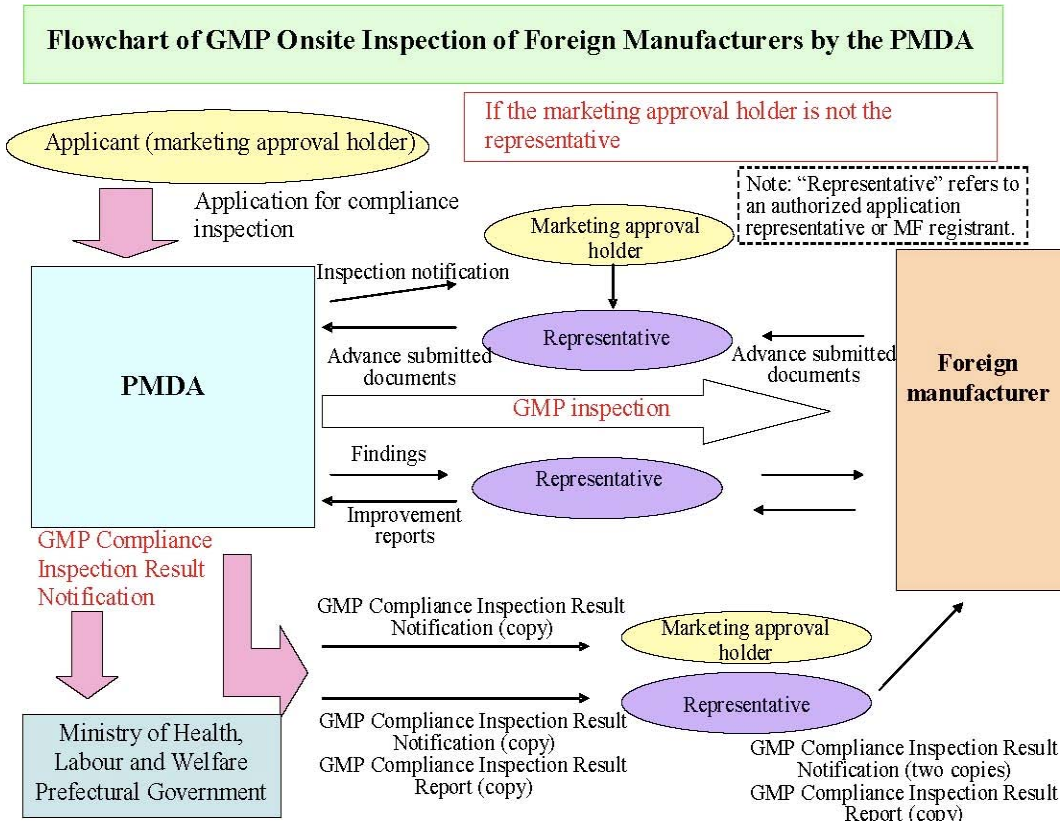
a. A marketing authorization holder that is applying for the marketing approval, or a marketing authorization holder that has obtained marketing approval, shall file an application with the PMDA for

GMP compliance inspection of foreign manufacturing sites. The PMDA shall conduct the inspection.

b. In principle, GMP compliance inspection shall be an onsite inspection by the PMDA. However, inspection may be conducted on documents only (hereinafter “document inspection”), by the PMDA’s judgment on GMP compliance etc. based on the product’s risk, the country’s GMP standards and their operation, and documents submitted for the inspection.

c. The PMDA shall report the results to the Ministry of Health, Labour and Welfare using the form ‘GMP Compliance Inspection Result Notification’. The PMDA shall issue a copy of the GMP Compliance Inspection Result Notification to the marketing approval holder that applied for the inspection, as well as a copy of the GMP Compliance Inspection Result Notification to the foreign manufacturer of which the onsite inspection was conducted. In the case of document inspection, a copy of the GMP Compliance Inspection Result Report is not issued.

The following flowchart demonstrates one scenario of the inspection requirement.



Drug Safety Surveillance in Canada

Canada's *Food and Drugs Act and Regulations* authorize Health Canada to regulate the safety, efficacy and quality of therapeutic products, which include pharmaceutical drugs, vitamins, vaccines and medical devices. Health Canada is the federal department responsible for licensing and regulation drugs in Canada, and for the post-market surveillance of these drugs.

Today, more than 20,000 pharmaceutical products are available for 33 million residents in Canada.[39] However, about 3-4% of drugs approved by Health Canada have been withdrawn from the market for safety reasons over the past two decades. Between 2005 and 2007, the percentage of drug withdrawal stood at 1.5% to 2%. Drugs which have been withdrawn from Canadian market since August 2004, are listed by Table 1:[40]

TABLE 7: DRUGS WITHDRAWN FROM THE CANADIAN MARKET SINCE AUGUST 2004 [40]

Generic Name	Brand Name	Approval Date	Withdrawal Date
Aprotinin	Trasylol	Oct. 3, 1995	Nov. 23, 2007
Estradiol dienanthate	Climacteron	1961	Oct. 22, 2005
Gatifloxacin	Tequin	Jan. 9, 2001	Jun. 29, 2006
Lumiracoxib	Prexige	Nov. 2, 2006	Oct. 3, 2007
Pergolide	Permax	1991	Aug. 30, 2007
Rofecoxib	Vioxx	Oct. 25, 1999	Sep. 30, 2004
Tegaserod	Zelnorm	Mar. 12, 2002	Mar. 30, 2007
Thioridazine	Mellaril	1959	Sep. 30, 2005
Valdecoxib	Bextra	Dec. 11, 2002	Apr. 7, 2005

Drug Regulation in Canada

The first step toward federal drug regulation in Canada was the enactment of the *Proprietary or Patent Medicine Act* in 1909. This Act was the first legislation to register medicines, which it limited to secret-formula, non-pharmacopoeial packaged medicines. The Act was the beginning of the protection of the public against medicines administered without medical supervision.

Canada's current system of drug regulation is evolved from the *Food and Drugs Act* of 1920, an act that codified all aspects of the domestic pharmaceutical industry. The *Food and Drugs Act* was amended in 1951 to require drug developers to seek approval from the federal government before advertising and distributing all pharmaceutical products. Pharmaceutical companies must seek Notices of Compliance (NOC) from the Canadian government. However, the regulations did not prevent the thalidomide tragedy of the early 1960s.

At present, Canada's drug regulation system focuses on pre-market activities. A manufacturer can market its drug once it has received a NOC from Health Canada. The manufacturer must meet a number of obligations, however as long as the drug causes no adverse reactions or the manufacturer does not need to make changes to the drug, it may never be subject to review by Health Canada again.[41]

[39] Health Canada, Health Products and Food Branch. (2006). *Access to Therapeutic Products: The Regulatory Process in Canada*
[40] Lexchin, J. *Drug Safety and Health Canada.* Canadian Centre for Policy Alternatives. Apr. 2009
[41] Health Canada website. Brief History of Drug Regulation in Canada. Available at: http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-renseign/hist-eng.php

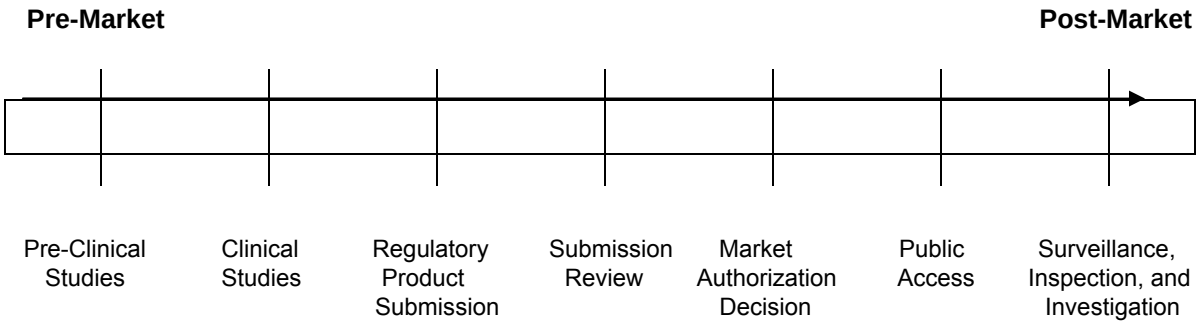
To gain access to the Canadian market, imported therapeutic products must meet the same standards as those manufactured in Canada. They are also subject to the post-market surveillance, inspection and investigation conducted by the Health Canada.

Pre-market Review

Before new therapeutic products enter the Canadian market, they must pass a regulatory review process by the Health Products and Food Branch (HPFB) at Health Canada. HPFB evaluates and monitors the safety, efficacy and quality of all therapeutic products available to Canadians.

HPFB also works with international organizations, including regulatory authorities in other countries, to harmonize regulatory standards and processes for therapeutic products, and ensure drug safety at home and abroad.

Once the results of the clinical studies of a new drug have indicated that its potential therapeutic value outweighs its adverse effects or toxicity, the manufacturer can seek authorization to market the product in Canada by filing a New Drug Submission (NDS) with HPFB. The clinical trials need not have been conducted in Canada.[39] In case the new product is a generic drug, the manufacturer should submit an Abbreviated NDS (ANDS). A Supplemental NDS (SNDS) is to be filed by the manufacturer, if certain changes are made to already-authorized products. For those drug products not meeting the definition of a "new drug", a Drug Identification Number (DIN) application must be filed.



Post-market Surveillance

Canada Vigilance Program is Health Canada's post-market surveillance program that collects and assesses reports of suspected adverse reactions (ARs) for health products marketed in Canada. The Program has collected reports of suspected adverse reactions since 1965. In Canada, health products include pharmaceuticals, biologics (e.g., fractionated blood products, and therapeutic and diagnostic vaccines), biotechnology products, natural health products and radiopharmaceuticals.

Under Canada's *Food and Drugs Act and Regulations*, manufacturers of health products are responsible for monitoring the safety of their products. It is mandatory for Market Authorization Holders (MAH), which include manufacturers and distributors, to submit AR reports to the Canada Vigilance National Office under prescribed format and timeline. MAHs are required to send, within 15 days, all reports of serious ARs that have occurred in Canada (domestic ARs) and all reports of serious unexpected ARs occurred outside Canada for the product they sell to other countries (foreign ARs) to the Canada Vigilance Program.

As part of Health Canada's Canada Vigilance Program, health professionals and consumers can report ARs or side effects to Health Canada on a voluntary basis.

Canada Vigilance Program publishes *Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products* to assist industry and health professionals to report ARs.

The Canada Vigilance Online Database allows access information reported to Health Canada about suspected adverse reactions to drugs and health products.

In addition, as part of Health Canada's post-market surveillance initiative, HPFB inspects manufacturing plants and other sites where activities involving products covered under the *Food and Drugs Act* are conducted to verify compliance with regulatory requirements.

MedEffect Canada

Canada was among one of the nine developed countries (including U.S.) that first participated in the WHO Programme for International Drug Monitoring in 1968, which is 30 years earlier than China's participation.[42] Health Canada is also ahead of many countries in allowing direct consumer reporting of ARs and in posting its entire database of AR reports on a publicly accessible web site.[43]

MedEffect Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php) is the backbone of Health Canada's ADR reporting and monitoring system. It is one of the deliverables of the Therapeutic Access Strategy (TAS) - a five-year strategy that began in 2003, to improve the safety, effectiveness and access to therapeutic products available to Canadians. The MedEffect program is comprised of a website, and a partnership initiative involving professional health care associations and consumer/patient groups.

MedEffect Canada provides consumers, patients, and health professionals with easy access to:

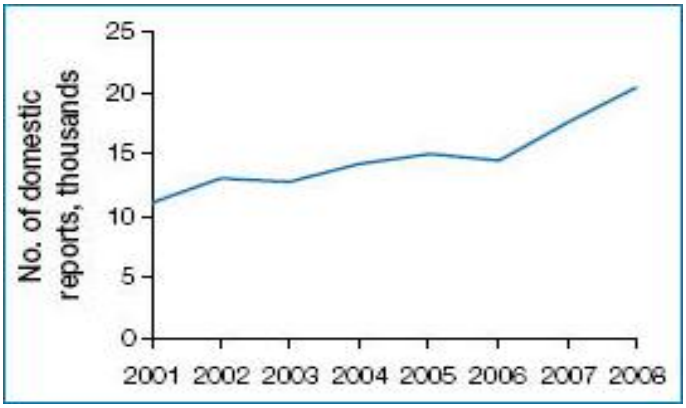
- Report an adverse reaction or side effect;
- Obtain new safety information on drugs and other health products; and
- Learn and better understand the importance of reporting side effects.

Adverse Reaction Reports

In 2008, Health Canada received 20,360 domestic AR reports for health products, of which 69.2% were considered to be serious. 71.8% of these AR reports were submitted by MAHs, while 22.6% were from consumers, patients and non-hospital based healthcare professionals. [44]

The number of domestic AR reports increased by 15.6% in 2008, compared with 2007 (Fig. 1). The number of foreign AR reports received from MAHs was 241,417 (Fig. 2). At this time, foreign reports are not included in the Canada Vigilance database. [44]

FIGURE 3: NUMBER OF DOMESTIC AR REPORTS RECEIVED BY HEALTH CANADA (2001 – 2008)

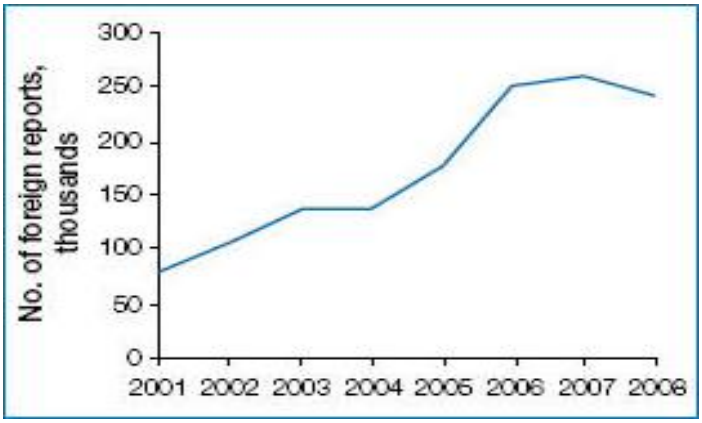


42 Source: WHO Programme for International Drug Monitoring website. Available at: http://www.who-umc.org/DynPage.aspx?id=13140&mn=1514

[43] Vitry A, Lexchin J, Sasich L, et al. Provision of information on regulatory authorities' websites. Internal Medicine Journal 2008;38:559–67.

[44]Health Canada. Adverse reaction and incident reporting – 2008. Canadian Adverse Reaction Newsletter Vol. 19, Issue 2, April 2009

FIGURE 4: NUMBER OF FOREIGN AR REPORTS RECEIVED BY HEALTH CANADA (2001 – 2008)



Canadian Adverse Reaction Newsletter (CARN)

CARN is a quarterly publication, which alerts health professionals and consumers to potential health concerns based on the review of drug-related case reports submitted to HPFB. The CARN is published quarterly by Health Canada's Marketed Health Products Directorate and has existed since 1991.

The newsletter and advisories are distributed as an attachment to the Canadian Medical Association Journal. It is also available on HPFB's website.

Drug Safety and Effectiveness Network

In December 2007, the Prime Minister of Canada - Stephen Harper, announced the Food and Consumer Safety Action Plan (FCSAP) to introduce "measures on food and product safety to ensure that families have confidence in the quality and safety of what they buy." The FCSAP outlines several measures to meet the Government's objectives, including establishment of the Drug Safety and Effectiveness Network (DSEN).

In the summer of 2008, the Canadian federal government announced it was allocating 1M Canadian dollars to establish the DSEN to strengthen post-market surveillance of health products. This was followed up in January 2009 with an additional 31 M Canadian dollars over the next four years, and 10 M Canadian dollars per year after that. This investment has shown the government's strong commitment to enhancing drug safety in Canada.

Health Canada partners with Canadian Institute of Health Research (CIHR) to establish the DSEN. New evidence generated via the DSEN will provide Health Canada with an important additional source of information for use in the ongoing assessments of drug products' safety risks. This evidence will also support decision-making on public reimbursement, and the safe and optimal prescribing and use of drugs within the Canadian health care system.[45]

The key objectives for establishing the DSEN are to increase the available evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and patients; and, to increase capacity within Canada to undertake high-quality post-market research in this area.

DSEN is expected to complement Health Canada's Vigilance Program and MedEffect Program to strengthen post-market surveillance of health products in Canada.

[45] Source: CIHR and Health Canada

Drug Safety Concerns in Canada

Although there has been no major drug safety incidents report in Canada in recent years, significant limitations in the Canadian legislation have been observed by Canadian policy experts, which have raised public concerns on Canadian drug safety surveillance system. For example, based on the *Food and Drugs Act and Regulations*, Health Canada is empowered to cancel the market authorization for drugs without prior negotiation with manufacturers, but it cannot force them to recall drugs deemed harmful from pharmacies. Another concern is that Health Canada has not established sufficient measurable standards for drug safety. For example, there is no standard for the length of time that it will take between the receipt of an ADR and when that ADR has been analyzed and posted on Health Canada's MedEffect Adverse Reaction Database. [40]

Chinese Pharmaceutical Exports to Canada

Compared with the U.S., Canada imports a considerably smaller amount of bulk vitamins, antibiotics and heparins from China each year. No safety incidents associated with these Chinese imports have been reported in Canada.

Brief Overview of U.S. Drug Regulatory Systems

Pharmaceuticals

The unique challenges facing the inspection and regulatory infrastructure of the United States' Food and Drug Administration (FDA) continue to be widely reported in the public domain[46]. Chinese firms continue to be relied on extensively by the U.S. Pharmaceutical and Dietary supplement industries. A great deal of the raw materials imported and used in pharmaceuticals and supplements are Active Pharmaceutical Intermediates (API),[47] which are required to comply with specific rules and regulations.[48] It has been reported that Chinese manufacturers have increasing experience with the Center for Drug Evaluation and Research (CDER) division of the FDA through Drug Master File (DMF) submissions.[49] Briefly, DMFs are submissions to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. More specifically, they would include raw ingredients, packaging materials, and excipients. A DMF is submitted solely at the discretion of the holder (person or company). The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application. Inspections of drug component producers are undertaken when there is an application under review that references a DMF for the manufacture of that ingredient.

There are four (4) types of DMF's:

Type II Drug Substance, Drug Product, Intermediates, and Materials Used in Their Preparation

Type III Packaging Material

Type IV Excipients, Colorant, Flavor, Essence, or Material Used in Their Preparation

Type V Other – Sterile manufacturing plants, biotech contract facilities, clinical, toxicology

As of the 2nd quarter of 2009, there were a total of 22,923 DMFs, updated on a quarterly basis, of which 9,926 are considered active (DMF was found acceptable for filing and is up-to-date).[50]

Composition of Active DMFs:

Type II: 6,939 or 69.91%

Type III: 2,010 or 20.25%

Type IV: 798 or 8.04%

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[46] http://www.fda.gov/cder/drug

[47] An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. FDA defines inactive ingredients as any component of a drug product other than the API, such as materials that improve the appearance, stability, and palatability of the product.

[48] Importation of Active Pharmaceutical Ingredients (API) Requirements FD&C Act 801 [21 USC 381]; http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVIIIImportsandExports/default.htm

[49] 'Biopharma CMOs in China', Ms. Eliza Zhou, BioPlan Associates July 2006

[50] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

Type V: 174 or 1.75%

This breakdown is similar to the composition of active DMF through January 2007.[51]

As of 2006, the Chinese manufacturers with the largest number of DMFs include: Zhejiang Hisun Pharmaceutical Co., Shanghai Pharmaceutical (Group) Co., Shandong Xinhua Pharmaceutical Co. and Tianjin Pharmaceutical (Group) Co.[52]

By the 1st quarter of 2009, changes in the dynamic landscape for supplying critical raw materials for potential import have resulted in other manufacturers leading the way in DMF submissions: Zhejiang Hisun Pharmaceutical Company, Ltd., Zhejiang Huahai Pharmaceutical Company, Ltd., Chemwerth, Inc., ALP Pharm Beijing Company Ltd., and Tai Heng Industry Company, Ltd. (See Table 9); At the time of this report analysis, according to FDA databases, the total number of active Chinese DMFs was 628. In the context of numerical magnitude, this equates to roughly 6.32% of all active DMF, but based on China's increasing role in the global pharmaceutical supply network, it is likely this percentage will continue to rise.

In light of continual environmental requirements in the pharmaceutical industry, the National Environmental Policy Act (NEPA) [53] requires that all government agencies prepare an Environmental Impact Statement (EIS) or a 'Finding of No Significant Impact' (FONSI) when they take an action (e.g., approving a drug application). Companies submitting an application are required to submit an environmental assessment (EA) or a waiver request, to permit FDA to determine whether an EIS or a FONSI is needed. [54] Since the FDA does not approve DMFs, no action is initiated, nor is an EA needed.

Prior Acknowledged Warnings

In light of recent inquiries of potential health and public safety impacts of unregulated use of Chinese-origin raw ingredients - the impetus of this report, there have been many previous notable documented inquiries, congressional testimonies, studies, analyses, and petitions[55] on this issue of increasing urgency.

Recent legislation introduced in the 111th Congress – HR 759 (also known as the Food and Drug Globalization Act of 2009), underscores the urgency and timeliness to amend the Federal Food, Drug, and Cosmetic Act of the FDA to improve the safety of food, drugs, devices, and cosmetics in the global market, and for other purposes. Areas of concern contained in the House bill, relevant and related to prior inquiries and testimonies, include:

- Inspection of producers of drugs and active pharmaceutical ingredients.
- Documentation for admissibility of drug imports.

[51] Drug Master Files presentation (revised) November 7, 2008; Dr. Arthur B. Shaw
[52] 'Biopharma CMOs In China', Ms. Eliza Zhou, BioPlan Associates July 2006
[53] http://www.epa.gov/compliance/assistance/sectors/pharmaceutical.html
[54] http://www.fda.gov/cder/guidance/1730fnl.pdf
[55] Synthetic Organic Chemicals Manufacturers Association Bulk Pharmaceuticals Task Force Petition, Docket# 2006P-0049, United States House of Representatives Committee on Energy and Commerce, Subcommittee on Oversight and Investigation - November 1, 2007; United States Government Accountability Office GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives;
Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program, April 22, 2008, United States Government Accountability Office GAO Report to Congressional Requesters;
Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program, September 2008, United States Government Accountability Office;
GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives-Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers, Thursday, November 1, 2007

- Drug supply quality and safety.
- Delay, limitation, or denial of inspection.
- Country of origin labeling.
- Non-distribution and recall of adulterated or misbranded drugs.
- Destruction of adulterated, misbranded or counterfeit articles offered for import.

This bill is in the first step in the legislative process. Introduced bills and resolutions first go to committees that deliberate, investigate, and revise them before they go to general debate. However, no matter how urgent an issue arises, the majority of bills and resolutions never make it out of committee.[56]

The above concerns contained in the House bill represent many of the issues brought up in prior forums and reports, as previously stated.[57] These issues include the following findings, which are non-exclusive:

FDA's effectiveness in managing the foreign drug inspection program continues to be hindered by weaknesses in its databases. FDA does not know how many foreign establishments are subject to inspection. Instead, FDA relies on databases that were not designed for this purpose. Furthermore, these databases contain inaccuracies that FDA cannot easily reconcile. One database indicates there were about 3,000 foreign establishments registered to market drugs in the United States in fiscal year 2007, while another indicates that about 6,800 foreign establishments actually imported drugs in that year. FDA recognizes these flaws. In addition, because the databases cannot exchange information, any comparisons of the data are performed manually, on a case-by-case basis.

FDA typically inspects relatively few foreign establishments. It is suggested that the agency may inspect about 7 percent of foreign establishments in a given year. According to preliminary findings of the Governmental Accountability Office (GAO) – an independent, non-partisan agency that works for Congress – at this rate, it would take FDA more than 13 years to inspect each foreign establishment once, assuming that no additional establishments require inspection.[58] From prior reporting on this matter, the record in China is particularly bad – from 2002 to 2006, an average of just 15 of 714 drug plants that export to the U.S. were actually inspected by FDA. At this rate, it would take more than 50 years to inspect all of the plants. [59] Moreover, it has been reported that the exact number of foreign establishments that have never been inspected is unavailable. Most of the foreign inspections performed are conducted as part of a review associated with processing an application to market a new drug - DMF, rather than inspections for monitoring the quality of marketed drugs. Although the FDA has used a risk-based process to develop a prioritized list of foreign establishments for inspections to monitor the quality of marketed drugs, few are completed in a given year.

Because the foreign inspection process involves unique circumstances that are not encountered domestically in the US, this increases the complexity of the situation. For example, in the past, FDA has relied on staff with prior experience inspecting domestic establishments to volunteer for inspections of

[56] http://www.govtrack.us/congress/bill.xpd?bill=h111-759 [Last Updated: Jul 12, 2009 8:37PM] Last Action: Jan 28, 2009: Referred to the House Committee on Energy and Commerce.
[57] See note 55
[58] Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program, April 22, 2008, United States Government Accountability Office GAO Report to Congressional Requesters
[59] 'The Safety Gap' New York Times Magazine November 2, 2008 Gardiner Harris

sites in foreign countries. Unlike domestic inspections to monitor the quality of a marketed drug, FDA does not arrive unannounced at a foreign establishment. It also lacks the flexibility to easily extend foreign inspections if problems are encountered, due to the need to adhere to an itinerary that typically involves multiple inspections in the same country.[60] Finally, as it relates to China, the linguistic barrier can make foreign inspections more difficult. FDA does not generally provide translators to its inspection teams. Instead, it has been the norm to rely on an English-speaking representative of the foreign establishment being inspected, rather than an independent translator.

Finally, GAO has indicated that FDA has faced certain logistical and staffing challenges unique to conducting foreign inspections. To address these concerns, the FDA has established foreign offices in Beijing, Shanghai, and Guangzhou, comprised of a total of eight FDA employees and five Chinese nationals in late 2008. The branch office in Beijing is primarily responsible for coordination between FDA and the Chinese regulatory agencies. The branches located in Shanghai and Guangzhou are supposedly focused on conducting inspections and working with Chinese inspectors to provide training as necessary. FDA has noted that the Chinese nationals primarily provide support to FDA staff, including translation and interpretation. It is hoped that these new FDA branches in Beijing, Shanghai, and Guangzhou will address these concerns more effectively.[61]

GAO testified in November 2007[62] that FDA's databases do not provide an accurate count of foreign establishments subject to inspection and do provide widely divergent counts. According to their findings, through one recent initiative the FDA has taken steps to improve its database intended to include foreign establishments registered to market drugs in the United States. This initiative may reduce inaccuracies in FDA's count of foreign establishments. However, these steps will not prevent foreign establishments that do not manufacture drugs for the U.S. market from erroneously registering with FDA. Further, to reduce duplication in its import database, FDA has supported a proposal that would change the data it receives on products entering the United States. However, the implementation of this proposal is not certain and would require coordination with multiple federal agencies. Efforts to integrate these databases have the potential to provide FDA with a more accurate count of establishments subject to inspection, but it is too early to tell. One immediate consideration could possibly call for increased accountability, when applicable, for the 'Agent' of the DMF Holder. This would hold the third party more responsible for accuracy, validity, and veracity of the submitted information.

The GAO's testimony also addressed gaps in the information technology infrastructure that weakens the processes for prioritizing the inspection of foreign establishments that pose the greatest risk to public health. While FDA recently expressed interest in obtaining useful information from foreign regulatory bodies that could help it prioritize foreign establishments for inspections, the agency has faced difficulties fully utilizing these arrangements in the past. For example, FDA had difficulties in determining whether the scope of other countries' inspection reports met its needs and these reports were not always readily available in English.[63]

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[60] United States Government Accountability Office GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives;
Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program, April 22, 2008, United States Government Accountability Office GAO Report to Congressional Requesters;
Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program, September 2008, United States Government Accountability Office;
GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives-Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers, Thursday, November 1, 2007

[61] 'FDA Seeks to establish Branch Office in China' Genetic Engineering & Biotechnology News September 1, 2008, Volume 28, Number 15; 'FDA outlines 'best practice' for importers' January 21, 2009; 'FDA launches global supply chain pilot scheme' January 15, 2009, www.outsourcing-pharma.com

[62] GAO Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives-Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers, Thursday, November 1, 2007

[63] Ibid

FDA inspects relatively few foreign establishments each year to assess the manufacturing of drugs currently marketed in the United States. From fiscal years 2002 through 2007, the FDA inspected 1,479 foreign drug manufacturers. Because the FDA does not know the number of establishments subject to inspection, the percentage of those inspected cannot be calculated with certainty. As the FDA plans additional inspections, it is important that it ensures that foreign and domestic establishments with similar characteristics are inspected at a similar frequency.[64]

In March 2009, another piece of legislation was introduced in Congress, S.525: Pharmaceutical Market Access and Drug Safety Act of 2009, which amends the Federal Food, Drug, and Cosmetic Act (FDCA) to revise provisions governing the importation of prescription drugs.[65] It is worth noting that China is the world's largest supplier of key ingredients for many pharmaceutical products to several of the countries identified in the bipartisan bill – Japan and Europe (Germany, Spain, Italy, Belgium, France, Netherlands - see Table 4). Backlash against proposed legislation has begun, with the Pharmaceutical Research Manufacturers of America (PhRMA), among others, publicly opposing the legislation based upon the acknowledged worldwide threat of counterfeit products.[66]

Notwithstanding this potential significant challenge to U.S. pharmaceutical research and biotechnology companies, many of these same drug manufacturers continue to increase the pace of outsourcing many R&D functions of the drug discovery and development process, as well as FDA required clinical trial obligations, to China in pursuit of reduced costs.

It is conceivable to believe the prospect of enormous lost profits to Big Pharma is a very compelling financial motivator to PhRMA, as has been suggested by Senator Byron Dorgan, the primary sponsor of the bipartisan legislation that the Congressional Budget Office (CBO) estimates would save American consumers $50 billion over the next decade, including more than $10 billion in federal government savings[67]. These estimates from the CBO are based upon a prior report ordered by the Senate Committee on Commerce, Science, and Transportation Congress on Senate Bill 1392 (S.1392) – Federal Trade Commission (FTC) Reauthorization Act of 2005, which would have authorized funding for the FTC through 2010. Legislation S. 1392 also proposed amendment to the Federal, Food, Drug, and Cosmetic Act (FDCA) to modify provisions governing the importation of prescription drugs to the United States – similar to the current proposed legislation – S. 525.[68]

Dietary Supplements

For the purpose of this report, it is recognized that in the U.S., a "dietary supplement" may be either a nutritional or food supplement; therefore "supplements" will be used, unless otherwise stated. Supplements as defined under the Dietary Supplement Health and Education Act of 1994 (DSHEA)[69] are products which supplement diet and contains one or more of the following ingredients: vitamins, minerals, fatty acids or amino acids. This contrasts with China's regulatory system, which treats supplements as drugs.

Historically, the regulation of dietary supplements has been a significant challenge for the Food and Drug Administration (FDA), which has only limited authority to regulate safety and no pre-market approval authority. The regulatory authorities applicable to dietary supplements are more analogous to that of

[64] Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program, September 2008, United States Government Accountability Office

[65] http://www.govtrack.us/congress/bill.xpd?bill=s111-525

[66] Bill could cripple FDA and harm patients; PhRMA by Nick Taylor, 12-Mar-2009 http://www.outsourcing-pharma.com; PhRMA Statement on Prescription Drug Importation, Washington, D.C. (July 10, 2009)

[67] Re-importation bill would punish big pharma's actions; Dorgan by Nick Taylor, 11-Mar-2009,

http://www.outsourcing-pharma.com

[68] http://www.cbo.gov/doc.cfm?index=6634&type=0

[69] Dietary Supplement Health and Education Act of 1994 Public Law 103-417, 103rd Congress

foods than drugs.[70] This is a considerable issue given that nearly 150 million Americans use dietary supplements annually. The size of the market has increased dramatically since the passage of the Dietary Supplement Health and Education Act (DSHEA) and is continuing to grow, presumably in part because of the lack of pre-marketing regulatory hurdles and exploding customer demand. As of 2005, the dietary supplement industry in the U.S. was a $21.4 B business[71] reflecting more than 29,000 dietary supplement products on the market.[72] Figure 4 represents the top U.S. Nutrition Industry Supply Companies in 2008 based on sales.

[70] 'A Hard Pill To Swallow: Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements' January 2009 William B. Schultz, Lisa Barclay, Project on Emerging Nanotechnologies

[71] "Fact Sheet–Dietary Supplements: Safe, Beneficial, and Regulated," Council for Responsible Nutrition. Available at http://www.crnusa.org/pdfs/CRN_FACT_DSSafeRegulatedBeneficial_07.pdf.

[72] Ibid

Figure 4: Top U.S. Nutrition Industry Supply Companies in 2008 *

Supply Companies	U.S. Raw Materials Sales Range ($mil)
DSM Nutritional Products	$250 - 300
BASF	$250 - 300
Glanbia Ingredients	$150 - 200
Cargill	$150 - 200
Martek Biosciences	$150 - 200
Century Foods International	$150 - 200
Solae	$150 - 200
ADM	$100 - 150
Kaneka Nutrients L.P.	$100 - 150
Pronova	$100 - 150
Cognis	$100 - 150
Protient	$50 - 100
Ocean Nutrition	$50 - 100
WILD Flavors Inc.	$50 - 100
Kerry	$50 - 100
Fortitech	$50 - 100
Naturex	$50 - 100
Bioriginal	$50 - 100
BI Nutraceuticals	$50 - 100
Balchem	$50 - 100
Stauber Performance Ingredients	$50 - 100
LycoRed Natural Products	$50 - 100
Sensus	$30 - 50
Dynamic Nutrition	$30 - 50
Sunrich (SunOpta)	$30 - 50
Danisco	$30 - 50
Nutrition 21	$30 - 50
Wright Nutrition	$30 - 50
Maypro	$30 - 50
P.L Thomas	$30 - 50
Purac	$30 - 50
JM Huber	$30 - 50
ZMC-USA	$30 - 50
Kantno Innovative Food Ingredients	$30 - 50
GTC Nutrition	$30 - 50
InterHealth Nutraceuticals Inc.	$30 - 50
Davisco	$30 - 50
Beneo-Orafti	$30 - 50
Zila Nutraceuticals	$30 - 50
Gadot Biochemical Industries	$30 - 50
Pharmore Ingredients	$30 - 50
Omya	$30 - 50
Main Street Ingredients	$30 - 50
Kingchem	$30 - 50
Loders Croklaan	$30 - 50
Jiangsu Jianshan Pharma	$30 - 50
Pharmachem	$30 - 50

Source: Nutrition Business Journal *database of raw material & ingredient suppliers. Revenues listed are U.S. nutrition industry raw material and ingredient sales only. *All revenues are approximations of 2008 sales that have been compiled from executives, industry analysts and published materials. Although* NBJ *has made every reasonable effort to be accurate, revenue figures are not the result of audits and therefore not guaranteed to be an accurate representation. Estimates are current as of 12/4/2008. Errors and omissions are unintentional.*

Given this backdrop, and in light of the limited regulatory authority that Congress has granted it over these products in the DSHEA, FDA faces significant challenges:[73]

1. Dietary supplements may be marketed to the public even though FDA has not reviewed studies and other information and before the agency has determined whether these products have met the statutory safety standard.

2. In order to remove a dietary supplement (other than a new dietary ingredient) from the market, FDA must demonstrate that the product presents "a significant or unreasonable risk of illness or injury."[74]

3. When FDA compiles an administrative record to support a regulatory action, the courts ordinarily will give deference to the agency's decision and will not overturn that decision unless it is arbitrary and capricious. However, in the case of dietary supplements, the court must review the scientific determination de novo, giving no deference to FDA's decision.

As one clear example, in the high-profile case of ephedrine alkaloids, FDA took nearly seven years to remove dietary supplements containing ephedra from the market. By this time, hundreds of reports of serious illness from the use of ephedra-containing products had raised safety concerns.[75] Under DSHEA, dietary supplements may be marketed to millions of consumers even after safety concerns have been raised, unless FDA can demonstrate that they are associated with a significant or unreasonable risk of illness or injury, as demonstrated in the following:

"As early as 1994, FDA began receiving reports of adverse events associated with the use of ephedra.

FDA first proposed regulating ephedra in 1997, but many of those who commented on that proposal, including the U.S. General Accounting Office, believed that FDA had not developed sufficient evidence to support its proposed actions.

In 2003, after reviewing peer-reviewed scientific literature, thousands of adverse event reports and the conclusion of a study by the RAND corporation reporting "more than 16,000 adverse events associated with the use of ephedra-containing dietary supplements, including heart palpitations, tremors and insomnia," FDA reopened the comment period on its 1997 proposed rulemaking on ephedra products.

In December 2003, FDA issued a press release recommending that consumers stop buying and using ephedra. FDA banned the sale of dietary supplements containing ephedra in April 2004, when it issued a final rule concluding that such products presented an unreasonable risk of illness or injury.

Dietary supplement manufacturers challenged the ban, but it was upheld by theTenth Circuit Court of Appeals in 2006. In 2007, the Supreme Court declined to review the ruling."[76]

DSHEA also provided FDA with limited pre-market review authority for "a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a

[73] See note 70, 71
[74] 21 U.S.C. § 342(f)(1)(A).
[75] Sources: http://www.npr.org/templates/story/story.php?storyId=850679, http://www.cfsan.fda.gov/~dms/ ds-ephe2.html, http://www.fda.gov/oc/initiatives/ephedra/february2004/ See note 60

[76] Ibid

significant or unreasonable risk of illness or injury." [77] Dietary ingredients are considered to be "new" if they were not marketed in the United States prior to October 15, 1994, the date DSHEA was enacted.[78]

DSHEA also provided FDA with the authority to issue regulations on Good Manufacturing Practices (GMP).[79] Issued in 2007, the GMP regulations for dietary supplements are intended to establish process controls that can minimize the likelihood of problems and variances in manufacturing as they occur in order to ensure that dietary supplements are manufactured, packaged, held and labeled in a consistent and reasonable manner. FDA has the authority to find a dietary supplement product adulterated if the manufacturer does not comply with GMP regulations.

Key elements of this Dietary Supplement GMP rule include:

1) Relevant only to dietary supplements, and not to dietary ingredients. This is a more narrow scope than was addressed in FDA's proposed rule in 2003.

2) Rule is relevant to all dietary supplements sold or offered for sale in the United States, so that even foreign firms will be required to meet the new manufacturing standards.

3) Every dietary ingredient used in a dietary supplement will be required to meet "100-percent identity testing," such that manufacturers will be required to "conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient." Manufacturers will also be required to "confirm the identity of other components."

It has been well documented that resource and financial constraints impede the FDA's capability to regulate dietary supplements. Add to this scenario the incorporation of widespread and unregulated raw materials sourced from China into many dietary supplements, and there remains great concern on this matter. The FDA report "Science and Mission at Risk: Report of the Subcommittee on Science and Technology" (Science Board Subcommittee Report), in November 2007[80] concluded that FDA cannot fulfill its mission because its scientific base has eroded, its scientific workforce does not have sufficient capacity and capability, and its information technology infrastructure is inadequate,[81] which reaffirms prior GAO findings.

The report also addressed resources available for the regulation of dietary supplements, which are the responsibility of the Office of Nutritional Products, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition (CFSAN).[82] The CFSAN office regulating dietary supplements has seen a dramatic reduction in resources in recent years.

In addition to its responsibility for monitoring the nation's food supply, the office is also in charge of:

1) Reviewing pre-market notifications and information submissions (91 new dietary ingredient notifications in FY 2007);[83]

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[77] 21 U.S.C. § 342(f)(1)(B)
[78] 21 U.S.C. § 350b(c)
[79] 21 U.S.C. § 342(g)(2). While DSHEA gave FDA the authority to issue GMP regulations for dietary supplements when it was passed in 1994, FDA did not issue final regulations on GMPs until 2007; http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm110858.htm
[80] "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," U.S. Food and Drug Administration. *available at* http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf.
[81] FDA Science and Mission at Risk: Report of the FDA Science Board's Subcommittee on Science and Technology. Estimated Resources Required for Implementation, Gail Cassell, Ph.D., on behalf of the Subcommittee and its members. February 25, 2008. at p. 7. *available at*: http://energycommerce.house.gov/Press_110/022508.ScienceBoardReport. EstimatedResources.pdf
[82] www.fda.gov/AboutFDA/CentersOffices/CFSAN/default.htm
[83] See Narrative accompanying FDA Foods Program Resources Table for FY 2009 FDA Budget, available at http://ww.fda.gov/oc/oms/ofm/budget/2009/toc.htm.

2) Checking health claims and promotional materials (more than 2500 structure/ function claims notifications in FY 2007);[84] and

3) Monitoring adverse event reports.

China Effect

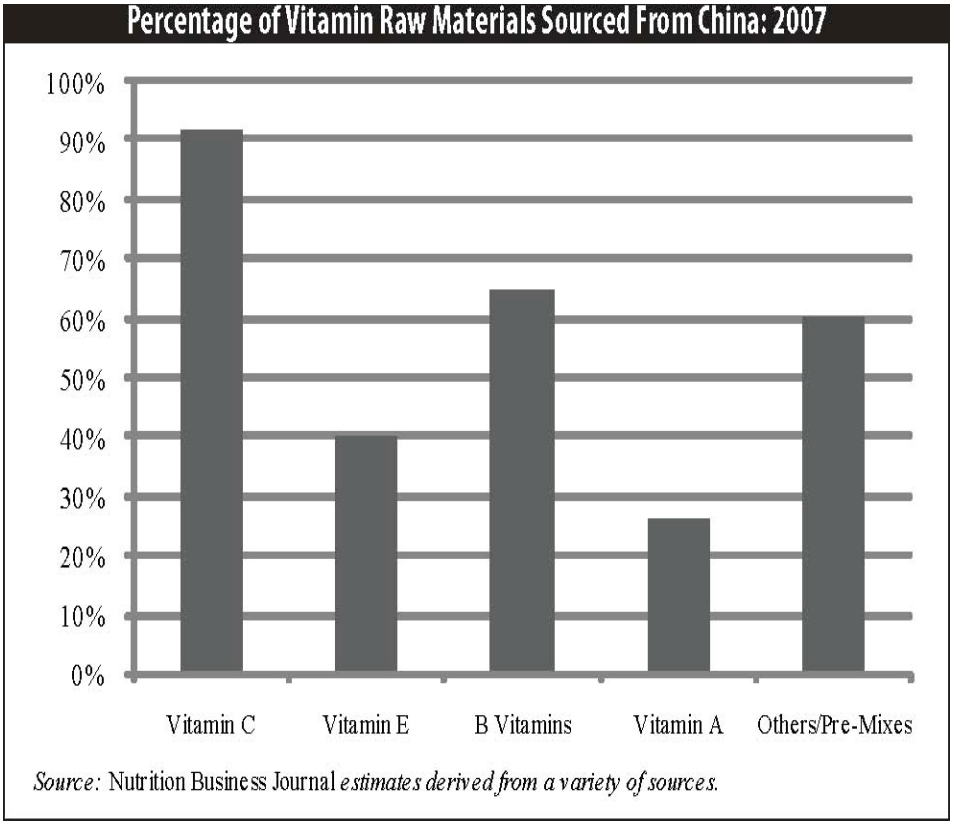
It is reported that China has come to dominate the vitamin raw material market over the last decade, controlling approximately one third of the world's vitamin production. To demonstrate China's emergence as a powerful force in the supply industry, the following charts of percentage of Vitamin Raw Materials imported from China for years 2001 to 2007 reflect this:

Sales of Raw Materials Imported From China by Individual Letter Vitamin 2001-2007

Supply from China %	2001	2002	2003	2004	2005	2006	2007
Vitamin C	55%	60%	61%	65%	75%	80%	92%
Vitamin E	15%	20%	21%	30%	35%	42%	40%
B Vitamins	40%	42%	45%	50%	55%	63%	65%
Vitamin A	15%	17%	17%	20%	32%	27%	26%
Other/Pre-Mixes	37%	36%	38%	42%	47%	59%	60%

Source: Nutrition Business Journal estimates derived from supply company surveys and interviews with executives.

[84] Ibid



Final Considerations and Recommendations

Beginning in 2007, China overtook Canada to become the largest source of total U.S. imports (~$322 B); with just over 16% of total U.S. imports.This trend has continued up to November 2009, in which, according to US trade data, China has captured ~19% of all imports. Based on US trade data normalized for uncompounded medicinal chemicals and their derivatives (i.e., generally for use by pharmaceutical preparation manufacturers), the estimated percentage of raw ingredients used in pharmaceuticals and supplements imported from China has gradually increased from ~2.6% to ~4.5% from 2006 to 2009 (YTD November) based on China's exports of uncompounded medicinal chemicals and their derivatives [NAICS code]. Taking into consideration the different defining methodologies for categorizing API, pharmaceuticals, etc. the underlying assumption for our analyses are that raw ingredients of pharmaceuticals and vitamins are classified under this code. Separately, our research analysis suggests that the U.S. relies quite heavily on Chinese suppliers for a number of imports of raw ingredients used in consumer healthcare treatments: heparin-related products, Vitamin products and their derivatives, acetaminophen, ibuprofen, and even acetosalicylic acid (ordinary Aspirin), all of which are in the top 25 of API exports to the U.S. One would expect this trend to continue with additional exports in the future.

In recent years, there have been numerous recalls and warnings issued by U.S. firms over various products imported from China due to health and safety concerns as outlined in this report. This has led many U.S. policymakers to question the adequacy of China's regulatory environment in ensuring that its exports to the United States meet U.S. standards for health, safety, and quality; as well as the ability of U.S. government regulators, importers, and retailers to identify and take action against unsafe imports (from all countries) before they enter the U.S. market.

Many reports, publications, and public testimonies assert that China's health and safety regime for export

products is fragmented and ineffective. The impediments are many: poorly enforced regulations, lack of inspections and ineffective penalties for code violators, underfunded and understaffed regulatory agencies and suspect interagency cooperation, the proliferation of fake goods and ingredients, the existence of numerous unlicensed producers, falsified export documents, intense business competition that often induces firms to cut corners, failure by Chinese companies to closely monitor the quality of their suppliers' products, government corruption and lack of accountability, especially at the local level. Chinese officials contend that most Chinese-made products are safe and note that U.S. recalls for health and safety reasons have involved a number of countries (as well as U.S. products). However, they have acknowledged numerous product health and safety issues.

Although it lies beyond the scope of this report, the counterfeiting of pharmaceuticals and supplements remains rampant, and poses special concerns for consumer health and safety. The United States notes its concern with the proliferation of the manufacture of counterfeit pharmaceuticals in China, among other countries, and the sale and distribution of counterfeit pharmaceuticals in many countries. A significant contributing factor in this problem is the unauthorized use of bulk active pharmaceutical ingredients (APIs) to manufacture counterfeit pharmaceuticals. For instance, in China, domestic chemical manufacturers that produce APIs can avoid regulatory oversight by not declaring that the bulk chemical is intended for use in pharmaceutical products. While China has acknowledged that this loophole must be addressed and has committed to expanding its regulations to control bulk chemicals used as the underlying source of many counterfeit drugs, the Office of the U.S. Trade Representative continues to urge China to adopt policies that will reduce the manufacture and distribution of unauthorized APIs.

Concerns over the health, safety, and quality of Chinese products could have a number of important economic implications. Relatively recently, both the United States and China have accused each other of using health and safety concerns as an excuse to impose protectionist measures, as reported in the case of imported drywall, and already some observers contend that similar issues of this nature could lead to growing trade friction between the two sides.

Interestingly, these international concerns over the safety of Chinese exports have not yet diminished the attractiveness of China as a destination for foreign investment in export-oriented manufacturing, including the U.S. pharmaceutical industry, as well as for other foreign firms that contract with Chinese firms to make and export other products under their labels (such as toys). China is engaged in ongoing efforts to restore international confidence in the health and safety of its exports through increased inspections, certification requirements, mandatory testing, etc., as evidenced by the high-level cooperative agreement between the U.S. Department of Health and Human Services and China's regulatory agencies.

The Food and Drug Administration (FDA), an agency within the Department of Health & Human Services (HHS), oversees the safety and effectiveness of human drugs and dietary supplements marketed and sold in the United States. Longstanding concerns regarding the capacity and capabilities of the FDA's foreign drug inspection program were brought to a new level and seriously debated in 2008 when heparin, a common blood thinner widely used by kidney-dialysis and post-surgical patients to prevent clots, and which was the cause of 81 U.S. fatalities,[85] was processed in China. Selected members of Congress have been fully informed and notified of the current situation and its potential consequences. In response to the increased outcry in the public arena, the FDA has launched initiatives to improve its Foreign Drug Inspection Program. The "Beyond our Borders" initiative focuses on international collaboration, building new systems, and working more closely with industry.[86] The agency is also enhancing information technology capabilities. In 2008, the agency received the green light from the State Department to create eight full-time FDA positions in China and announced it is hiring five local Chinese nationals as inspectors. On November 19, 2008, the first overseas office opened in Beijing, China

[85] 'New Data Link Heparin Deaths to Chinese Batches, FDA Says', Washington Post, Tuesday April 22, 2008; 'Heparin's Deadly Side Effects' Time/CNN Thursday, November 13, 2008, etc.

[86] Investigations – Broken Government FAILURE: LACK OF ADEQUATE FOREIGN DRUG OVERSIGHT; FAILURE: FDA FAILURE TO ENSURE DRUG SAFETY; The Center for Public Integrity, http://www.publicintegrity.org/investigations/broken_government/; 'FDA Seeks to establish Branch Office in China' Genetic Engineering & Biotechnology News September 1, 2008, Volume 28, Number 15; 'FDA outlines 'best practice' for importers' January 21, 2009; 'FDA launches global supply chain pilot scheme' January 15, 2009, www.outsourcing-pharma.com

primarily responsible for coordination between FDA and the Chinese regulatory agencies: the State Food and Drug Administration and the Administration of Quality Supervision, Inspection and Quarantine. The branches located in Shanghai and Guangzhou are reportedly structured to focus on conducting inspections, and working with Chinese inspectors to provide training as necessary. As reported previously, the GAO, outside experts, non-partisan agencies, and other concerned constituents have put forth and made public to members of Congress many fundamental recommendations for consideration and implementation.

Aside from internal distractions relating to perceived point of conflict arrangements, collaborations, poor morale, frequent scandals and other impeding factors, it is believed both in and outside the agency that the FDA has reached (or is extremely close to approaching) a breaking point.[87] It has been argued, with increasing momentum, that a complete segregation of the responsibilities of the FDA should be seriously evaluated.[88] As a leading member in Congress, Representative John Dingell, Chairman Emeritus of the House Committee on Energy and Commerce and the sponsor of the Food and Drug Globalization Act of 2009, has said, "You've got an agency that quite frankly is either non-functional, or dysfunctional, or maybe all of the above".[89] Another Congressional leader on FDA reform, Ranking Member of the Senate Committee on Finance Senator Chuck Grassley of Iowa, has also expressed profound concerns about frequent failures of management responsibilities and oversight, and personnel staffing at the Center for Drug Evaluation and Research (CDER).[90]

To address weaknesses in FDA's oversight of foreign establishments manufacturing drugs for the U.S. market, the Commissioner of FDA should:

- Require that establishments manufacturing drugs for the U.S. market update their registration annually.
- Explore a move towards increased accountability in DMF submissions, when applicable, for the "Agent" of the DMF Holder. This would distribute the responsibility for accuracy, validity, and veracity of the submitted information.
- Establish mechanisms for verifying information provided by the establishment at the time of registration.
- Ensure that information on the classification of inspections with serious deficiencies is accurate in all FDA databases.
- Conduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics.
- Perform timely inspections of foreign establishments that have received warning letters to determine continued compliance.
- Continue to make the case to Congress regarding the urgency of providing FDA with the resources necessary to properly regulate dietary supplements, and to improve IT infrastructure capabilities for better coordination.

[87] 'Food safety system near "breaking point":FDA' Christopher Doering, Tuesday March 18th, 2008 Reuters.com
[88] 'FDA Behind in Food Safety Audits' May 19th, 2009 NEWSInferno.com; 'PROMISES, PROMISES: FDA lags in food safety audits', Mary Clarke Jalonick AP Writer, May 18th, 2009 salon.com
[89] 'Is The FDA a broken agency?' Critics: Tainted peanuts, peppers, blood thinner highlight need for overhaul; AP March 3, 2009, MSNBC.com;
[90] 'Senator slams FDA "mismanagement"' Nick Taylor November 6th, 2008, http://www.inpharmatechnologist.com/Industry-Drivers/Senator-slams-FDA-mismanagement