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**Value Creation through Modernizing Chinese Medicine**

by

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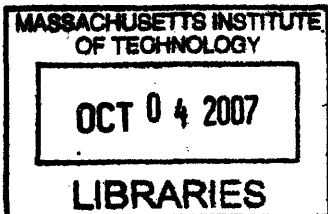
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## Table of Content

Abstract.....	1
1. Introduction.....	2
1.1 Accumulated Value in Chinese Herbal Medicine .....	3
1.1.1 Value accumulation in a long history.....	3
1.1.1.1 <i>Han</i> Dynasty (A) (206 B.C.-220 B.C.): Early classification according to herbal toxicological properties – an herb-centric view .....	4
1.1.1.2 <i>Han</i> Dynasty (B) (206 B.C.-220 B.C.): Application of herbal treatments according to disease processes – a host-centric view.....	5
1.1.1.3 <i>Tang</i> Dynasty (618-907 A.D.): Integration of pharmacy, clinical medicine and education – formation of philosophy of individualized medicine.....	6
1.1.1.4 <i>Song</i> Dynasty (960-1279 AD): Chinese herbal pharmacopoeias – efforts to standardize herbal formulations .....	7
1.1.1.5 <i>Song</i> and <i>Ming</i> Dynasties (960-1644 A.D): Acupuncture, surgeries, meditation, qigong and herbs – formation of holistic medicine .....	9
1.1.2 Unique medical philosophy .....	11
1.1.2.1 Organic one – systematic and holistic philosophy.....	12
1.1.2.2 <i>Yin-yang</i> – philosophy of balance .....	12
1.1.2.3 <i>Wuxing</i> .....	14
1.1.2.4 <i>Qi</i> .....	15
1.1.2.5 Mixed herbal formulas – an untapped value for the world drug market and a new hypothesis .....	16
1.2 Current Value Utilization Efforts by Global and Chinese Pharmaceutical Companies.....	17
1.3 Efforts to Modernize Chinese Herbal Medicine .....	19
1.3.1 Singleton drug development pathway.....	19
1.3.2 Mixed formula development pathway .....	20
2. Critical Paths to Value Realization.....	23
2.1 Regulatory Systems – US FDA and Chinese SFDA.....	23
2.1.1 Overview.....	23
2.1.2 Comparison of organization structures of FDA and SFDA.....	25
2.1.3 Comparing important statistical data between SFDA and FDA – new drug applications and approval rate .....	31
2.1.4 Comparing approval processes between SFDA and FDA .....	32

---

2.1.5 Comparing NDA review standards between SFDA and FDA .....	42
2.1.5.1 New drug application requirements .....	43
2.1.5.2 Pre-clinical research.....	51
2.1.5.3 Clinical trial of drugs .....	51
2.1.5.4 Investigational new drug (IND) applications.....	52
2.1.5.5 Time limit of new drug review.....	53
2.1.5.6 Communication between reviewer and applicant .....	56
2.1.5.7 Modern (western type) and traditional medicines .....	56
2.1.6 Trend of SFDA under the context of globalization.....	56
2.2 Modernization of Chinese Herbal Medicine.....	57
2.2.1 Singleton drugs .....	58
2.2.2 Botanical drugs .....	59
2.2.3 Combination drugs.....	59
2.2.4 Quality, standards and consistency - problems and improvements in producing Chinese herbal medicine.....	60
2.2.4.1 Fingerprinting technology and material quality control .....	61
2.2.4.2 Pre-clinical research – toxicity and pharmacokinetics.....	64
2.2.4.3 Clinical trials – design and efficacy evaluation .....	66
2.2.4.4 Manufacturing quality control .....	67
2.2.5 Fingerprint technologies and quality control of Chinese herbal medicine .....	68
2.3 Value Formation from Public Domain Knowledge to Private Property - Analysis of Literatures and Patents on Chinese Herbal Medicine.....	70
2.3.1 Introduction.....	70
2.3.2 Methodology .....	72
2.3.3 Analysis of literature statistics .....	74
2.3.4 Patent statistics.....	78
3. Case Studies .....	81
3.1 Metformin .....	81
3.1.1 Introduction.....	81
3.1.2 Development history of metformin.....	83
3.1.3 Initial success, new insights and continued research .....	87
3.2 PGG Derived from Lagerstroemia Speciosa (Banaba).....	92
3.2.1 Introduction.....	92

---

3.2.2 Research history on banaba .....	93
3.2.3 Development and commercialization of PGG .....	95
3.3 Grapes, Red Wine and Resveratrol .....	100
3.3.1 Introduction.....	100
3.3.2 Research about resveratrol’s beneficial effects.....	103
3.3.3 Anti-diabetic drug development.....	106
4. Discussion .....	108
4.1 Value-Realization Platforms and Models.....	108
4.2 “Bridge” Opportunities .....	108
5. Conclusion .....	109
References.....	110
Attachments .....	115

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## Abstract

My first hypothesis in this thesis is that there is significant value vested in traditional Chinese medicine that can be captured by converting them into ethical drugs through scientific analysis, screening and validation. Further, holistic treatment is a key difference between traditional Chinese medicine and western-type chemical drugs, which makes Chinese medicine a very valuable category of knowledge. Using mixed formula is a primary method of treatment in Chinese medicine. It is the application of distinctive medical philosophies of Chinese herbal medicines in practices, reflecting the uniqueness and advantages of Chinese medicine. For example, there are 96,592 mixed formula recorded by “Dictionary of Chinese Medicine Mixed Formula” published in 1997. My second hypothesis in this thesis is that value can be created and captured, under the globalization context, from mixed herbal formulas for the mainstream world market with the aid of fingerprint technologies.

To enter western markets as officially approved drugs through critical pathways, both scientific and regulatory, Chinese herb drugs must demonstrate sound evidence for safety and efficacy. I address in this thesis one of the central concerns of the pharmaceutical companies and FDA, that is, how quality control and material consistency is assured and how toxicity and drug kinetics of Chinese herbal medicines, either in its raw form, its purified form, its composite extract form or its mixed formula form, may be measured with reasonable scientific certainty and what would be the likely trajectory of further research.

My thesis research involves the following aspects: firstly, I characterize, by and through historical review and analysis, the formation of unique Chinese holistic medical philosophy to apply herbal medicines, particularly mixed herbal formulas, to systematically modulate the human body to prevent illnesses, to combat health problems and to restore balanced health; secondly, I performed a comparative study on the regulatory systems between Chinese SFDA and US FDA to provide insights on the trend of harmonic convergence of laws and regulations and challenges going forward, including collection and extrapolation of relevant statistical data; thirdly, I researched emerging fingerprint technologies to address the central issues of standardization, quality control, material consistency, safety and efficacy measurements of Chinese herbal medicines; fourthly, I performed data collection on major Chinese sources of published literatures and patent applications/grants for public and private medicinal knowledge formation, which may be viewed as a surrogate indicator for embedded economic value in the system, to compare trend and gaps between China and developed countries; and lastly, I presented three case studies of development of an-diabetic drugs from herbal sources, to illustrate how value may be created and captured through using modern technologies to tap into the accumulative knowledge base in herbal medicine.

The thesis concludes that there are significant values to be captured, by and through cross-border collaborations under the globalization context, from Chinese herbal medicine. Both ethical single molecular entity (singleton) herb-derived drugs and mixed formula herb-derived drugs may be created going forward.

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# 1. Introduction

In this age of globalization, featured by free flow and optimized allocation of capital, technology, information and service in the global context, economic interdependence and interaction between countries are becoming stronger and stronger. Globalization can bring many benefits, both tangible and intangible - ideas, reforms, goods, investments, and even revolutions. China's participation in globalization is increasingly important to the world. When the global economic growth remains weak in the past decades, China's economy is one of the few bright spots. China has also provided the world with the largest consumption market. When more than 1.3 billion people become well-off, the incremental demand on everything will be enormous.

In the pharmaceutical industry, the trend of globalization and China's participation has redefined the landscape and is bringing about new opportunities. On the one hand, the Chinese pharmaceutical market is growing at an impressive double digit pace with a projected value of \$25 billion by 2008.<sup>1</sup> On another hand, Chinese medicine, particularly herb-based medicine with a wealth of accumulated empirical effectiveness in treating various illnesses, may become a new funnel of therapeutics. In this context, we ask the question, can Chinese herbal medicine, which has helped Chinese people maintain their health for thousands years, become an important value in the global drug development in the pharmaceutical industry? Can it be an emerging source of new drug development aiming at not only the Chinese ethnic market but the world market in both developed and developing world? If the answer to this question is in the affirmative, what are the means and ways to discover and realize this value?

My first hypothesis is that there is significant value vested in Chinese herbal medicine. This statement, seemingly obvious, is undergoing a heated debate not only in China, but also in the US and other developed markets. A high profile case, for example, is US FDA's official ban of *ephedra* (an extract form of Chinese herb *mahuang*, which may relieve cough and asthma, raise a person's energy and produce weight-loss) due to its adverse effects in a small number of cases linking to heart attack, stroke and sudden death because of its ability to raise blood pressure, increase heart rate and speed up brain activity. To date, appeals have been filed in a vain effort to vacate such a ban, and most interestingly, *ephedra* is still widely distributed and used by a significant number of users in the US despite the FDA's official action. To address my hypothesis, the first set of questions is to ask why an herbal product, such as *mahuang*, which has been used for thousand years in Chinese medicine and proven to be effective in many applications, would encounter such a severe regulatory penalty due to its toxicity effects. How are toxicity and drug kinetics of Chinese medicine, either in its raw form, its composite extract form, its mixed formula or its purified form, being measured? What are the differences in the regulatory processes and standards, say, in the US FDA and Chinese

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<sup>1</sup> Summary of Advantages and Disadvantages of Increasing Pharmaceutical R&D Outsourcing to India and China, Frost & Sullivan research report, July 22, 2005

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SFDA? Is it possible to converge such systems to develop a universally accepted global standard or technical standardization? Aside from differences in levels of technology, is there anything intrinsically different in characterizing Chinese herbal medicine of different compositions? The introduction part of the thesis attempts to answer the above questions, so that the problem can be defined and a basic landscape can be laid out to characterize the value or potential value of Chinese herbal medicine.

## **1.1 Accumulated Value in Chinese Herbal Medicine**

### **1.1.1 Value accumulation in a long history**

To appreciate the value and benefits of Chinese herbal medicine, we shall first review its developmental trajectory. The purpose of this review is not simply for a layout of significant historical events or landmark publications, rather, as the following narrative will demonstrate, the intention is to illustrate a basic understanding of Chinese herbal medicine, which has evolved over a long history from a herb-centric view by characterizing the short-term therapeutic effects and side effects produced by various herbs into an interactive view, where body and herbs are working together to combat diseases and produce optimized health conditions in a time- and stage-sensitive manner; and further into an integrated view, where herbal medicine is only one element of the total multi-variant dynamic human-environment system, through which the human body continuously modulates itself and responds to the external environment at the aid of the herbal medicine. In this cognitive evolution about the relationships between the human body, disease states and nature, the core understanding of traditional Chinese medicine is one that any and all solutions to health problems are already vested in nature, because any unhealthy and disease condition is essentially an internal imbalances that causes the human body to become susceptible to diseases such as invasion of *shanghan*. By mixing various natural products, particularly herbal medicines and other natural treatments such as acupuncture and massage, the internal defense system and energy may be mobilized and the internal system re-modulated. From modern cellular and molecular biology perspective, perceivably, such *yin-yang* modulations induced by various herbal treatments must have been intimately involved in the activation and regulation of multiple signaling pathways and modulation of genetic circuitries that selectively express certain molecules and proteins, which in turn produces desirable health outcomes.

This holistic view or systemic view in traditional Chinese medicine is fundamentally different from what we term a scientific view, where the causal relationship between a drug and response is largely linear, highly repeatable and predictable. The traditional Chinese medical theory views the total human system in a much higher context; it describes any and all health problems in a non-linear and continuously changing perspective, it not only focuses on the relief of immediate symptoms, but also long-term cultivation of the internal human defense system so that a balanced healthy state can be restored and sustained. Using today's terminology, both the mixtures of herbal medicines and the human hosts are working on a non-linear and systematic fashion – a concept that often puzzles westerners. In recent years, systems biology developed very fast in western scientific circles. From this new systematic perspective, the non-linear human systems is

reduced to many finite elements with quantitative and linear relationships, and such finite elements, by and through collaborative synergies, produce a complex biological system. This new scientific trend in the western world, quite amazingly, dubs seamlessly with the philosophy and concepts in the core of traditional Chinese medicine. At the application and practical levels, many treatments of diseases are becoming “systematic,” instead of single drug modalities, combinatorial drugs, analogous to Chinese herbal medicinal mixtures at least at the conceptual level, are increasingly being applied in clinical settings to produce a more effective and sustainable therapeutic effect or with reduced side effects. For example, the “cocktails” for HIV treatment, the combinatorial multi-drug treatments for cancer and infectious diseases, just to name a few. Now, let’s first look at its history.

Traditional Chinese medicine has a long history of 5000 years, dating back to the period of the *Huang Di* (Yellow Emperor), the first Chinese emperor. In remote antiquity, when struggling against nature, ancient Chinese people discovered some plant and food items that had specific properties and could relieve or eliminate certain symptoms and diseases. Then finding and using herbal medicine began together with many theories and methods of practicing medicine, such as diagnostic methods of inspection, listening, smelling, pulse-taking, and treatment methods of combining herbal remedies, acupuncture, cupping, breathing exercise therapy, systematic exercise, hydrotherapy, etc. This knowledge has accumulated generation after generation, including experiences, practice skills and theories, which have great practical value but its scientific implications have been poorly understood and are waiting to be further characterized.



Figure 1.1.1 History of China<sup>2</sup>

Shen-nong.com is a website that provides information about the history of Chinese medicine, referring to books and articles, such as *A Brief History of Chinese Medicine* written by Peng Yoke Ho & F. P. Lisowski<sup>3</sup>. I summarize some important developments in the following text and point out the value implications in these developments.

### 1.1.1.1 Han Dynasty (A) (206 B.C.-220 B.C.): Early classification according to herbal toxicological properties – an herb-centric view

Among developments during Han Dynasty (206 B.C.-220B.C.) summarized by Shen-nong.com,<sup>4</sup> an important book came out, named “*Shennong Bencaojing*” (Classic of Herbal Medicine). The name of the author is not known.

<sup>2</sup> <http://www.shen-nong.com/eng/history/references.html>

<sup>3</sup> <http://www.shen-nong.com/eng/history/references.html>

<sup>4</sup> <http://www.shen-nong.com/eng/history/qinhan.html>



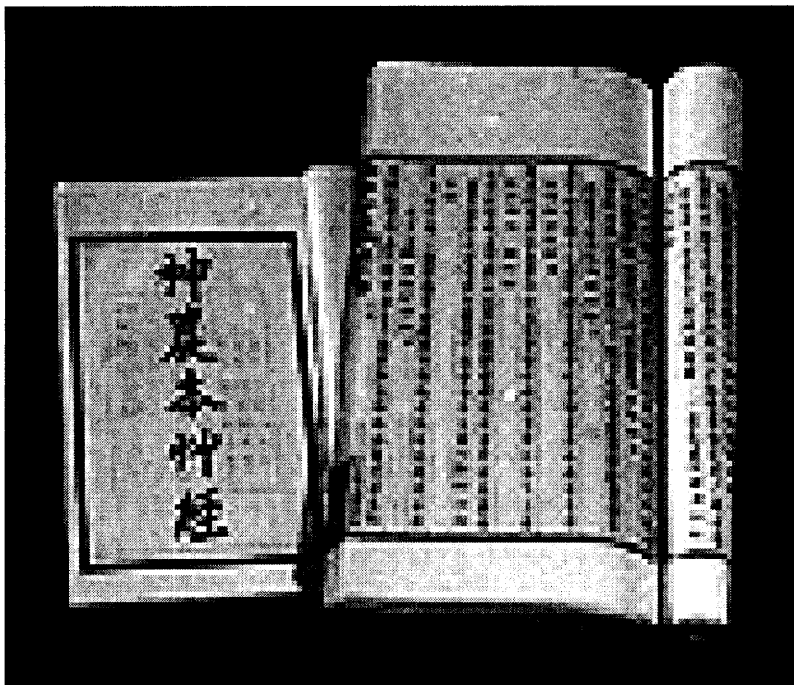


Figure 1.1.2 *Shennong Bencaojing*<sup>5</sup>

This landmark book is a comprehensive summary of 365 Chinese medicines, of which 252 originate from plant, 67 from animals, and 46 from minerals. It divides these medicines into three categories based on their respective toxicological properties. The first category has 120 medicines, they are non-toxic and have functionalities to preserve vitality or extend life, such as the well-known *ginseng* (*panax ginseng*). The second category consists of 120 medicines that can be used to treat illness and enhance a person's health, but the herbs in this category, such as *Chinese angelica* (*angelica sinensis*) and *ephedra* (*mahuang*), could sometimes be toxic and should be used carefully for certain ailments. The third category includes 125 toxic medicines with side effects, and was preserved for treating specific diseases. For example, the herb *croton* (*croton tiglium*) may be prescribed to treat illnesses with edema or eliminate phlegm. This book may represent the initial efforts in Chinese medical history to use accumulative empirical evidences to characterize the herbal medicines according to their level of toxicity and side effects, which has guided Chinese folk doctors for decades to carefully select and use these medicines according to the intended purpose of prescription.

#### **1.1.1.2 Han Dynasty (B) (206 B.C.-220 B.C.): Application of herbal treatments according to disease processes – a host-centric view**

Also during the *Han* Dynasty, several prominent physicians emerged<sup>6</sup>. The most famous one is Zhang Zhongjing, who was respectfully addressed as “sage of medicine” and wrote an important medical book, named “*Shanghan Zabinglun*” (Discourse on Fevers and

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<sup>5</sup> <http://www.shen-nong.com/eng/history/qinhan.html>

<sup>6</sup> <http://www.shen-nong.com/eng/history/qinhan.html>

Miscellaneous Illnesses), dealing with the treatments of many febrile conditions. Later in the *Song* Dynasty (960A.D.-1279A.D.), this book was rewritten and divided into two books called “*Shanghanlun*” (Treatise on Febrile Diseases) and “*Jinkui Yaolue*” (Summary from the Golden Chest). The significant effect of doctors in this time and their publications is the layout of foundation of Chinese medicinal philosophy, which views the disease conditions and symptoms as time series events and herbal treatments must be dynamically adjusted according to the host’s illnesses at different stages of a disease process – marking the initial formation of interactive medicine.

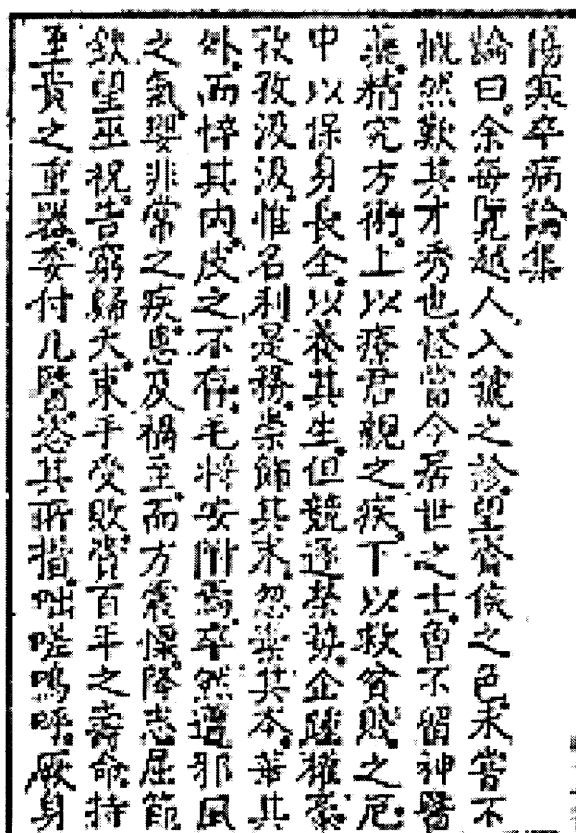


Figure 1.1.3 *Shanghan Zabinglun*<sup>7</sup>

### 1.1.1.3 *Tang* Dynasty (618-907 A.D.): Integration of pharmacy, clinical medicine and education – formation of philosophy of individualized medicine

From the information provided on shen-nong.com, we can find that during the *Tang* Dynasty (618-907 A.D.), an Imperial Academy of Medicine was founded and run by the government to serve the emperor, his family and nobles. This academy had two divisions, a clinical doctors division and a pharmacy division. The pharmacy division helped maintain the Imperial Academy’s herb plantation and focused on the standardization of herb processing. This academy is also a medical education institution with lectures and apprenticeship. If a student failed the final examination required for graduation, he would be dismissed from the academy. Doctors were promoted based on their treatment success

<sup>7</sup> <http://www.shen-nong.com/eng/history/qinhan.html>

rate, a system that measures the outcome of the treatments rather than standardizing the treatment methodology or herbal formulation, which were highly variable subject to the specifics of the target disease process and patients. Herbal King Sun Simiao in the *Tang* Dynasty is one of the most influential physicians in the history of Chinese medicine, famous by his application of medicine and his adherence to an ethical code. His best known works are “*Qianjin Yaofang*” (Prescriptions Worth a Thousand Gold for Emergencies or Precious Prescriptions for Emergencies) and “*Qianjin Yifang*” (Supplement to the Essential Prescriptions Worth a Thousand Gold or Supplement to Precious Prescriptions). The first set is comprised of 30 volumes and lists 5,300 prescriptions. The second set is also made up of 30 volumes and lists 2,571 prescriptions.<sup>8</sup> When woodblock printing was improved by Bi Sheng in 1040 A.D. with the invention of movable type, many medical classics were rewritten and many medical texts were published under government supervision or individually.

During the above period, the herbal medicine was not an independent discipline, but became integrated with clinical practice and medical education. The medical practice and herbal medicine was more of an art than science, because the proliferation of combinatorial herbal treatment formulas and many of the formulations of various herbs were highly individualized according to the basic patient parameters such as age and previous health conditions, disease processes and stages, and sometimes according to individual doctor’s preferences and accumulative experience.

#### **1.1.1.4 Song Dynasty (960-1279 AD): Chinese herbal pharmacopoeias – efforts to standardize herbal formulations**

The *Song* Dynasty (960-1279 AD) witnessed scholarly compilation of many pharmacopoeial texts. The following is a summary of important pharmacopoeial texts in the Song Dynasty (960-1279 AD)<sup>9</sup>:

<b>Date</b>	<b>Author</b>	<b>Title of Pharmacopoeias</b>	<b>Comments</b>
973	Ma Zhi with others	<i>Kaibao Bencao</i> (Herbal Medicine of the Kaibao Era)	This herbal text expanded the number of drugs to 983 and modified their classification.
1057	Su Song and colleagues	<i>Jiayou Buzhu Bencao</i> (Complete and Annotated Materia Medica of the Jiayou Era)	The number of drugs was increased to 1,083.
1061	Su Song and colleagues	<i>Tujing Bencao</i> (Illustrated Materia Medica)	This was the first time illustrations were included in a pharmacopoeia.
1108	Tang Shenwei	<i>Zhenglei Bencao</i> (Classified Materia Medica)	A unique pharmacopoeia listing 1,558 drugs with illustrations; it remained the model for the next 500 years.
1116	Kou Zongshi	<i>Yanyi Bencao</i> (Development of Herbal Medicine)	This book clarified the properties and pharmacology of herbs.

<sup>8</sup> <http://www.shen-nong.com/eng/history/suitang.html>

<sup>9</sup> <http://www.shen-nong.com/eng/history/five.html>

Besides pharmacopoeias, many prescription books were also published. “*Taiping Shenghuifang*” (Prescriptions from the Pharmacy of Harmonious Assistance), commissioned by the government and written by Wang Huaiyin at the end of the tenth century, listed a total of 16,834 prescriptions and gave details of the prescription, herbs (drugs) used, syndromes and pathology. The following are some important prescription texts in the *Song* Dynasty (960-1279 AD)<sup>10</sup>:

Date	Author	Title of Prescription Book	Comments
1107 -1110	Chen Shiwen and Pei Zongyuan	<i>Taiping Huimin Hejijufang</i> (Prescriptions from the Pharmacy of Harmonious Assistance)	This book lists 788 prescriptions and gives information on how to prepare and use drugs. It represents the first government-published prescription book in the world.
1111 -1117	Cao Zongxiao and other medical officers	<i>Shengji Zonglu</i> , (General Catalogue of Divine Assistance)	This book lists 20,000 prescriptions and describes the causes, symptoms and cures for different illnesses.
1253	Yan Yonghe	<i>Jishenfang</i> , (Prescriptions for Saving Life)	This was an individually published text. The decoction known as <i>gui pi tang</i> is still used today.

The relevance of the above pharmacopoeias and prescription texts to this thesis is that most of the herbal drugs were in raw form with limited processing or treatments in these pharmacopoeias and prescriptions were in composite formulas rather than as single herbs, which is substantially different from western style pharmacopoeias that increasingly characterize the drugs’ properties, effectiveness and side effects in their stand-alone applications. Additionally, the formulations of the 20,000+ herbal prescriptions are by far not exclusive, rather, the prescriptions were meant to represent only the “core” formulas and the doctors were always at the liberty to change or adjust the composition and quantities of the herbs according to the host conditions and disease processes or stages. Further, the treatments were always on an experimental mode, in the sense that each prescription would always be based on the host responses to previous “trial” treatments – a real option time series proposition, if I were to use a modern concept to describe the continuously information-capturing, learning and actions.

The core idea underlying the above Chinese herbal treatments is derived from the philosophy that any unhealthy state is an imbalance of bodily *yin* and *yang*, and illnesses and symptoms are only the superficial manifestation of internal imbalances. The purpose of the treatments is not only to relieve the symptoms, but more importantly, to eliminate the root causes. It is also important to appreciate that many Chinese herbs, used singularly or in composite formulas, are meant to mobilize the human defense system such as “*qi*” (energy) and “*xie*” (blood), and through such mobilization, the human body will build necessary “troops” to combat the illnesses. Using today’s scientific concepts, the input of herbal treatments do not necessarily proximately cause the treatment outcome

<sup>10</sup> <http://www.shen-nong.com/eng/history/five.html>

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in the short run, at least not in a very linear fashion, because the herbs could only work through the complex human mechanism, which is not only different from person to person, but also its internal pathways and mechanisms are very difficult to delineate. To further illustrate this point, for example, modern medical scientists have discovered that none of the individual herbal components in some very effective anti-febrile herbal formulas have anti-bacterial effects from controlled *in vitro* experiments, nonetheless the formulas could effectively combat pneumonia caused by bacteria. As I will illustrate further in this thesis, even in cases that a single herb may be very effective in treating a certain medical condition, but when we use current scientific deductive methods to analyze the effective chemical components, we are often puzzled by the findings. For example, we are currently analyzing an herb in China's Yunnan Province, which has long been commercialized as *QianLieAn* to be effective in treating non-bacterial prostatitis. We have narrowed it down to 7 chemical compounds, among which three have shown limited but weak effects and the remaining four are not effective at all regardless of dosage when used singularly. But when we combine all 7 compounds together, however, the composite drug works wonders (author's private research data). We instantly realize that the synergies created among and between these individually ineffective components may be the true direction of the pharmacological development going forward. We must not only use deductive methods as science has advanced, but more importantly, use inductive methods to navigate the complex world of combinatorial pharmacology, a road less traveled but most promising.

#### **1.1.1.5 Song and Ming Dynasties (960-1644 A.D): Acupuncture, surgeries, meditation, qigong and herbs – formation of holistic medicine**

During this period many different medical theories and schools, as well as treatment modalities became more mature. The various ideas further converged into a fundamental understanding that internal and external treatment should be combined to preserve health and treat illnesses. The developments during the *Ming* Dynasty include methods for achieving analgesia, aseptic techniques and homeostasis contributed to various surgical treatments. Among these new Chinese medical technologies, acupuncture, was also advanced during this period. Two life-size male bronze statues were cast, complemented by a book called "*Tongren Shuxue Zhen Jiu Tujing*" (Illustrated Manual of the Bronze Man Showing Acupuncture and Moxibustion Points). These statues had 657 acupuncture points drilled into them which were filled with water and covered with wax. When a student needed the acupuncture point correctly, water would leak out.

The book "*Waike Zhengzong*" (The Genuine Surgery), written by Chen Shigong, covered a series of surgically treatable diseases and many effective prescriptions. The book outlined the surgical procedure for the repair of a "slashed throat," the use of copper wire to excise nasal polyps under local anesthesia, and described in detail cancer of the lip and breast. These were the earliest surgical records in the history of traditional Chinese medicine.



Figure 1.1.4 *Waike Zhengzong*<sup>11</sup>

With regard to the herbal medicine, another landmark book was written by a very productive writer and seasoned medical practitioner Li Shizhen. The book was called “*Bencao Gangmu*” (Compendium of Material Medical), which is one of the most comprehensive and highly regarded Chinese medical texts. The book summarizes most available information about herbal medicine in the sixteenth century. Li added 374 new medicines (mostly herbs) in his text in a list of previously known 1,892 medicines and included over 1,000 illustrations. Classification of medicines in the “*Bencao Gangmu*” differed from previous pharmacopoeias in that he developed 16 headings: 1-water, 2-fire, 3-earth, 4-metal, 5-stone, 6-plant, 7-grain, 8-vegetable, 9-fruit, 10-tree, 11-products derived from garments and tools, 12-insect creatures with scales (reptiles, fish), 13-creatures with shells, 14-bird, 15-quadruped, and 16-products of human origin. This book was supplemented by another book called “*Bencao Gangmu Shiyi*” in the *Qing* Dynasty. The fascination for ancient classics re-emerged during the *Qing* period and many were re-edited, such as the “*Huangdi Neijing*” (The Yellow Emperor’s Medicine Classic), “*Shanghanlun*” (Treatise on Febrile Diseases) and “*Jinkui Yaolue*” (Summary of the Golden Chest).<sup>12</sup>

These medical publications formed a very comprehensive body of medical knowledge that were referred to and supplemented by medical practitioners. The medical practitioners usually combine herbal formulas with all other available technologies such as acupuncture, qigong and surgeries to treat the patient in a holistic fashion. Overall, this represents the formation of holistic medical theory and practice.

Since the beginning of the 19th century, however, with western medicine entering and developing rapidly in China, traditional Chinese medicine’s development was affected severely, even considered as unscientific and feudal after the Opium Wars. After the foundation of the People’s Republic of China, the government affirmed the policy to

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<sup>11</sup> <http://www.shen-nong.com/eng/history/ming.html>

<sup>12</sup> <http://www.shen-nong.com/eng/history/ming.html>

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protect traditional Chinese medicine, but for a long period of time, the schools of traditional Chinese medicine and the western medicine were separated into different camps. Traditional Chinese hospitals were so named and herbal medicines were the primary treatment modalities. The western hospitals dispensed pills and practiced surgeries as the primary treatments.

From empirical perspective, over the past thousands of years, traditional Chinese medicine, by and through consistent practice, learning, research and scholarly summation, has developed a set of both practical and balanced health care system, which is affordable, safe, efficacious and effective. Herbal medicine is viewed as a central and integral element of this system.

### **1.1.2 Unique medical philosophy**

If Chinese herbal medicine, over thousands of years, produced positive health benefits, helped combat many grand epidemics and other natural health hazards, and eventually preserved and sustained the largest population on earth, why can't we simply use the modern technology to dissect the proven herbs or herbal formularies and find the most effective compounds in these herbs, herbal powders or composites? In other words, if the value is empirically obvious, why couldn't we easily capture it? The answer to this question is central to this thesis.

In the past centuries, particularly in the past decades, many researchers and scientists have attempted to utilize the latest technologies to screen, isolate and purify molecules and compounds from herbs and indeed have achieved compelling successes. If we go through western pharmacopoeias, we could identify plentiful drugs that are traceable one way or another herbal origin, from drug for congestive heart failure *digoxin* to the wonderful anti-cancer drug *taxol*, to the three cases that I would present later in this thesis. But many efforts along these research paths or most of the efforts in fact, are fruitless, particularly in recent years, despite the availability of modern chemical technologies in isolating and fast-screening chemical compounds. There are a few hypotheses we could postulate, for example, first, the low-hanging fruits are already taken; second, the extract from the plant is no longer necessary because the recombinatorial chemistry can basically reconstruct from many known compounds. My hypothesis, to partially explain this phenomenon of reduced productivity in using reductive scientific research to develop herb-based drugs, is that many of the herbal medicines must retain their composite formula in order to maintain clinical efficacy and effectiveness. In other words, I believe that the conventional single molecule screening approach through identifying single herb-derived compounds is one method to capture the value in herbal medicine, but by far not the only "scientific" method. Characterizing composite herbal compounds or mixtures through fingerprint related technology opens a new avenue to extracting the value in herbal products. Such methods may be cheaper, faster and may result in affordable and effective medicine for preventing and treating illnesses, and potentially improve quality of life and prolong productive life.

This seems to be a bold hypothesis because it deviates from conventional scientific wisdom. This wisdom requires finding a chemical entity that is minimally required to produce a therapeutic effect(s). One may argue that putting a bunch of mixed compounds which are not well characterized individually and make a collective pharmaceutical claim,

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is simply unscientific.

To address the viability of the hypothesis and start to answer these scientific concerns, let's review the Chinese philosophies relevant to traditional Chinese medicine in general and to herbal medicine in particular. With a basic understanding of these philosophies, I hope we can establish some common concepts and communicative language.

During the long Chinese history, Chinese medicine created and consummated some unique medical philosophies, including the concepts of organic one, *wuxing* (five evolutions or elements), *qi*, and *yin-yang*, as well as the use of mixed formula.

### **1.1.2.1 Organic one – systematic and holistic philosophy**

As stated in the early part of this thesis, the Chinese organic one concept is fundamentally similar to the philosophy underlying the present day systems biology. The concept of organic one is the central tenet of Chinese medical theories, which views the body as a unified system of connections that, once stimulated, can help other parts of the body to maintain health. This is a concept of holism. Holism is a key difference between traditional Chinese medicine and western modern medicine, which makes Chinese medicine a very valuable category of knowledge. As stated earlier in this thesis, the Chinese organic one concept is fundamentally similar to the philosophy underlying the present day systems biology, which is still under fast development, thanks to the modern computing technologies and advanced algorithms.

### **1.1.2.2 Yin-yang – philosophy of balance**

Theory of *yin-yang* was used by ancient Chinese people to explain the observed phenomena in nature. The theory is based on two basic components: *yin* and *yang*, which combine in a complementary manner and form a method for explaining relationships between objects. Gradually, this logic was developed into a system of thought that was applied to other areas, such as medical practices.

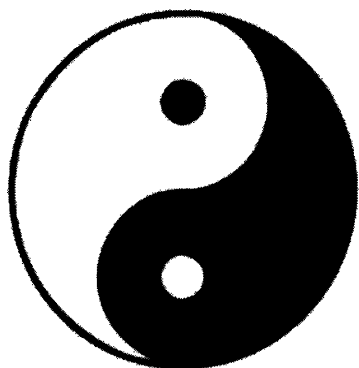


Figure 1.1.5 Symbol of *yin-yang*<sup>13</sup>

Usually, *yang* is associated with energetic qualities; while on the other hand, *yin* is associated with the physical form of an object and has less energetic qualities.

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<sup>13</sup> <http://www.shen-nong.com/eng/principles/whatyinyang.html>



The properties of *yin* and *yang* include: (1) *yin* and *yang* oppose each other while mutually controlling and inhibiting each other at the same time, resulting in a continuous state of dynamic balance; (2) *yin* and *yang* mutually create and depend on each other, the activity (*yang*) of the body is nourished by its physical form (*yin*) and the physical form is created and maintained by the body's activity so as to achieve a balanced state of health; (3) *yin* and *yang* change and grow in a cyclic and balanced manner; (4) *yin* and *yang* can transform into each other when one aspect goes to an extreme.<sup>14</sup>

According to the *yin-yang* theory, the body's organs and tissues can be classified to *yin* and *yang* based on their functions and locations. "The upper body belongs to *yang* while the lower body belongs to *yin*. Other *yin yang* pairs in the body include the interior (*yin*) versus the exterior (*yang*), the front (*yin*) versus the back (*yang*), the inside (*yin*) versus the outside (*yang*) of the limbs and the five *yin* organs versus the six *yang* organs. Each organ can also be further divided into *yin* and *yang* aspects such as heart *yin* and heart *yang* and kidney *yin* and kidney *yang*."<sup>15</sup> Health is achieved when *yin* and *yang* are in harmony and *yin yang* disharmony is the cause of disease and physiological disorders. Patients were diagnosed according to their disharmony pattern. There are eight principal disharmony patterns as shown on the following table<sup>16</sup>.

	<b>Disharmony Pattern</b>	<b>Yin/Yang</b>	<b>Manifestations</b>
1	Interior	<i>Yin</i>	An interior pattern is generated by internal disharmony such as a disorder of organ function.
2	Exterior	<i>Yang</i>	An exterior pattern is generated by "external influences" such as wind and cold (i.e. common cold).
3	Cold	<i>Yin</i>	A cold pattern is manifested by signs such as a pale face, cold limbs, aversion to cold, clear urine, or watery stools. The signs are usually related to non-excitatory physiological functions.
4	Heat	<i>Yang</i>	A heat pattern is manifested by signs of a red face, high fever, dislike of heat, dark urine, or constipation. The signs are usually related to excitatory physiological functions.
5	Deficiency	<i>Yin</i>	Signs of frail and weak movements, tiredness, and shortness of breath, low voice, or dizziness indicate a deficiency pattern. The signs are usually related to lack of energy of normal functions.
6	Excess	<i>Yang</i>	An excess pattern exhibits signs of heavy movements, heavy and coarse respiration, or discomfort when touched with pressure. The signs are usually related to an excess/accumulation of evils/metabolic waste.
7	<i>Yin</i>	<i>Yin</i>	General pattern groups for yin manifestations include interior, cold and deficiency patterns.
8	<i>Yang</i>	<i>Yang</i>	General pattern groups for yang manifestations include exterior, heat and excess patterns.

<sup>14</sup> <http://www.shen-nong.com/eng/principles/propertiesyinyang.html>

<sup>15</sup> <http://www.shen-nong.com/eng/principles/application1yinyang.html#1>

<sup>16</sup> <http://www.shen-nong.com/eng/principles/application1yinyang.html#1>

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Herbs also contain *yin* and *yang* properties and taste differently. Cold and cool nature herbs belong to *yin* while hot and warm herbs belong to *yang*. *Yin* herbs taste sour, bitter and salty, and *yang* herbs taste sweet and pungent. In formulating a treatment, correct herbs must be identified to adjust the disharmony pattern in the patient and thus help maintain the body's balance and health. It is essential to understand that both *yin* and *yang* properties coexistence in anything, inside human body, inside an herb, side an herbal formula, etc. Such a seemingly paradoxical thinking is often confusing to a person trained in western ways of logical thinking, but is so fundamental to traditional Chinese medicine.

### 1.1.2.3 *Wuxing*

To interpret their observations of the natural world, ancient Chinese people developed the theory of *wuxing*, after the theory of *yin-yang*. This theory asserts that substances can be divided into five basic elements: wood, fire, water, metal and earth, each containing unique characteristics and properties. Ancient medical practitioners used this theory in medical practices, viewing these five elements corresponding to different aspects of the natural world and the body as follows:<sup>17</sup>

	Wood	Fire	Earth	Metal	Water
Orientation	East	South	Middle	West	North
Season	Spring	Summer	Late Summer	Autumn	Winter
Climate	Wind	Summer Heat	Dampness	Dryness	Cold
Cultivation	Germinate	Grow	Transform	Reap	Store
Yin Organ	Liver	Heart	Spleen	Lung	Kidney
Yang Organ	Gall Bladder	Small Intestine	Stomach	Large Intestine	Bladder
Orifice	Eye	Tongue	Mouth	Nose	Ear
Tissues	Tendons	Vessels	Muscles	Skin & Hair	Bones
Emotions	Anger	Joy	Pensiveness	Grief	Fear
Color	Blue/ Green	Red	Yellow	White	Black
Taste	Sour	Bitter	Sweet	Pungent	Salty
Voice	Shout	Laugh	Sing	Cry	Groan

Dual modulation exists among five elements and organs belonging to different elements.

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<sup>17</sup> <http://www.shen-nong.com/eng/principles/whatfiveelements.html>

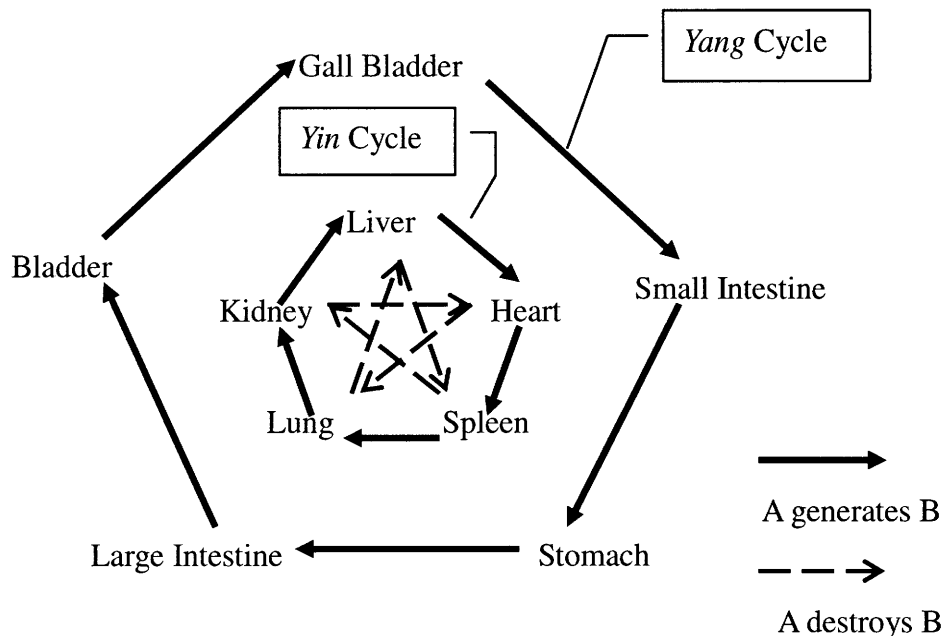


Figure 1.1.6 Dual modulation exists among five elements and organs

The relationships of the five elements play an important role in maintaining a balanced lifestyle. A simple illustration considering season changes is as following. “During the spring season, which belongs to the wood element, we should avoid excessive anger in order to stay healthy. In the winter season, which belongs to the water element, our bodies prefer to store energy so rest is important. Storage is an important function of the water element; therefore, in winter it is advisable for people to go to bed early. Even today, the application of the five elements theory remains relevant in promoting health. Understanding the relationships between the elements is the first step to achieve a harmonious balance in nature and life.”<sup>18</sup> The above statement would for sure sound like complete nonsense to a western reader, because anyone with rudimental scientific training or basic understanding of human anatomy would not believe this theory for a split second. But once the theory is applied together with traditional Chinese medicine, it works quite well. The five elements, human organs and *yin-yang* are not physical materials, but symbols of invisible mechanics that regulate human being’s life processes.

#### 1.1.2.4 *Qi*

In traditional Chinese medicine, *qi*, blood and body fluids are the most important fundamental substances. *Qi* is the life energy or life force flowing within the body. It refers to the physiological functions of organs and meridians. *Qi* in the human body comes from two main sources. The first is inherited from our parents at conception, known as the "innate vital substance." The second source is derived from essential substances in nature such as the air we breathe, food and water. Both the inherited and the acquired vital energies are further processed and transformed by the organs.

<sup>18</sup> <http://www.shen-nong.com/eng/principles/applicationfiveelements.html>

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There are four types of *qi*: inborn *qi*, pectoral *qi*, nutritive *qi* and protective *qi*. For example, the pectoral *qi* protects against evils, like the immune system which helps prevent disease from occurring or spreading. It moves outside the blood vessels and circulates in different areas from nutritive *qi*. Internally, it will be distributed to the diaphragm and scattered around the chest and abdominal cavities. Externally, it moves between the skin and muscles providing protection. Protective *qi* not only guards against illness and disease, but also regulates the sweat glands and pores and provides nourishment for the skin, hair and muscles.<sup>19</sup>

Cultivating, preserving and streamlining the *qi* is central to the host-centric medical theory and also one of the reasons why the same herbal formula would produce different results on different hosts and why the same disease in different hosts would require different herbal formulas. Once the conditions of the host *qi* are introduced as an additional set of decision variables, the herbal formula becomes highly customized according to each person's specific situations. This is why, thousands of years ago, Chinese medicine already laid out the principles of individualized medicine as we know today.

#### **1.1.2.5 Mixed herbal formulas – an untapped value for the world drug market and a new hypothesis**

Using mixed formula is a primary method of treatment in Chinese medicine. It is the application of the unique medical philosophies of Chinese medicine in practices, reflecting the uniqueness and advantages of Chinese medicine. Diseases are complex, so single ingredients have trouble achieving good efficacy, while two or more ingredients mixed together through certain processes can produce much better effects. In the long history of fighting various diseases, Chinese physicians found that some herbal medicines would produce unusual actions when mixed, leading to enhanced efficacy, reduced toxicity, or efficacy for other diseases. Accumulation of such findings led to knowledge of different matching formulas among certain herbal medicines. When Chinese physicians treated patients, they designed formulas according to a theory of balancing effects of efficacy, support, safety and induction for other treatments. The formula was created not only for the control of symptoms but also for a transition or restoration to a desirable healthy state. Thousands of mixed formula were developed and validated as effective during thousands of medical practices in China. For example, there are 96,592 mixed formula recorded by "Dictionary of Chinese Medicine Mixed Formula" published in 1997. In the face of wide availability of western-style drugs that consistently produce predictable efficacies, many mixed herbal formulas still are used in today's treatments in China, particularly for many hard-to-treat diseases and chronic health problems, an evidence of their efficacy.

Summarizing the above, we derive a new hypothesis: there must be values to be created and captured through understanding and commercializing these proven formulas. Such a new value-creation system is alternative and in addition to the current analytical methodology to narrow down to a single chemical compound, which has been known to

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<sup>19</sup> <http://www.shen-nong.com/eng/principles/qi.html>

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be a most expensive and lengthy process and the success rate is diminishing. The answer appears to be a no-brainer, but the question is how? How do we characterize these formulas without understanding exactly what chemical ingredients are contained in them? How do we to standardize the processes and measurements so that each batch of such formulas is consistent? How can we be assured that these products would fulfill the regulatory requirements for safety and efficacy? Let's move on from here.

## **1.2 Current Value Utilization Efforts by Global and Chinese Pharmaceutical Companies**

With the drying up of the new drug development pipelines and inspired by many successful stories in discovering new drug-like compounds from Chinese herbs, the perceived value of Chinese medicine is attracting more and more attention in the world. Major pharmaceutical companies such as Hoffmann La Roche, GlaxoSmithKline, Eli Lilly, Novartis and Pfizer have established joint ventures and wholly owned subsidiaries in China. For example, Novartis has established six joint-venture companies or projects in China and employs over 1,700 employees. Novartis also trains Chinese researchers in Switzerland. Novartis is establishing itself in pharmaceutical development. It is also bringing in experts from Europe to China to establish clinical trial centers in Chinese hospitals, which will allow the company to perform clinical trials in China. Novartis has recently invested \$100 Million and established its first R&D center in China, which is the sixth worldwide. It is also experiencing a sales growth of 25.0 percent annually in China.<sup>20</sup>

At the same time, Chinese pharmaceutical companies also began to seek financing in international financial markets, pursue mergers and acquisitions, form partnerships with global pharmaceutical companies, and apply for drug approval in other regulatory schemes. For example, a Chinese herbal medicine company named *Tongjitang* Chinese Medicine Company has successfully completed its initial public offering on the NYSE.<sup>21</sup> In this globalized value utilization process, there is a bridge opportunity. On the one side, western pharmaceutical companies face increasing drug innovation gap and cost escalation pressure to develop new drugs, with their irreversible sunk investments in advanced drug development technologies, instruments and other capital assets.

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<sup>20</sup> Summary of Advantages and Disadvantages of Increasing Pharmaceutical R&D Outsourcing to India and China, Frost & Sullivan research report, July 22, 2005

<sup>21</sup> <http://retailroadshow.com/>

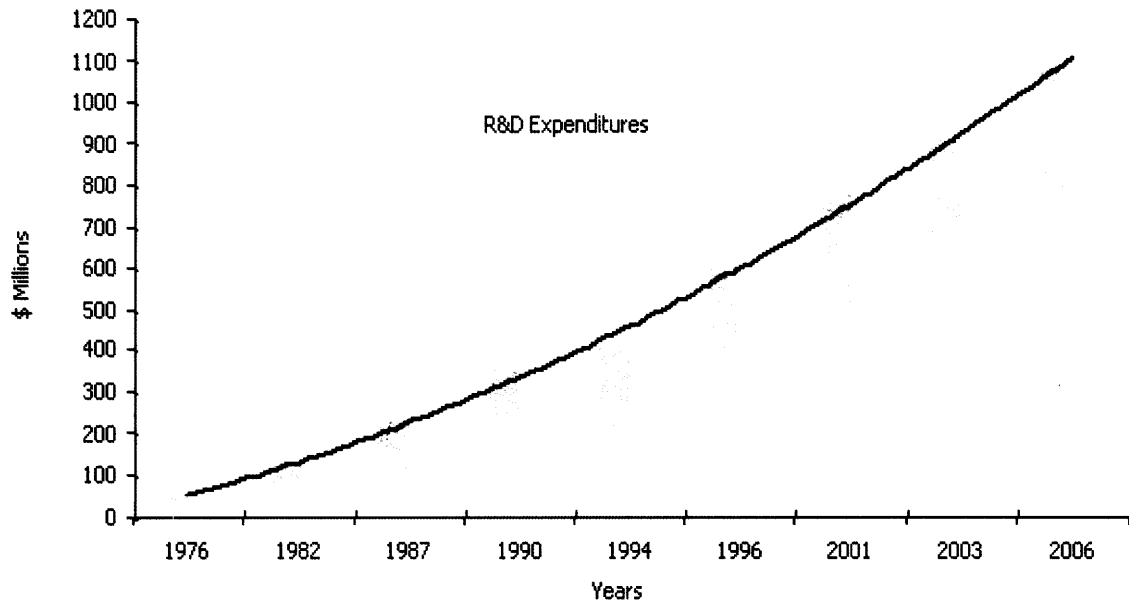


Figure 1.2.1 Increased R&D expenditure per approved drug<sup>22</sup>

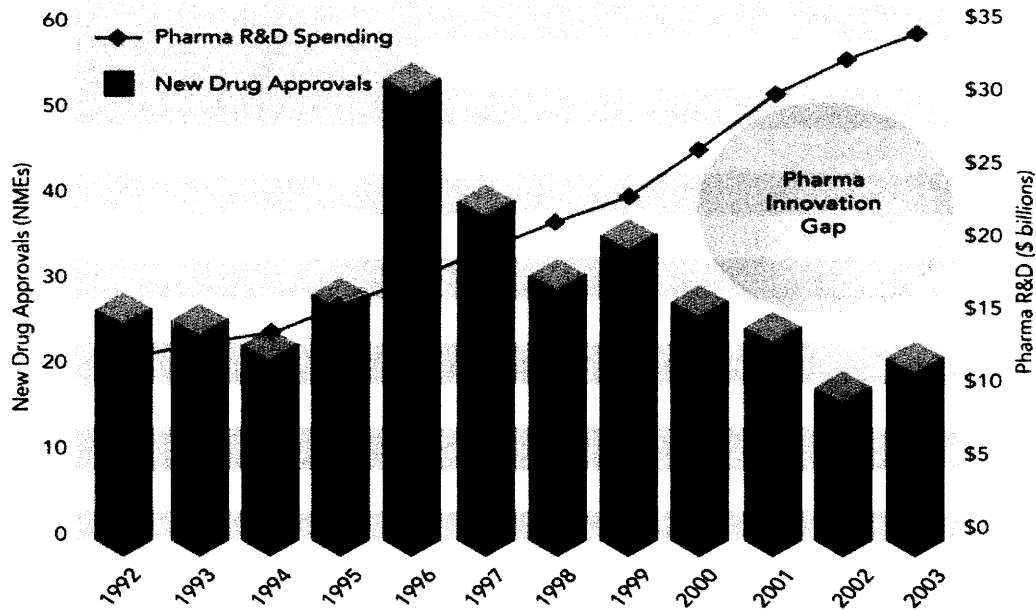


Figure 1.2.2 Widening pharmaceutical innovation gap<sup>23</sup>

On the other side, many Chinese pharmaceutical companies have accumulated significant knowledge about Chinese medicine with a long period of practical usage as well as

<sup>22</sup> Summary of Advantages and Disadvantages of Increasing Pharmaceutical R&D Outsourcing to India and China, Frost & Sullivan research report, July 22, 2005

<sup>23</sup> Prescription for Progress: The Critical Path To Drug Development, Robert Goldberg, Ph.D. and Peter Pitts, A Working Paper of the 21st century FDA Task Force, June 2006

academic and industrial researches. They have lower R&D costs relative to their western counterparts, and a large pool of research talents who understand western technology and skills. But this knowledge base, this pool of qualified researchers and intermediate products has apparently been undercapitalized or underutilized. Very limited Chinese herbal drugs are sold in the western mainstream markets and a very small number of herb-derived drugs have made their ways through the US regulatory system as officially approved drugs. This following figure is a simplified illustration for the potential bridge opportunity, which, under the current globalization trend and cross-border collaborations, may unleash the hidden values in Chinese herbal medicine.

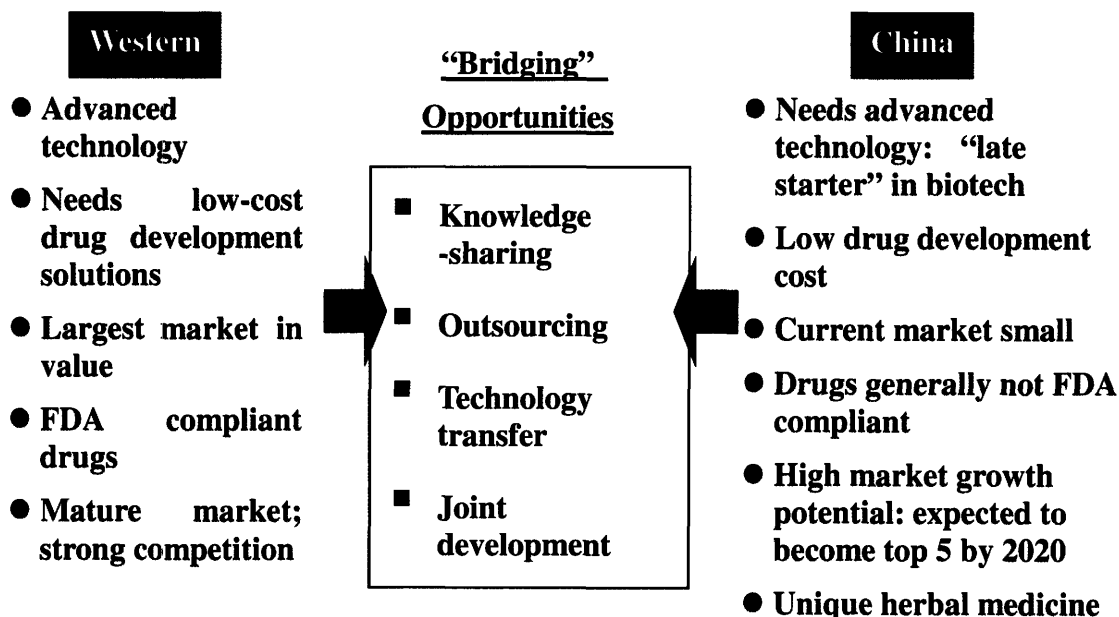


Figure 1.2.3 Bridging opportunity between western world and China

### 1.3 Efforts to Modernize Chinese Herbal Medicine

To enter western market as officially approved drugs, Chinese herbal medicines must demonstrate scientifically sound evidence for safety and effectiveness, as well as chemical properties and mechanisms. The fast advancements in the analytical and biological sciences, along with innovations in genomics and proteomics provide powerful tools to validate such medicines. This is a well established developmental pathway for Chinese herbal medicine and is being practiced by most international pharmaceutical companies. I call it the singleton drug development pathway. There is potentially another herb-derived drug development pathway for the world mainstream market; I tentatively name it the alternative pathway in hypothesis for this thesis, or mixed formula herb drug development pathway. Let me describe the concepts first.

#### 1.3.1 Singleton drug development pathway

The most commonly followed developmental trajectory, or rather, a logical thought process, is to look for efficacy leads from empirical clinical evidence or laboratory evidence of various individual Chinese herbs and use these leads as the starting point for

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new drug development. The purpose of this pathway is to screen, by various extracting, isolating and purification technologies, the effective molecules that may meet safety and efficacy requirements in IND or NDA regulatory processes. Once a drug is approved, the drug may be marketed in the US and/or in the world.

Among the first compounds derived from Chinese herbs to enter the Western pharmacopoeia was ephedrine, an amphetamine-like stimulant, firstly isolated by a Japanese researcher in late 19<sup>th</sup> century from the Chinese medicinal herb *mahuang* (*ephedra sinica*), which was used to treat congestion. It is a common ingredient in over-the-counter decongestants and prescription medications for bronchial asthma, among other products. *Mahuang* is also used in nonprescription dieting aids, and as a legal way to get high, dubbed “herbal ecstasy.” But an increasing number of reports of adverse effects have prompted several countries to ban nonprescription uses; such countries include the United States.

The recent significant drug derived from a Chinese medicinal herb is a compound called artemisinin from herb *qinghao*, or *artemisia annua*, a relative of the sweet wormwood found in North America. The traditional texts identified *qinghao* as beneficial for treating fever; the researchers found that artemisinin killed even chloroquine-resistant strains of plasmodium, the parasite that causes malaria. Recent work in US and European labs suggests that artemisinin may also have anticancer properties. Novartis eventually joined forces with Chinese partners and patented the compound and received FDA approval. Although artemisinin has delivered great value to humankind, the original Chinese researchers earned almost nothing. Zhou Weishan, a chemist at the Shanghai Institute of Organic Chemistry who led the efforts to synthesize artemisinin, says they “never patented any part of the work.”<sup>24</sup>

Later in this thesis, with some detail I will use three real world examples to delineate how herbs/plants have been developed or are being developed into FDA-approvable singleton drugs. These three examples, hopefully, will shed some light for drug development companies on how knowledge is accumulated, opportunities sensed and captured, and value created through modern chemical and molecular technologies. The first example, metformin, is a successful example of plant-derived singleton drugs for diabetes that has received FDA approval. The second example is an on-going research on herb *banaba*-derived PGG and its derivatives, which has undergone decades of purification and validation, and is now targeting the diabetic market. The third example is the compound resveratrol, originally derived from grape skin, is being developed into a fast-track diabetic drug.

### **1.3.2 Mixed formula development pathway**

One of the central themes of this thesis is to argue, as laid out in the previous pages, that much of the value of traditional Chinese medicine is embedded in the mixed formulas it has accumulated over thousands of years and validated continuously through clinical applications. These formulas were developed and built up according to the unique

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<sup>24</sup> The New Face of Traditional Chinese Medicine, SCIENCE , 10 January 2003 Vol. 299 pp188-190.



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Chinese philosophy of treating the illnesses to provide long-term and holistic/systematic solutions to optimize the total health condition, prevent illnesses from coming back and restore the human body's internal equilibrium/balance, rather than focusing on the symptoms which are only manifestations of the disease processed or targeting organs in a narrowly defined context, as most western medical theories often so define them. As such, this thesis emphasizes the method of modernizing Chinese herbal medicine by using modern scientific methods to analyze and validate Chinese herbal medicine mixed formulas, optimize the formula to improve efficacy and reduce side-effects, and manufacture under modern and strict quality management systems.

The above concept is based on compatibility theory in traditional Chinese medicine. Compatibility theory of mixed formula is developed in accordance with the theory of different natures of herbal medicine and the theories about the mechanisms of human defense system under different diseases. This is the foundation of using composite ingredients in disease treatments to realize various efficacies or to improve efficacies when combined with other treatments. Compatibility theory of mixed formula is a theory about the differences in biologic effects when changing the mixture of various ingredients, reflecting the organic mixture of effective components of different herbal medicines and the collaborative synergies among and between different activated pathways, processes or targets, although at the moment such complex molecular mechanisms are less well understood. Further, compatibility theory is not about simple mixing of different ingredients, but about the integrative formulation involving primary herbs and other associated herbal ingredients that exercise effects of synergistic efficacy enhancement, toxicity reduction, and host health modulation. If analyzed with modern chemical technologies, these effects may result from changes in chemical characteristics and biologic effects of one or more ingredients after mixing, or effects on multiple targets and multiple action processes after mixing. Efficacy of mixed formula may derive from direct action on receptors, but more effects may derive from the changes in the chemical environments caused by the mixed formula, which then act on receptors or other biologic processes.

There have been extensive published articles, particularly in Chinese journals, about using various modern technologies and methods to understand the mixed formulas. Summarily, some of the modernization researches of mixed formulas focus on how to use modern chemical and biological theories and technologies to analyze the isolated and combinatorial constituents of effective mixed formulas and to understand the characteristics of different biological targets or markers in experimental animal and in actual patients after treatment with mixed formulas, in an effort to correlate the symptoms and disease pathology with the mixed formulas. In this research area, apparently, using system biology research methods may be better suited than the reductive scientific research methods when analyzing mixed formula of Chinese medicine because of the systematic and holistic philosophy underlying the Chinese medicine, while chemical analysis of each ingredient of mixed formula may act as the starting point to analyze the whole formula. Once the efficacy and safety can be validated, researches may further optimize the mixed formula to understand how variances in ingredients or the amounts of different ingredients and different mixing methods would affect the efficacy or safety profiles of the formula. For example, Monte Carlo analysis may be applied to randomly selected samples. Scientific analysis methods can be used to understand the effective

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components, the chemical characteristics of the effective components, and the relationship of each ingredient to the efficacy. Modern extracting technology, such as solvent extraction technology, solid-phase extraction technology, reversed-phase chromatography, membrane separation, and supercritical extraction technology, can be applied to validate the effective portion of mixed formula. In short, as generations of Chinese doctors have experienced and repeatedly illustrated, special synergistic effects will emerge when mixing various ingredients of a mixed formula, such effect may include coordination, efficacy enhancement, toxicity reduction, and so on. So drugs developed from modernized mixed formula may have unexpected good results with respect to issues of safety and efficacy, the central concerns surrounding any medication agents.

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## **2. Critical Paths to Value Realization**

Creating and capturing value in Chinese herbal medicine involves success in various areas and alignment of various necessary elements, which, altogether, form the critical paths. Understanding the major elements and defining characteristics of each would help us understand the space and platform of operations, for example, the limitations and restrictions imposed by the legal and regulatory systems. In the following pages, this thesis provides a comparative perspective of the history, operating principles, structures, processes, rules and regulations of the United States Food and Drug Administration (FDA), and the Chinese State Food and Drug Administration (SFDA) that are important and relevant to the theme of this thesis, to provide a sketch of the harmonic efforts in converging the regulatory systems, the point of divergence and the challenges. Understanding and comparing the two regulatory systems provides an important knowledge base in constructing a practical and feasible critical path(s) in creating and realizing the value in Chinese herbal medicine in the cross-border collaborations and in the optimized usage of research results, the accumulative public domain knowledge and intellectual properties, clinical trial data and other contributory factors. Due to the limitation of the length of this thesis, however, such a system description and comparison is necessarily on a brief or conceptual level.

### **2.1 Regulatory Systems – US FDA and Chinese SFDA**

#### **2.1.1 Overview**

Compared to the Chinese SFDA, the US Food and Drug Administration has a much longer history and originated from very different constitutional assumptions and congressional mandates. It is one of the United States oldest and most respected consumer protection agencies. According to the official FDA website, FDA ensures that the food we eat is safe and wholesome, that the cosmetics we use will not harm us, and that medicine, medical devices, and radiation-emitting consumer products such as microwave ovens are safe and effective. FDA also oversees feed and drugs for pets and farm animals. Authorized by Congress to enforce the Federal Food, Drug, and Cosmetic Act and several other public health laws, the agency monitors the manufacture, import, transport, storage, and sale of \$1 trillion worth of goods annually, at a cost to taxpayers of about \$3.00 a person. In short, FDA's work can be categorized into five types of jobs or activities: new products review, monitoring, standards and regulations, research and enforcement.

While in China, the earliest drug management agency was established as an office under the Ministry of Public Health after the founding of communist China in 1949. In 1982, a national drug administration was established under the national economic commission. Not until 1998, an official national drug administration was restructured under the direct supervision of the State Council. In 2003, according to the restructuring plan of the State Council approved by the First Plenary Session of the 10th National People's Congress and "the State Council Notice on Government Structuring" (No.8.2003.), the current State Food and Drug Administration (SFDA) was founded on the basis of the previously known State Drug Administration. The State Food and Drug Administration is under the direct supervision of the State Council, which is in charge of comprehensive supervision on the safety management of food, health food, cosmetics, medical devices and drugs.

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From SFDA's official statements, its main responsibilities are:<sup>25</sup>

1. To organize relevant authorities to draft laws and regulations on 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 the safety of food, health food and cosmetics carried out by relevant authorities.
3. To organize and carry out investigation and impose punishment on serious safety accidents of food, health food and cosmetics; delegated by the State Council, 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; sum up 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.
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, draw up, 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 inferior drugs and medical devices in accordance with the law.
10. To regulate radioactive pharmaceuticals, narcotics, toxics, psycho-tropics, and other

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<sup>25</sup> <http://www.sfda.gov.cn/eng/>

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controlled drugs and devices in accordance with law.

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

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.

14. To undertake other work assigned by the State Council.

As the above outline indicates, the Chinese SFDA is a new, independent, powerful, fast-changing and also turbid administrative department of the PRC state government. Comparing to US FDA, the scope of the power of SFDA is very similar.

## **2.1.2 Comparison of organization structures of FDA and SFDA**

### **FDA**

FDA is an administrative agency within the Department of Health and Human Services and consists of eight centers/offices, which are listed below.

Center for Biologics Evaluation and Research (CBER)

Center for Devices and Radiological Health (CDRH)

Center for Drug Evaluation and Research (CDER)

Center for Food Safety and Applied Nutrition (CFSAN)

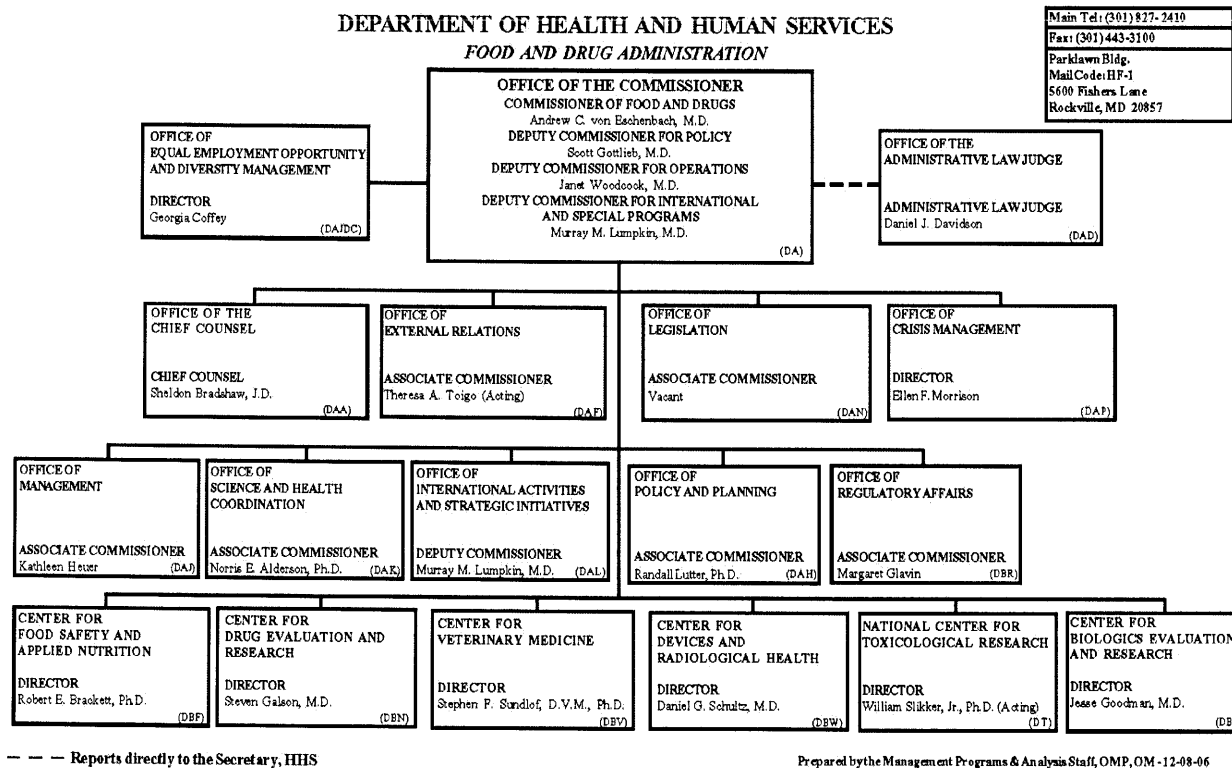
Center for Veterinary Medicine (CVM)

National Center for Toxicological Research (NCTR)

Office of the Commissioner (OC)

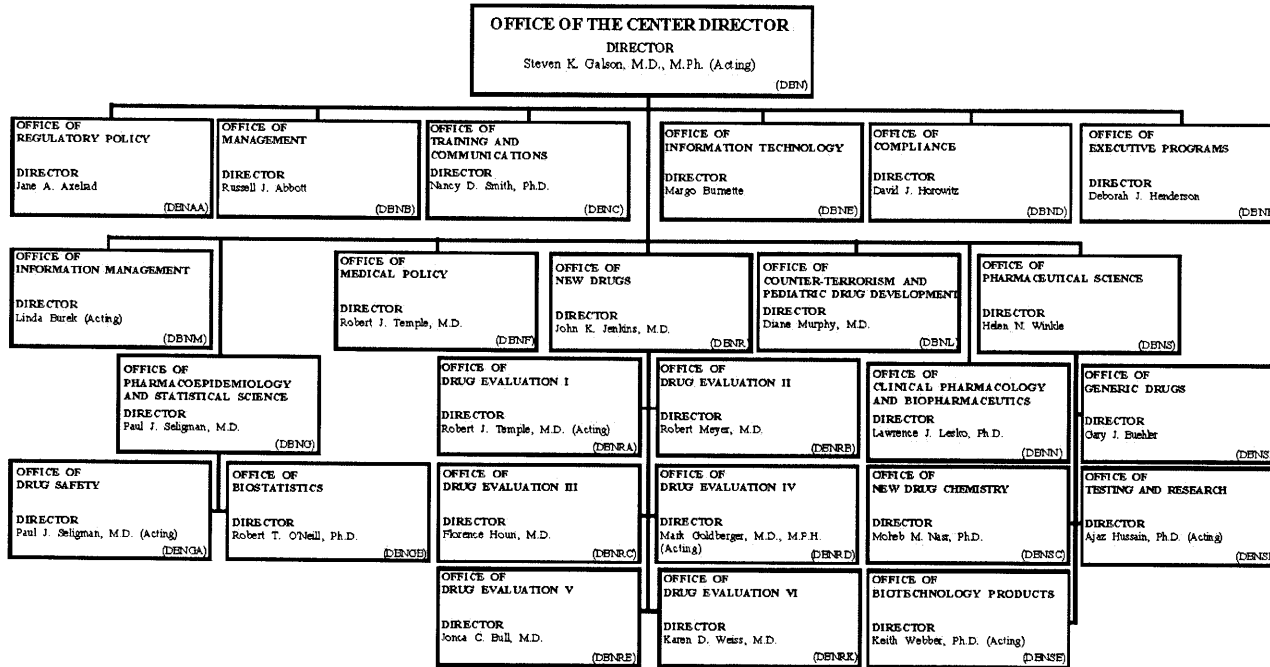
Office of Regulatory Affairs (ORA)

The following are several organization charts of FDA<sup>26</sup>:



<sup>26</sup> From FDA Website: <http://www.fda.gov/oc/orgcharts/orgchart.html>

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**



Prepared by the Division of Management Systems, OMP, OM - 02-04-05

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According to FDA's official website, the Center for Drug Evaluation and Research (CDER) is responsible for the evaluation of new drugs before they can be sold. The Center's review of new drug applications not only prevents quackery, but it provides doctors and patients with the information they need to use medicines wisely. From aspirin to cancer treatments, CDER ensures that the benefits of drug products outweigh any known risks. The Center has oversight responsibilities for prescription, over-the-counter and generic drugs. This responsibility includes products that many consumers usually do not associate as drugs, such as fluoride toothpaste, dandruff shampoos and sunscreens. CDER carefully evaluates the benefits and risks of drugs and ensures that consumers have access, as quickly as possible, to promising new treatments. The Center oversees the research, development, manufacture and marketing of drugs. CDER ensures truth in advertising for prescription drugs and monitors the use of marketed drugs for unexpected health risks. If unexpected risks are detected after approval, CDER takes action to inform the public, change a drug's label, or--if necessary--remove a product from the market.

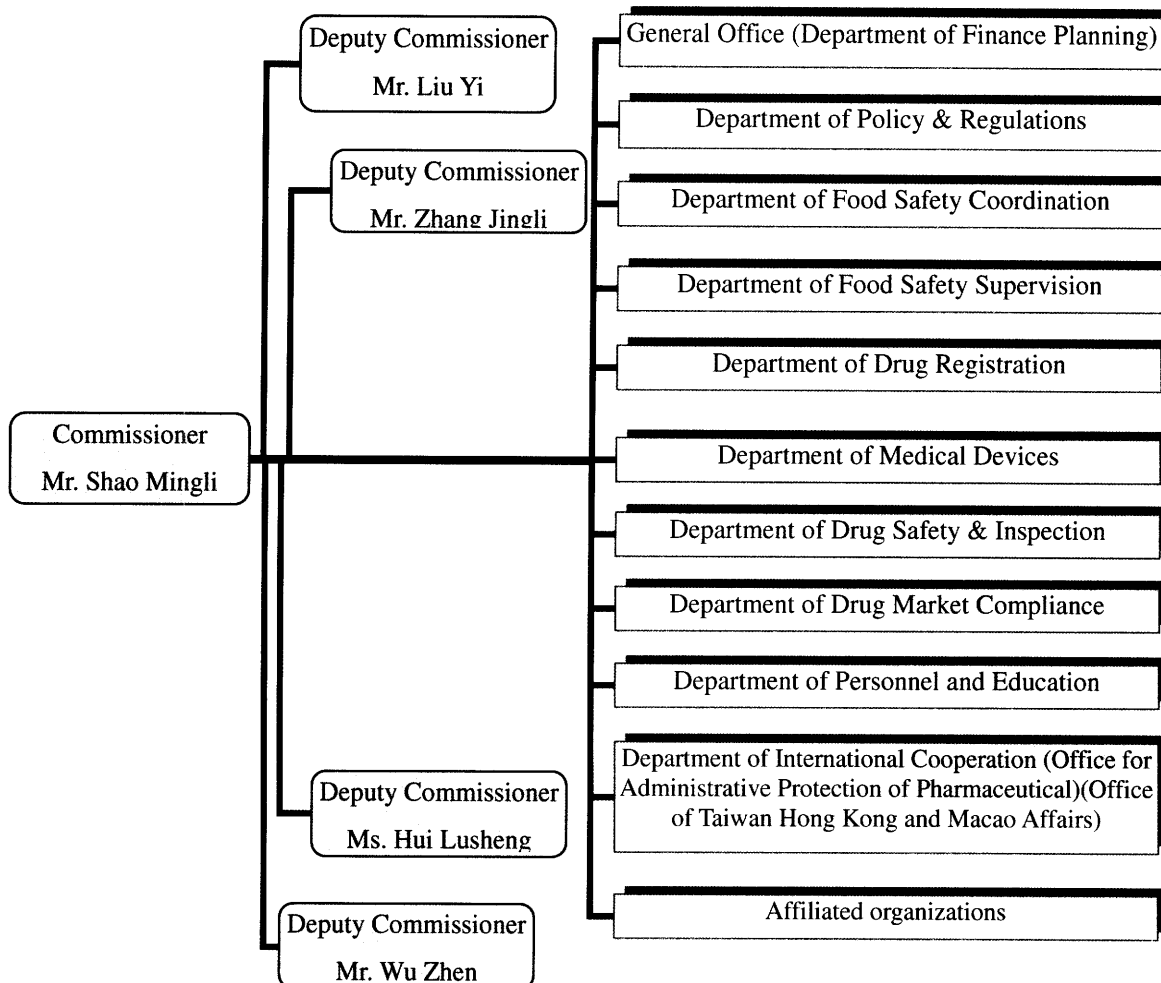
### **SFDA**

The organization structure of Chinese SFDA is as follows<sup>27</sup>:

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<sup>27</sup> <http://www.sfda.gov.cn/eng/>





According to the official website of the SFDA<sup>28</sup>, the responsibility of Department of Policy & Regulations is to draft and revise drug administration law, regulations and policies; organize relevant authorities to draft law and regulations for the safety management of food, health food and cosmetics, and draw up comprehensive supervision policies; make proposals for legislation plans; organize and carry out reviewing, coordinating and issuing of administrative provisions; supervise administrative law-enforcement and take charge of the work of hearing, undertake administrative reconsideration, responding to prosecution, and compensation; give guidance on the development of legal system in the food and drug administration system; organize and take on news briefing, publicity and publishing of newspapers and periodicals.

The responsibility of Department of Food Safety Coordination is to organize relevant authorities for drawing up work plans for the safety management of food, health food and cosmetics and supervise their enforcement; carry out comprehensive supervision over the safety management of food, health food and cosmetics in accordance with laws; organize

<sup>28</sup> <http://www.sfda.gov.cn/eng/>

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and coordinate safety supervision carried out by relevant authorities on food, health food and cosmetics; delegated by the State Council, organize, coordinate and unfold specific law-enforcement inspection activities over safety of food, health food and cosmetics; organize and coordinate with relevant authorities to improve reporting system of safety accidents of food, health food and cosmetics; investigate and draw up emergency rescue plans for the safety of food, health food and cosmetics; organize, coordinate and cooperate with relevant authorities to carry out emergency rescue work; generally coordinate testing and evaluation work for safety of food, health food and cosmetics, and give guidance to the construction of food safety monitoring and evaluation system; carry out relevant work of research and coordination in unified standard of food safety; organize drawing up research plan for the methods and means of national key technical supervision on food safety and supervise its implementation; collect information on safety of food, health food and cosmetics, analyze and forecast safety situation, evaluate and prevent potential risks for food safety; in conjunction with relevant authorities to formulate provisions on releasing of safety information for food, health food and cosmetics and supervise their implementation; sum up safety information for food, health food and cosmetics from relevant authorities and release to the public on a regular basis; undertake other work assigned.

The responsibility of Department of Food Safety Supervision is to conduct investigation and prosecution on extraordinarily serious accidents in accordance with laws; be responsible for routine work of the Supervisor-General for National Food Safety and other assigned work.

The responsibility of Department of Drug Registration is to draft and revise national drug standards; formulate and update product lists of immediate packaging materials and containers to drugs, and the requirements and standards for their medical use; take charge of registering new drugs, drugs with national standards, import drugs, immediate packaging materials and containers to drugs; implement protection system for traditional Chinese medicinal preparations; give guidance to work of drug testing institutions nationwide; draft criteria of marketing authorization for health food, and take charge of approval of health food.

The responsibility of the Department of Drug Safety & Inspection is to organize the implementation of drug classification system, review and promulgate OTC drug list, formulate national essential medicines list; be in charge of drug reevaluation and review of drugs to be withdrawn; set up and improve adverse drug reaction monitoring system; draw up and revise Good Agriculture Practice (GAP), Good Manufacturing Practice (GMP), and practice for preparations produced by medical institutions, and supervise their implementation; formulate Good Laboratory Practice (GLP), Good Clinical Practice (GCP) in consultation with relevant authorities and supervise their implementation; review drug clinical study institutions; take charge of organizing and supervision on certification of GMP in accordance with laws; regulate narcotics, toxics, psycho tropics and other controlled drugs and devices; supervise the licensing of drug manufacturing, and pharmaceutical preparations in medical institutions; draft criteria for licensing health food manufacturers.

The responsibility of the Department of Drug Market Compliance is to draft and revise Good Supply Distribution (GSP) and supervise its implementation; supervise quality of drugs and medical devices of manufacturers, distributors and users, organize and

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implement national sampling and testing of drugs and medical devices, release national quality bulletin for drugs and medical devices on a regular basis; investigate and prosecute illegal activities of manufacturing and selling counterfeit and inferior drugs and medical devices; supervise the licensing of distributors for drugs and medical devices, regulate specialized market of Chinese crude drugs; be in charge of supervision on drug advertisements, on-line drug information service and transactions, give guidance to the reviewing of advertisement of health food.

### **2.1.3 Comparing important statistical data between SFDA and FDA – new drug applications and approval rate**

As briefly outlined above, although the administrative power, the organizational structures between the Chinese SFDA and the US FDA are very similar, the statistical data provides completely different stories.

The FDA has a continuous and scientific statistics for the new drug applications and approvals. Exact numbers can be obtained from the FDA Website conveniently. While the new drug application and approval data of SFDA is much more opaque, it is not published or displayed in any statistics database. I collected the data from some scattered news or research articles, in other word, the number of SFDA is not from the same source, it's mixed. But I believe the following data is credible.

From January to June, 2006, the SFDA approved 4,635 applications in all. Among them, imported drug 172, with 120 kinds; new drug approvals of 1,363, with 939 chemical medicines, 356 traditional Chinese medicines, 67 biochemical medicines; 3,099 drugs compliant with existing state standards, with 2,557 chemical medicines, 494 traditional Chinese medicines.<sup>29</sup>

In 2005, the SFDA approved 1,113 new drugs, in the same time; the FDA approved 81 new drugs. In 2004, the SFDA received 10,009 new drug applications and the FDA received 148 applications.<sup>30</sup>

In 2003, the SFDA received drug registration applications of more than 17,000, and approved 6,806 new drug applications, an increase of 128.5% over the previous year. Approved 4,222 clinical trials of new drugs, an increase of 346.3% over the previous year; Approved 1,351 manufacture applications, in increased 66.4% over the previous year. Most of these approvals were granted after June of 2003, the time the new SFDA was established.<sup>31</sup>

In the year 2005, the new drug approval ratio of SFDA/FDA=1,113/81. The multiple is more than 13. And in the year 2004, the new drug application ratio of

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<sup>29</sup> From: <http://www.sfda.net.cn/topic.php?filename=16016&extra=page%3D2>

<sup>30</sup> From:

<http://www.baidu.com/s?lm=0&si=&m=10&tn=myie2dg&ie=gb2312&ct=0&wd=%B9%FA%BC%D2%CA%B3%C6%B7%D2%A9%C6%B7%BC%E0%B6%BD%B9%DC%C0%ED%BE%D6+%C5%FA%D7%BC+%D0%C2%D2%A9+%C9%EA%C7%EB+%B8%F6&pn=40&cl=3>

<sup>31</sup> From: <http://blog.sina.com.cn/u/47132c32010002k0>

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SFDA/FDA=10,009/148. The multiple is more than 67.

During the last decade, particularly after the official establishment of the new SFDA, with a much smaller budget the staff, the number of new drug applications and approvals of SFDA far exceeds that of the US FDA. This fact has two immediate implications, one, the Chinese pharmaceutical companies were highly productive in producing new drugs, including generic drugs and foreign drugs as well as traditional Chinese medicinal formulations, and two, a far more significant implication, the processes and quality standards of approval must be very different.

### **2.1.4 Comparing approval processes between SFDA and FDA**

FDA's application process is direct application and one level review. The CDER has a 60-day primary review (including formal review). These applications which do not meet the standard or the technologic specifications should be rejected and disapproved.

The following charts highlight the NDA approval processes used by FDA:

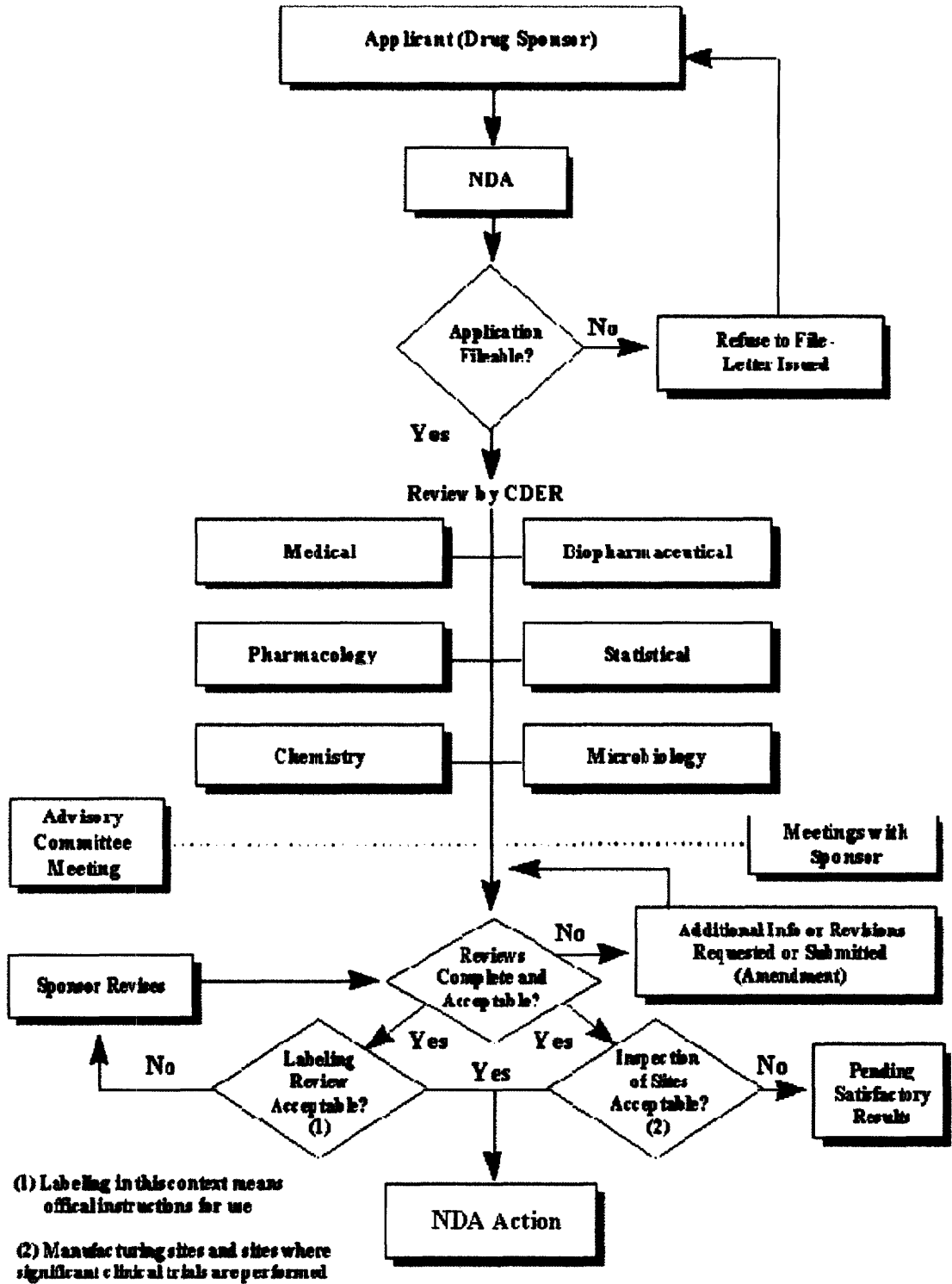
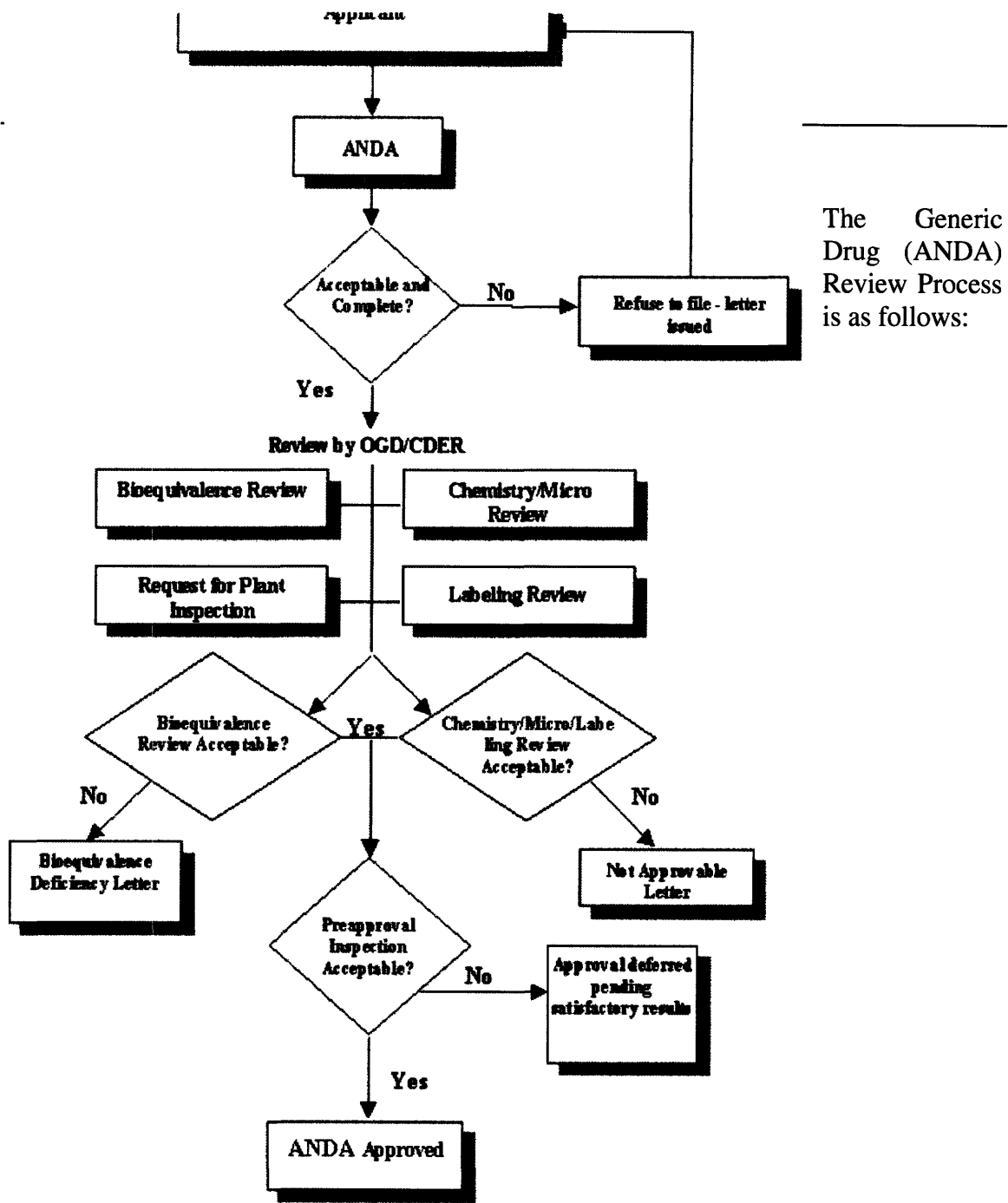


Figure 2.1.1 NDA review and approval processes used by FDA<sup>32</sup>

<sup>32</sup> The CDER handbook of FDA, <http://www.fda.gov/cder/handbook/>



The Generic Drug (ANDA) Review Process is as follows:

Figure 2.1.2 Generic Drug (ANDA) Review Process used by FDA<sup>33</sup>

Consistent to the Chinese hierarchical administrative system, the SFDA's NDA application process is in multiple levels and has at least two levels of reviews. The applicant should submit the application to the regional (food) drug administrations for the formal examination and an original review. Then the regional (food) drug administrations should submit the application to the SFDA. After receiving the application materials, the SFDA shall make an overall review of the application file. If it considers that the

<sup>33</sup> The CDER handbook of FDA, <http://www.fda.gov/cder/handbook/>

Consistent to the Chinese hierarchical administrative system, the SFDA's NDA application process is in multiple levels and has at least two levels of reviews. The applicant should submit the application to the regional (food) drug administrations for the formal examination and an original review. Then the regional (food) drug administrations should submit the application to the SFDA. After receiving the application materials, the SFDA shall make an overall review of the application file. If it considers that the application materials meet the relevant requirements, it would issue the applicant an Approval Document on Drug Registration and a New Drug Certificate.

The reviewer of formal examination and an original review in regional (food) drug administration is not the reviewer of the overall review in SFDA. So it means the process of new drug application in China will have two independent reviews. The new drug applicant must submit protocols and results of clinical trials. The processes for clinical trials and new drug application (including imported drugs) reviews are illustrated as follows.

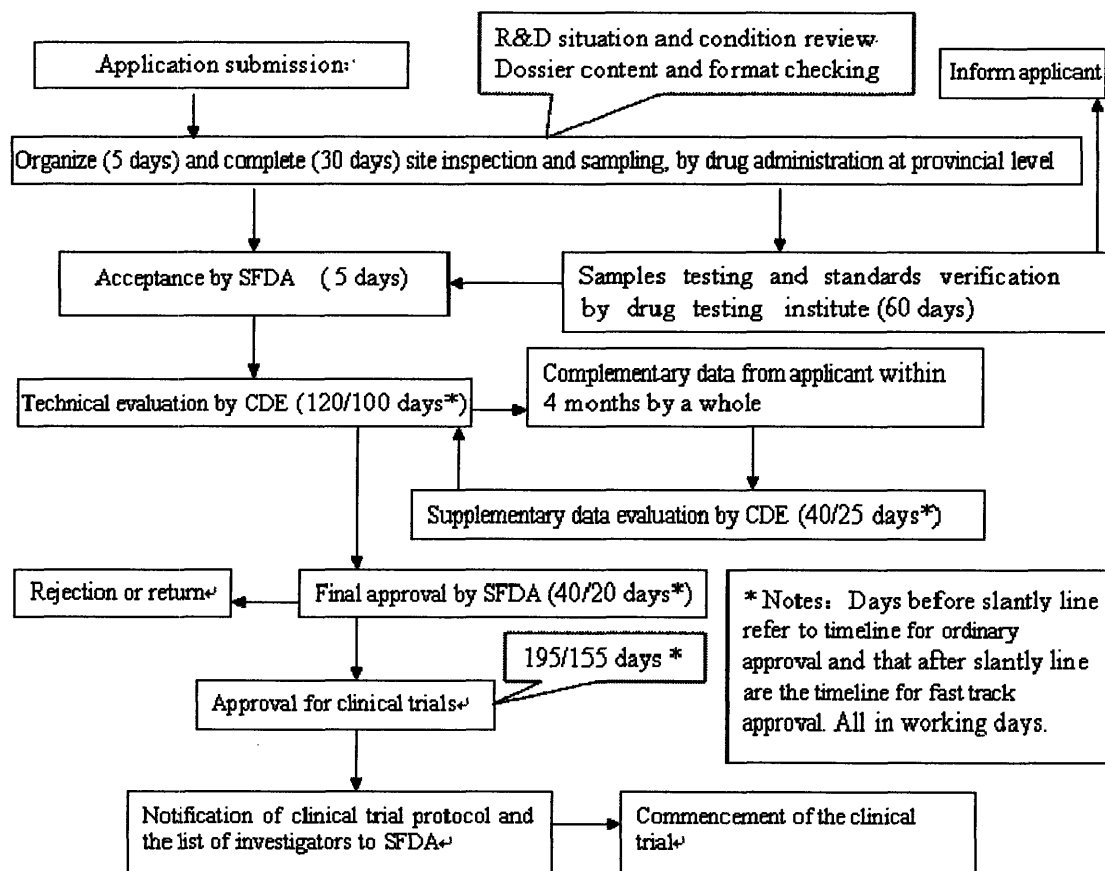


Figure 2.1.3 SFDA- Application and approval procedure for clinical trials<sup>34</sup>

<sup>34</sup> <http://www.sfda.gov.cn/eng/>

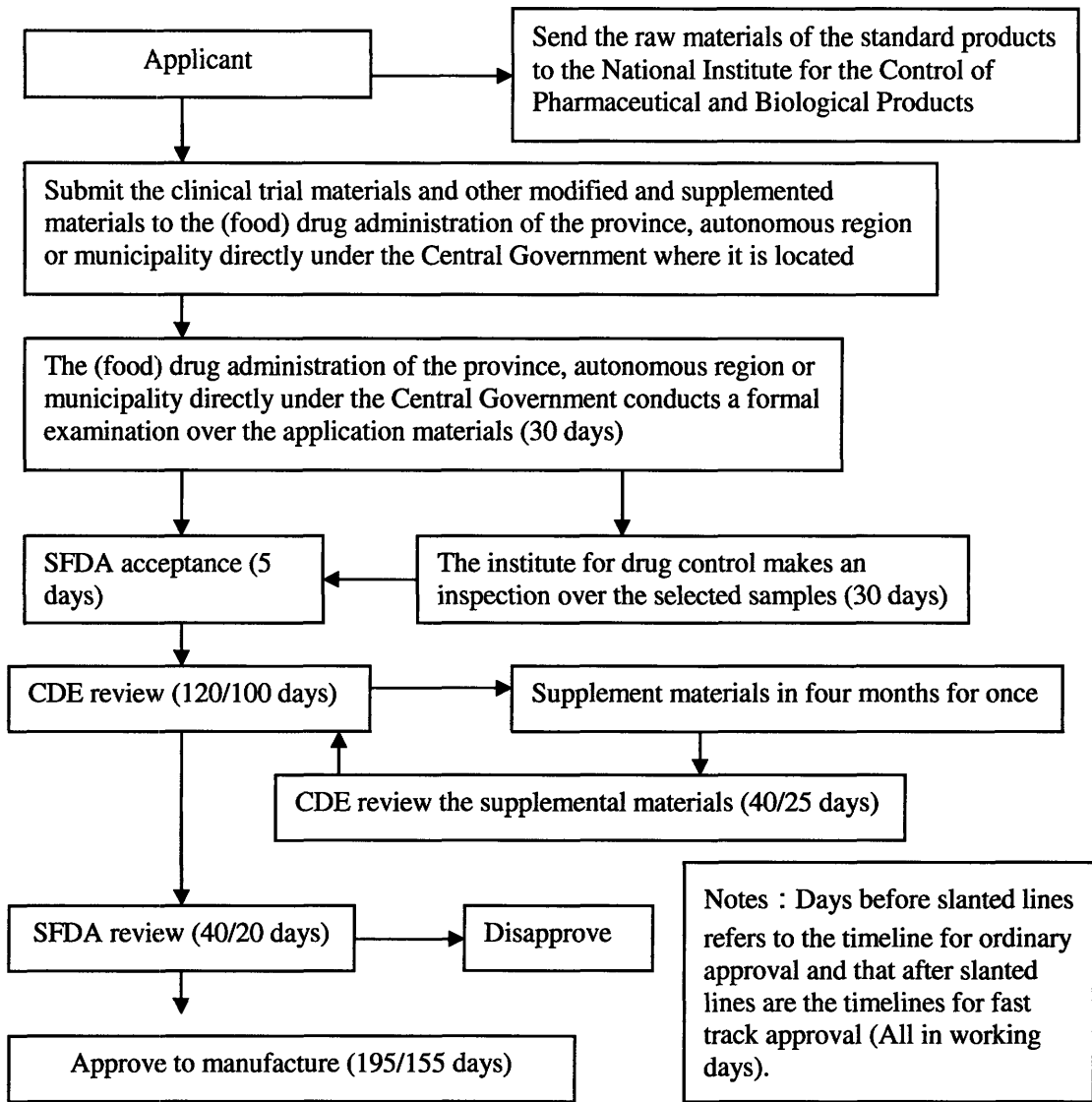


Figure 2.1.4 SFDA – New drug examination and approval process<sup>35</sup>

<sup>35</sup> <http://www.sfda.gov.cn/eng/>



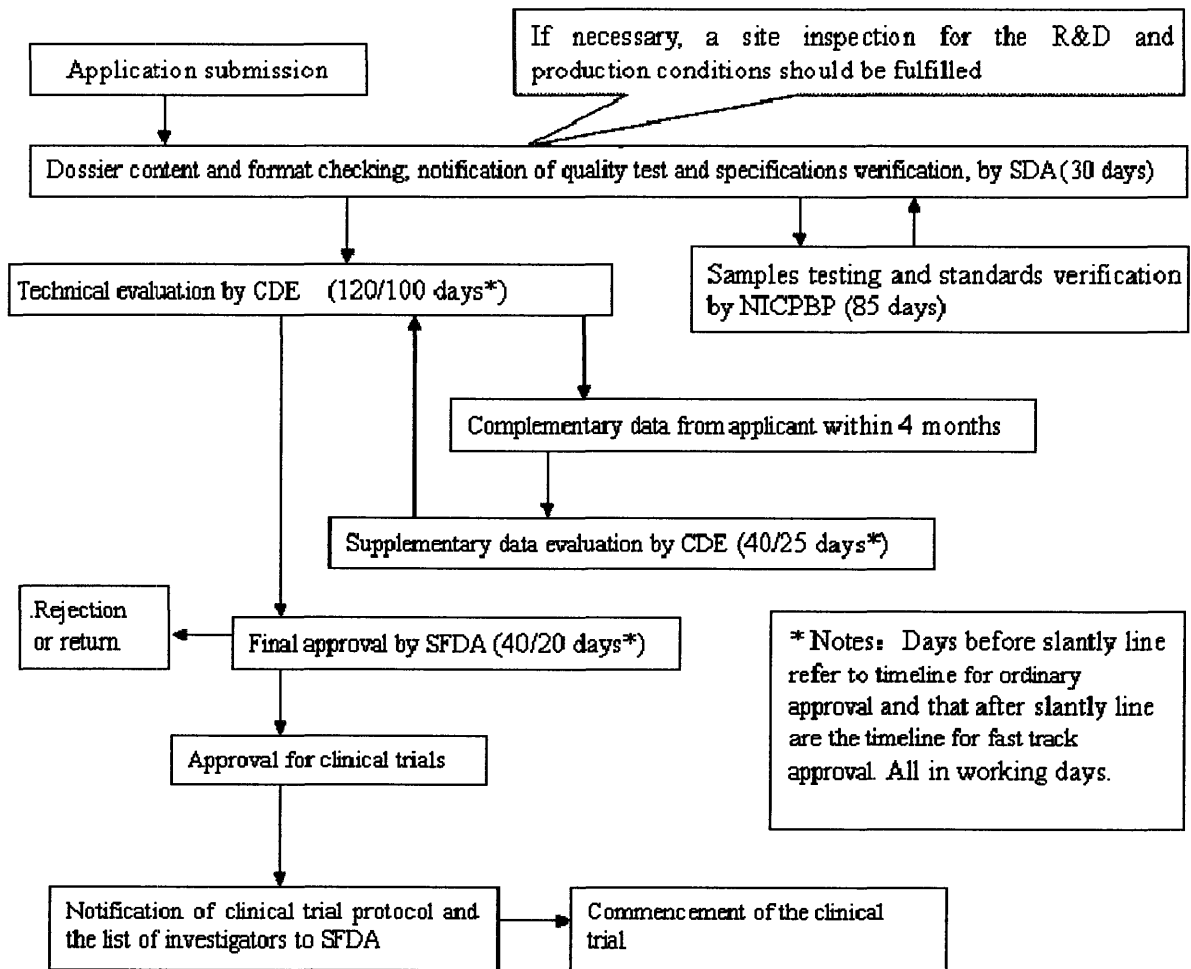


Figure 2.1.5 SFDA - Application and approval procedure for imported drugs (1)<sup>36</sup>

<sup>36</sup> <http://www.sfda.gov.cn/eng/>

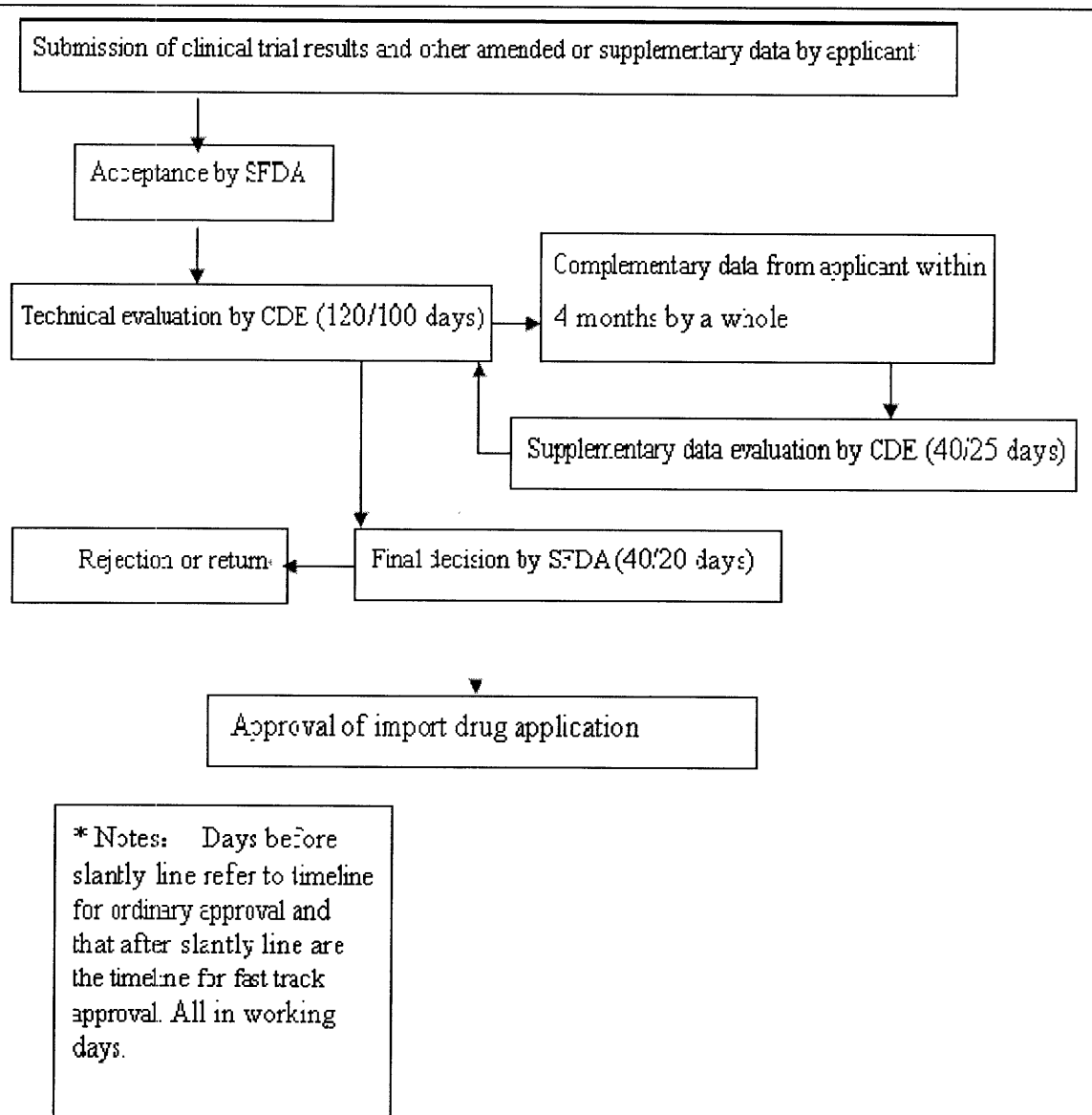


Figure 2.1.6 SFDA - Application and approval procedure for imported drugs (2)<sup>37</sup>

<sup>37</sup> <http://www.sfda.gov.cn/eng/>

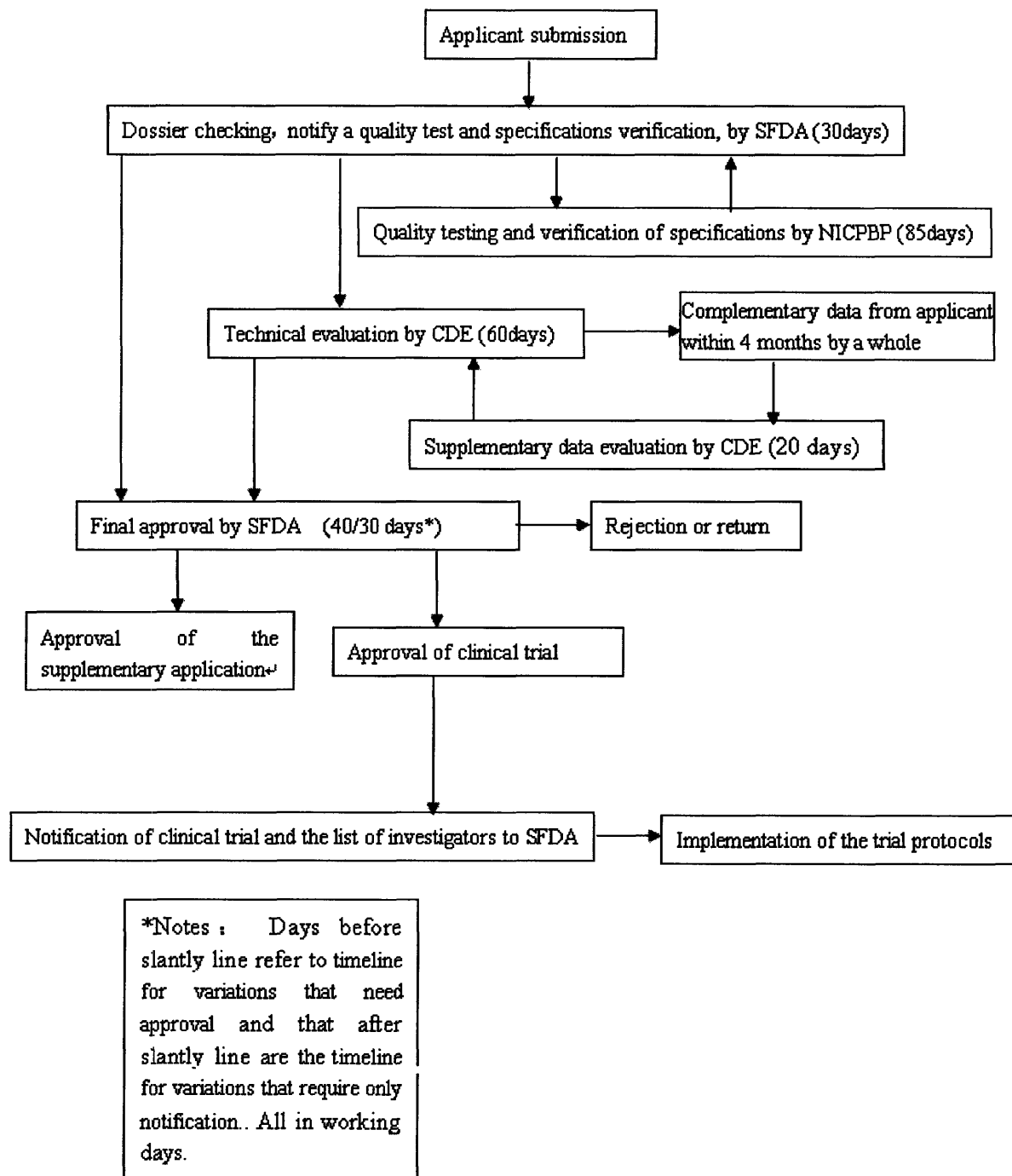


Figure 2.1.7 SFDA - Supplementary application and approval procedure for imported drugs (1)<sup>38</sup>

<sup>38</sup> <http://www.sfda.gov.cn/eng/>

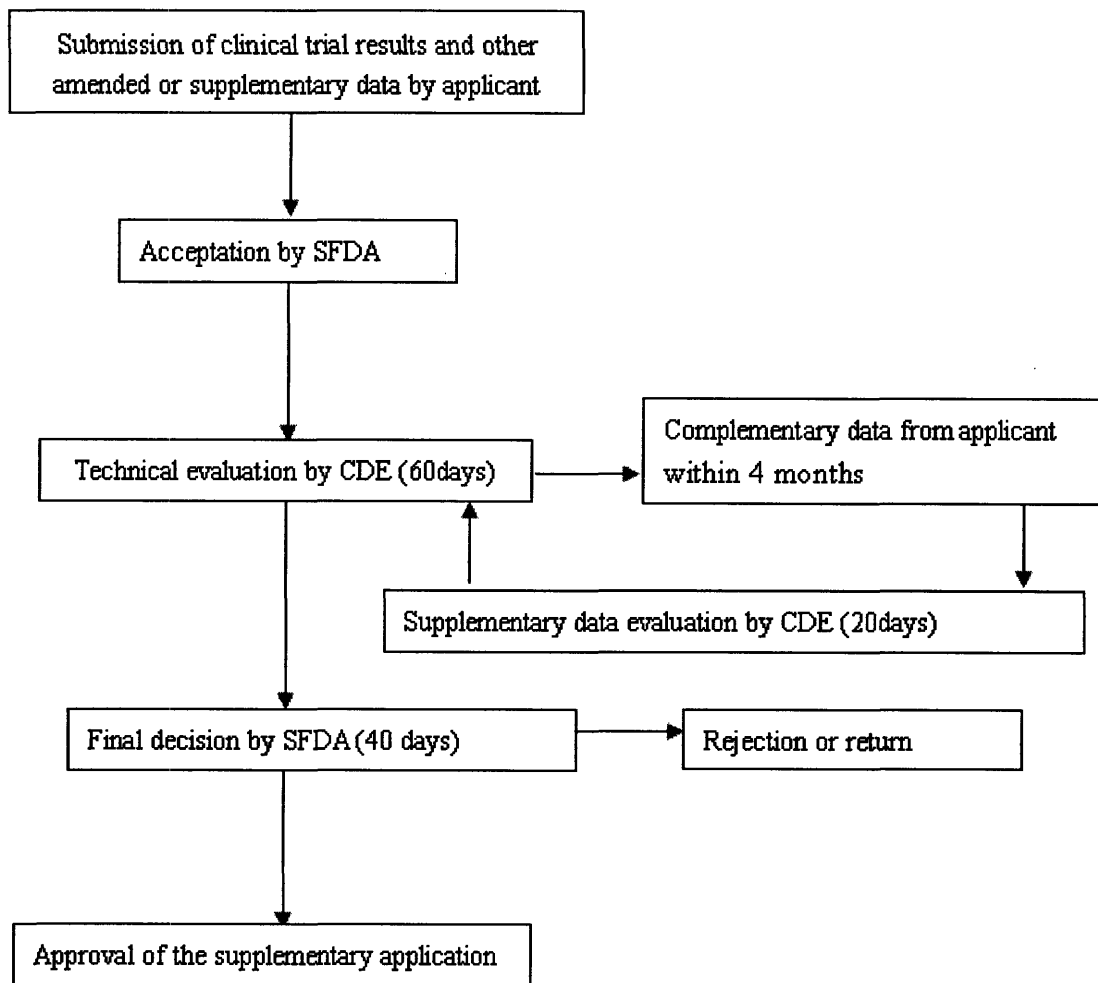


Figure 2.1.8 SFDA - Supplementary application and approval procedure for imported drugs (2)<sup>39</sup>

<sup>39</sup> <http://www.sfda.gov.cn/eng/>

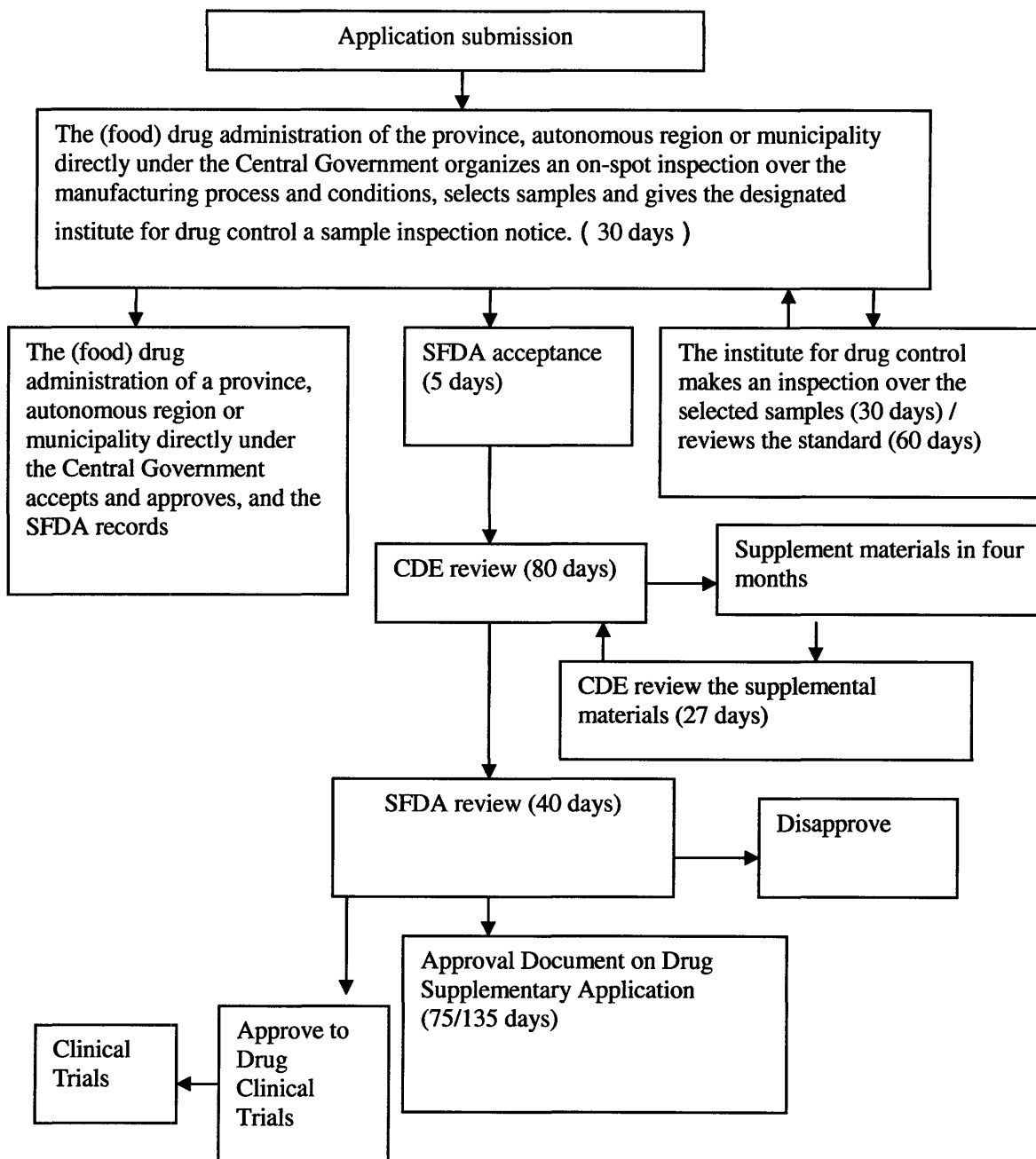


Figure 2.1.9 SFDA - Drug Supplementary Application and Examination & Approval process (1) <sup>40</sup>

<sup>40</sup> <http://www.sfda.gov.cn/eng/>

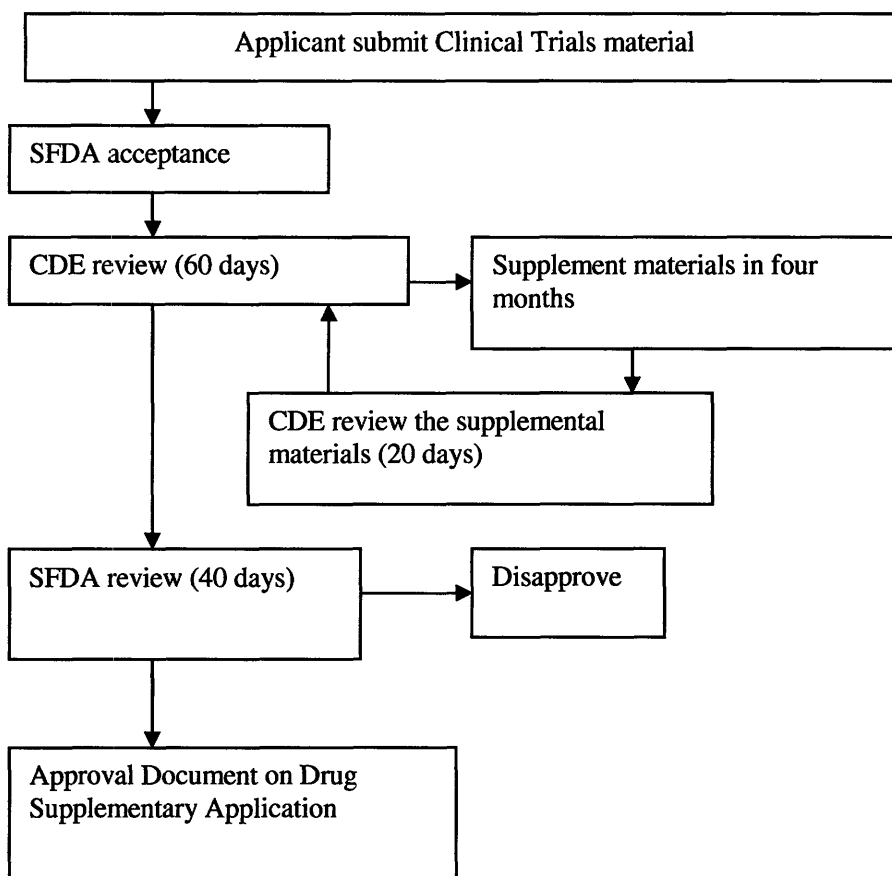


Figure 2.1.10 SFDA - Drug Supplementary Application, Examination & Approval procedure (2)<sup>41</sup>

## 2.1.5 Comparing NDA review standards between SFDA and FDA

Before making direct comparison, we need to make sure that we are comparing apples and oranges. First of all, the term “new drug” is different between China SFDA and the US FDA. Most of the new drugs in the United States refer to the true newly created entities. But many “new drugs” in the statistics are not actually new drugs, but drugs that have already been on the market for some time, but are not registered yet as a new drug.

<sup>41</sup> <http://www.sfda.gov.cn/eng/>

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This partially explains why the number of new drug application is so large in China in recent years; the SFDA was playing a catch-up game.

Second, in case of US FDA, the standards of new drug approval are universally and equally applied and extremely stringent. The processes and requirements of new drug approval must accord with a series of well established requirements or standards, which are usually well understood by pharmaceutical companies and have been in use or in practice for a long time. The approval/application ratio of SFDA is far higher than that of the FDA and the standards of approval in SFDA are often arbitrary and subject to reviewers' personal discretion or administrative corruptions. Of particular note, the power in the Chinese SFDA system are hierarchically distributed among the regional (provincial) and central administrations, which creates a structure-induced divergence of standards: each province has an incentive to obtain more drug approvals for pharmaceutical companies in its own geographical region for economic development and tax revenue purposes, and as a consequence, there has been a tendency to relax the review standards. For the central SFDA office, the reviewers must somehow balance the number of new drug approvals among various provinces, and as a result, the de-facto standards are not that consistent across different provinces.

The following paragraphs further compare the specific aspects of the new drug application, examination/review and approval requirements or standards. Due to the limitation of the length of this thesis, I would focus on areas relevant to the thesis and also at a much outlined level. The description is mostly a summary of information from the official government websites (FDA and SFDA).

#### **2.1.5.1 New drug application requirements**

In SFDA, Application to Market a New Drug for Human Use or as an Antibiotic Drug for Human Use, for example, NDAs may consist of as many as 15 different sections: Index; Summary; Chemistry, Manufacturing, and Control; Samples; Methods Validation; Package and Labeling; Non-clinical Pharmacology and Toxicology; Human Pharmacokinetics and Bioavailability; Microbiology (for anti-microbial drugs only); Clinical Data; Safety Update Report (typically submitted 120 days after the NDA's submission); Statistical; Case Report Tabulations; Case Report Forms; Patent Information; Patent Certification; and Other Information. In the SFDA, the Measures for the Administration of Drug Registration have 5 annex to regulate the registration classification and the requirements for application materials: Traditional Chinese Medicines, Chemical Drugs, Biological Products, Drug Supplementary, and Drug Re-registration. In each document there are specific requirements for the drug registration.

Most of the SFDA requirements, from the perspective of content and formalities, are very similar to US FDA requirements. It is widely believed that the SFDA was established largely following the FDA's model. But these requirements do have differences.

The registration classification for Traditional Chinese Medicine (TCM) is a special type of SFDA drug registration system. The requirements of TCM have some common requirements such as summation of materials, pharmaceutical materials, materials of pharmacology and toxicology, clinical materials, etc. But there are some extraordinary requirements, such as the source of medicine and the identify data; the environment of material production, botanical growth characteristics, formulation description, plant or

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transplant techniques; as well as provision of the samples of plant and minerals. In case of a plant sample, it should include flower, fruit, and seed, etc. As specified by the Drug Administration Law of the People's Republic of China, the required application materials of Traditional Chinese Medicines, Chemical Drugs, and Biological Products are summarized into the tables in the following pages.



<b>Requirements for Application Materials of New Drug Application (Chinese SFDA)</b>					
<b>Traditional Chinese Medicines and Natural Medicines</b>		<b>Chemical Drugs</b>		<b>Biological Products</b>	
<b>Summarize materials</b>	1.Name of the drug	<b>Summarize materials</b>	1.Name of the drug	<b>Summarize materials</b>	1.Name of the drug
	2.Certificate documents		2.Certificate documents		2.Certificate documents
	3.Goal and the reason of project		3.Goal and the reason of project		3.Goal and the reason of project
	4.Research result summary and evaluation		4. Research result summary and evaluation		4. Research result summary and evaluation
	5.Draft of drug specifications and explanation of draft and reference		5. Draft of drug specifications and explanation of draft and reference		5. Draft of drug specifications and explanation of draft and reference
	6.Packing, tag design draft		6.Packing, tag design draft		6.Packing, tag design draft
<b>Pharmaceutical materials</b>	7.Summary of pharmaceutical research materials	<b>Pharmaceutical materials</b>	7. Summary of pharmaceutical research materials	<b>Pharmaceutical materials</b>	7. Summary of pharmaceutical research materials
	8.Source of medicine and the identify data		8.Research materials and literature materials of manufacture raw, processed materials, preparation prescription and technique		8.Research materials of manufactured raw and processed materials
	9.Environment of drug, growth character, configuration description, plant or implantation technique, machining and facture, etc.		9.Trial materials and literature materials of the corroborant chemistry structure or configuration		9.Research materials of original fluid or raw material manufacture technique, assured theory, experimental data, and validate data
	10.Draft of medicine standard and the explanation draft, providing medicine standard matters and materials		10.Trial materials and literature materials of quality research		10.Research material of preparation prescription and technique, source, quality standard and relevant literature

thereof.		of supplementary materials
11. Provide samples of plant and mineral, the plant sample should include flower, fruit, and seed, etc.	11. Draft of medicine standards and the explanation for the draft, provide the medicine standard matters or comparison matters	11. Quality research materials and relevant literature, including the preparation and demarcate of reference sample or comparison sample, and the comparison to the alike product marketed at home and overseas
12. Research and literature material of manufacture techniques, source of supplementary materials and quality standards	12. Report of sample inspection	12. Manufacture and examination record of clinic trial samples
13. Trial materials and literature materials of the corroborant chemistry structure or configuration	13. Source, quality standard and inspection report of raw material medicines and supplementary materials.	13. Draft of manufacture and examine regulations, the explanation draft and examine method, validate materials plus
14. Trial materials and literature materials of quality research	14. Trial materials and literature materials of the drug stability research	14. Primary stability research materials
15. Draft of medicine standards and the explanation for the draft, provide the medicine standard matters and materials thereof	15. Reason and quality standard to the wrapper and container of direct contact product	15. Reason and quality standard to the wrapper and container of direct contact product

	16.Report of sample inspection		16.Summary of pharmacology and toxicology		16.Summary of pharmacology and toxicology
	17.Trial materials and literature materials of the drug stability research		17.Main pharmacodynamics trial materials and literature materials		17.Main pharmacodynamics trial materials and literature materials
	18.Reason and quality standard to the wrapper and container of direct contact product		18.General pharmacological research trial materials and literature materials		18.General Pharmacological research trial materials and literature materials
Materials of pharmacology and toxicology	19.Summary of pharmacology and toxicology	Materials of pharmacology and toxicology	19.Acute toxic trial materials and literature materials	Materials of pharmacology and toxicology	19.Acute toxic trial materials and literature materials
	20.Main pharmacodynamics trial materials and literature materials		20.Long-term toxic trial materials and literature materials		20.Long-term toxic trial materials and literature materials
	21.General pharmacological research trial materials and literature materials		21.Research materials and literature materials of imitability (local, body, photosensitive toxicity ), hemolytic and local stimulus ( blood vessel, skin, mucosa, muscle, etc ) , such a special safety trial relates to local or systemic administration		21.Animal pharmacokinetics trial materials and literature materials
	22.Acute toxic trial materials and literature materials		22.Trial materials and literature materials of interaction effect of multi-component in		22.Mutation test materials and literature materials

		pharmacodynamics, toxicity, pharmacokinetics	
23.Long-term toxic trial materials and literature materials		23.Mutation test materials and literature materials	23.Reproductive toxicity trial materials and literature materials
24.Research materials and literature materials of imitability (local, body, photosensitive toxicity ), hemolytic and local stimulus ( blood vessel, skin, mucosa, muscle, etc ) , dependent trial, special safety trial related to local or systemic administration		24.Reproductive toxicity trial materials and literature materials	24.Carcinogenicity test materials and literature materials
25.Mutation test materials and literature materials		25.Carcinogenicity test materials and literature materials	25.Immune toxicity and/or immunogenicity research materials and literature materials
26.Reproductive toxicity trial materials and literature materials		26.Dependent trial materials and literature materials	26.Research materials and literature materials of hemolytic and local stimulus ( blood vessel, skin, mucosa, muscle, etc ) such a special safety trial related to local or systemic administration
27.Carcinogenicity test materials and literature materials		27.Trial materials and literature materials of non-clinic pharmacokinetics	27.Drug efficiency, toxicity, pharmacokinetics interactive trial materials and literature materials of multi component of compound preparation

	28. Animal pharmacokinetics trial materials and literature materials		28. Summarize of the clinic trial materials home and overseas	28. Dependent trial materials and literature materials
Materials of Clinic	29. Summary of clinic trial	Clinic trial materials	29. Plan of clinic trial and draft of research project	29. Summary of clinic trial materials home and overseas
	30. Plan of clinic trial and draft of research project		30. Handbook of clinical researcher	30. Plan of clinic trial and draft of research project
	31. Handbook of clinic researcher		31. Draft of letter of consent and knowledge, letter of approval from ethics committee	31. Draft of letter of consent and knowledge
	32. Draft of letter of consent and knowledge, letter of approval from ethics committee		32. Clinic trial report	32. Handbook of clinical researcher and letter of approval from ethics committee
	33. Clinic trial report			33. Clinic trial report
				Otherwise
			34. Brief research summary of the pre-clinical trial	
			35. Summary and trial data which relates to improving the technique, perfecting the quality standard and pharmacology and toxicology, during the clinic trial	
			36. Amended content and amended reason to the authorized regulation	
			37. Stability trial research materials	
			38. Manufacture and examination record	

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					of three continual samples
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### **2.1.5.2 Pre-clinical research**

As part of FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing non-clinical data from past *in vitro* laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the US population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans. During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Genetic toxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

In the SFDA, "The pre-clinical trial of new drugs for applying for drug registration" must include: synthetic techniques, extraction methods, physical and chemical properties, purity, choice of form of this drug, selection of prescriptions, preparation techniques, inspection methods, quality indicators, stability, pharmacology, toxicology, nucleic acid dynamics, etc. As for traditional Chinese medicine preparations, the sources and processing of the original medicine materials, etc. shall also be included. As for biologic products, the sources, quality standards, preservation conditions, biological features, inheritance stability and immunological study of the primary raw materials such as microbial and toxic species, cell line or organism, etc. shall also be included. The agency for pre-clinical trial of new drugs for applying for drug registration in China is Regional Drug Administration and Central SFDA. After the preclinical trials, the applicant must perform clinical trials.

The emphasis on the part of SFDA in evaluating preclinical trials, as the above two paragraphs show, appears to be partially on the chemical and physical characteristics of the proposed new drugs, to make sure its quality/quantity consistency.

### **2.1.5.3 Clinical trial of drugs**

In the United State NDA application process, the applicant must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including: whether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks; whether the drug's proposed labeling is appropriate, and, if not, what the drug's labeling should contain; whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity. The purpose of preclinical work, such as animal pharmacology/toxicology testing, is to develop adequate data to warrant a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate pre-market testing ground for approvable drugs. During these trials, an investigational compound is administered to humans and is

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evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

In SFDA, an applicant shall conduct clinical trials when applying for the registration of a new drug. Such clinical trials are divided into four phases: I, II, III and IV. Before a new drug is approved for marketing, phases I, II, and III clinical trials shall be conducted. Under certain circumstances, the applicant may, upon approval, only conduct phases II and III clinical trials or only phase III clinical trials. Phase I clinical trials are the preliminary trials on clinical pharmacology and human body safety evaluation, which aim to observe the degree of tolerance of the human body against the new drug and the drug dynamics, and provide the basis for working out the dosage administration scheme. Phase II clinical trials are the preliminary evaluation of the treating effects, which aim to preliminarily evaluate the treating effect and safety of the drug on the target patients with the applicable disease, and also to provide the basis for the determination of study design and dosage administration scheme for the clinical trial in phase III. Various methods may be employed for the study design of this phase in light of the specific study purpose, including the randomized controlled trial. Phase III clinical trials represent the confirmation phase of the treating effect, which aim to further verify the treating effect and safety of the drug on the target patient with the applicable disease, to evaluate the relationship between interest and risk, and to eventually provide adequate basis for the examination of the drug registration application. Generally, the trials shall be randomly controlled with sufficient samples. Phase IV clinical trials: the phase of application study conducted by the applicant independently after the new drug comes onto the market, which aims to examine the curative effect of the drug and the adverse reactions when it is widely used, to evaluate the relationship between interest and risk when the drug is used in ordinary or special groups and to improve the dosage administration.

From a comparative note, the four phases of clinical trials are defined very similarly between the two regulatory systems. Of note, in response to growing reports of adverse side-effects related to the drugs on the market, the Chinese SFDA has also established and funded a special agency by the name of Drug Post-Market Side-Effect Surveillance Center in an effort to timely discover and act on the effects produced by the existing approved drugs. This thesis author, by and through his Chinese company, was engaged to provide a consulting report on the history, structure, process and evolution of the US FDA's post-market drug monitoring system. Many of the recommendations in this consulting report were eventually adopted.

#### **2.1.5.4 Investigational new drug (IND) applications**

Investigational New Drug application process (IND) of the FDA is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials). Generally, this includes processes which generate data and information in the following three broad areas: animal pharmacology and toxicology studies; preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans; manufacturing information, including information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure the company



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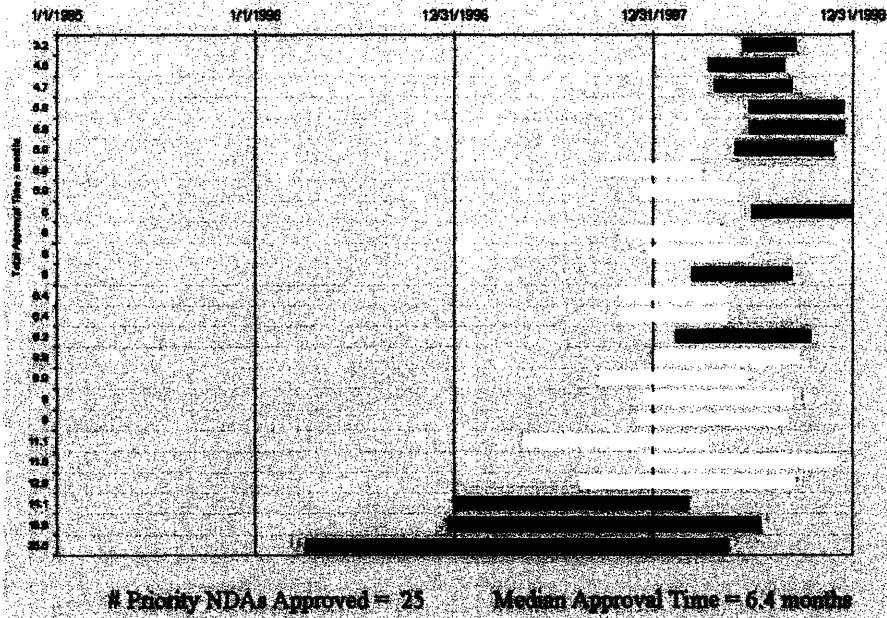
can adequately produce and supply consistent batches of the drug; and proposed Clinical Protocols and Investigator Information, which include detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Besides that, information on the qualifications of clinical investigators—professionals (generally physicians) who oversee the administration of the experimental compound—should be provided to assess whether they are qualified to fulfill their clinical trial duties.

In SFDA, there is not such a distinct process similar with IND. The function is performed by the combined processes of Pre-Clinical Trial of New Drugs, the Clinical Trial of Drugs, and the Administration of Clinical Trials. These requirements, in essence, would match the requirements of Pre-Clinical Research and IND in the SFDA.

#### **2.1.5.5 Time limit of new drug review**

Every year in the FDA, there is different submission cohorts (e.g., NMEs, priority NMEs, NDAs, etc). Many submitted are approved within a year of submission, but some are not if the FDA has additional questions or because FDA standards have not been met. An effect of submission trends on statistics shows that, in times where the number of submissions is increasing, the older applications have less impact on the median approval time; in times where the number of submissions is decreasing, older applications may dominate the median approval times. The total approval time is the time from first submission to approval. It includes all FDA review time as well as the time spent by the sponsor in responding to FDA questions. There is also a priority NDA application category in the FDA process for policy reasons such as for urgently needed drugs. In 1998, there were 25 priority DNAs approved with a median time of 6.4 months. In 2002, there were 11 priority DNAs approved with a median time of 16.3 months. We could perceive two trends: (1) the priority NDAs approval number is decreasing from 1998 to 2002; (2) the Median Approval Time is increasing. The following charts show the situation of Priority NDAs Approved in the years 1998 and 2002:

## Priority NDAs Approved in CY 1998



## Priority NDAs Approved in CY 2002

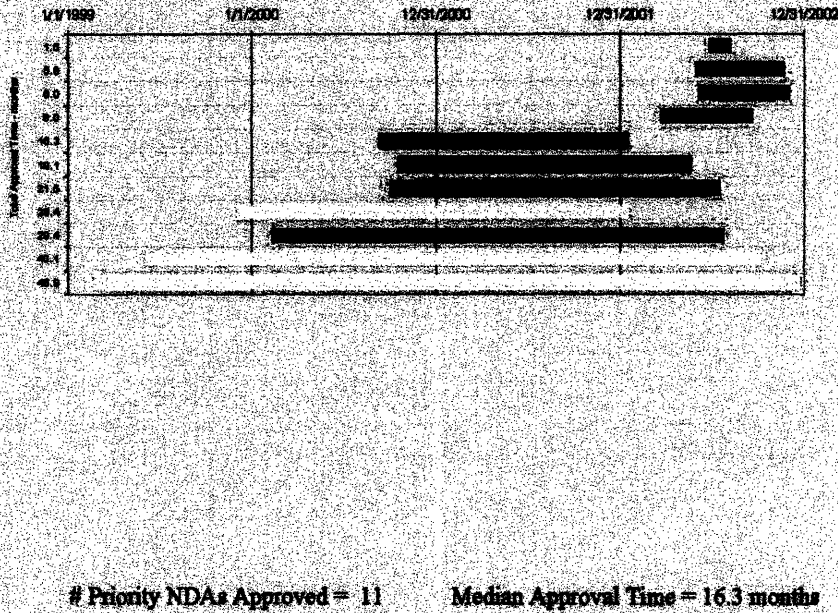


Figure 2.1.11 Priority NDAs Approved by FDA in the years 1998 and 2002 <sup>42</sup>

<sup>42</sup> Median Approval Time Statistics, [www.fda.gov](http://www.fda.gov)

The exact data of SFDA's total approvals is not published, but the relevant laws regulate the time limit of drug review. The Measures for the Administration of Drug Registration change the old regulation about the time limit of drug review. The time span of drug review decreased in most of the steps. The content and time limit of SFDA drug review is summarized in the table below:

Steps	Agent	Acceptance Time limit	Items should finished	Finish time limit
Primary review	Provincial registration administration	5 days	Acceptance; on-spot inspection; sample; send a notice to the designated institute for drug control; submit the examination opinions; inspection report and application materials to the SFDA and notify the applicant	<b>30 days</b>
	The provincial institute for drug control		Check and test the samples, submit inspection report and verification opinions to the SFDA	<b>Generic drugs: 30 days; special drugs and antibiotics: 60 days</b>
				Check and test the samples, verify the drug standards
Acceptance	SFDA	5 days	Accept the review	<b>5 days</b>
	NICPBP	Imported drug 30 days	Accept the review, and notify the NICPBP	<b>30 days</b>
			Arrange the check and test	<b>5 days</b>
Technology review	CDE		Check and test the samples, verify the drug standards	<b>60 days</b>
			Review the standard	<b>20 days</b>
			Technology review	<b>Clinical Trial and Manufacturing of New Drugs: 120 days (expedite 100 days)</b> <b>Drugs with Existing</b>

<b>Approval</b>		<b>State Standards: 80 days</b> <b>Supplementary materials: 40 days (expedite 30 days)</b> <b>Supplementary application: 60 days</b>
	SFDA	examine and approve <b>40 days</b>

### 2.1.5.6 Communication between reviewer and applicant

During the course of reviewing an application, the CDER of the US FDA usually communicates with sponsors about scientific, medical, and procedural issues that arise during the review process. Communications may take the form of telephone conversations, letters, faxes or meetings. This system could avoid needless investment and repeated research, and reduce the misplay and the cost.

The communication system between the reviewer and the applicant is not established in the SFDA process. It lacks communication and is considered to be a source for bureaucratic misunderstanding, arbitrary decisions and rent-seeking corruptive activities.

### 2.1.5.7 Modern (western type) and traditional medicines

In China, the SFDA classifies drugs into “Modern and traditional medicines.” The modern medicines usually refer to drugs developed by modern scientific technological methods and the traditional medicines generally refer to the methods used for preventing and treating disease according to the traditional medicinal theory. The main sources of traditional medicines include herbal (plant) medicines, animal medicines, and mineral medicines.

In a summary note, the explicit requirements of new drug applications are very similar between the two systems, but the de-facto or execution standards and the outcomes are very different. The FDA’s requirements and standards are very transparent and well published; while the SFDA’s substantive standards are largely opaque and subject to reviewer’s arbitrary discretion. A significant difference is that there is no official means of communication between the reviewers and the applicants in the SFDA’s new drug examination process.

## 2.1.6 Trend of SFDA under the context of globalization

Under the globalization context, particularly in the last decade, the Chinese drug registration laws and regulations have been amended and redrafted several times, in an effort to harmonize with international practices. SFDA's new regulations have followed FDA's model and practices in many substantive aspects. In promoting availability of commonly used OTC drugs, as part of medical insurance reform, SFDA released its first

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list of over-the-counter (OTC) medications in June 1999, and in 2000, the state began to regulate OTC and prescription drugs separately. SFDA did so to encourage patients to purchase OTC medicines for less serious diseases, thereby reducing the country's overall medication expenditures and hospital visits. As a systematic quality control measure, the SFDA requires pharmaceutical companies to obtain GMP certificates to be licensed to sell their pharmaceutical products in China. In 2005, SFDA launched a regulation on drug research and supervision management aimed at enforcing the GLP to investigative drugs, traditional Chinese medicine injections and biotechnology products. The regulation aims to help China's drug research and development gain international recognition.

The old regulations have no restriction to the applicant, so individuals could be a new drug applicant. The amended regulations change the requirement, and at the same time the regulations distinguish the domestic applicant and foreign applicant. Now, an applicant for drug registration refers to an institution that files an application for drug registration, bears the corresponding legal liabilities, and holds the drug approval certification documents after the application is approved. A domestic applicant shall be an institution that is lawfully registered within China who bears civil liabilities independently, while an overseas (foreign) applicant is a lawful overseas drug manufacturer. When an overseas applicant applies for the registration of drug import, its office based in China or an entrusted agency within China shall go through the formalities for the registration of the imported drug(s).

In terms of patents, the new regulations require that the applicant shall provide explanations on its ownership and statement of no infringement upon the patents of others. If any dispute arises after the application for drug registration is approved, the parties concerned shall settle the dispute through negotiations by themselves, or through the patent administrative department or the people's court pursuant to the relevant laws and regulations. With regard to generic drugs, an applicant may file a registration application within 2 years before the expiration of the patent of that drug. The SFDA could issue to it the registered number of drug approval, an Imported Drug Registration Certificate or the Pharmaceutical Product Registration Certificate after the patent expires.

The above are some highlights of the fast-track convergence of laws and regulations of the Chinese SFDA toward the international and US standards or customary practices, which provide regulatory foundation for creating and capturing value in the cross-border development and marketing of pharmaceutical products, this is also true to herb-derived pharmaceutical products. The execution and enforcement of Chinese SFDA laws and regulations remain a major concern for the international players, however, despite the plausible laws, processes and standards in the print forms.

## **2.2 Modernization of Chinese Herbal Medicine**

The following pages address the central theme of this thesis, how to modernize Chinese medicine so that such pharmaceutical products can become ethical drugs and enter the mainstream international markets, particularly the US market which is the single largest market in the world and will likely remain so for a long period of time. In this section of the thesis, the author will not only write about the development of refined chemical compounds from Chinese herbal medicine, a critical pathway I call "original pathway" or

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“singleton pathway,” but also address the hypothesis of developing future ethical drugs from Chinese mixed formulas, I term it the “mixed formula pathway” or “alternative pathways.” The former has many successful examples in the past, but the pathway is becoming less productive and increasingly costly lately; the latter is built on a different philosophy and perceivably much less expensive, may represent one of the “disruptive” solutions to the healthcare crisis in the world. This thesis will take several pages to describe the quality assurance measures Chinese companies are currently using and the “fingerprint” technology that may hold promise to partially resolve the standardization and quality consistency issues that are often associated with raw herbal products or mixed herbal formulas.

### **2.2.1 Singleton drugs**

One potential development of Chinese herbal medicine is to derive singleton (chemical) drugs from therapeutically effective compound in herbal extracts. Artemisinin, derived from *Artemisia annua L (qinghao)* is a good example of this kind of development. Chinese herbal medicines have been used by Chinese people to resolve many health problems that are not curable by western chemical drugs, so Chinese herbal medicines may be viewed as valuable research indicator for new chemical drugs. The major advantage of this method is that, once the effective therapeutic compound is identified, the structure of it may be modified and effects optimized using the same chemical screening technology and molecular signaling pathway validation technologies conventionally used in the chemical drug development. Such new drug, once successful developed, is a chemical drug in fact, rather than Chinese herbal medicine. The standard drug development processes, such as pre-clinical research and clinical trials will be done as if it were is a western chemical drug. The major disadvantage of this type of singleton drug is the high level of purification and it often targets a singular mechanism or molecular signaling pathway and produces a specific effect. Such effect may be very efficacious in the short run once introduced into the human body, but its action is often transient and sometimes with inevitable side-effects.

For many helpful Chinese herbal medicines, as discussed at length at the beginning sections of this thesis, the therapeutic effects only display when the whole herb with many chemical compounds or, more often, many herbal and other ingredients are used together as a whole as mixed formula. When examined separately, each of the compounds may not have evident therapeutic effect on targeted molecular pathways or clinical diseases, and some of them may even show increased toxicity. For example, a drug named Zemaphyte, compounded from 10 herbs used by traditional Chinese medical practitioners, was once found to have therapeutic effect on eczema. As a whole, it is effective in treating erythema (redness), surface damage to the skin, sleep disturbance and itching, but no single herb was found to be singularly responsible for this efficacy. For these mixed formula medicines, it would be hard to convert them into singleton (chemical) drugs.

In short, the chemical purification method may greatly leverage the technologies currently used by western chemical drug development, and is easy to be understood by scientists practicing in western pharmaceutical companies, but it can only realize partial value in Chinese herbal medicine.

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## 2.2.2 Botanical drugs

The US FDA now recognizes botanical drugs as a special class; the following summarizes the guidance from FDA websites for botanical drugs:

1. Botanical drugs are derived from vegetable matters and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, even the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, the CMC documentation that should be provided for botanical drugs may be different from that for synthetic or highly purified drugs, whose active constituents can be more readily chemically identified and quantified.
2. In such circumstances, FDA will rely instead on a combination of other tests (e.g., spectroscopic or chromatographic fingerprints, chemical assay of characteristic markers, and biological assays), controls (strict quality controls of the botanical raw materials and adequate in-process controls), and process validation (especially for the drug substance) to ensure the identity, purity, quality, strength, potency, and consistency of the botanical drug.
3. Botanical drug products that are derived from a single part of a plant (e.g., leaves, stems, roots, seeds), or from an alga or macroscopic fungus (e.g., a mushroom), are not considered to be fixed-combination drugs within the meaning of 21 CFR 300.50 and 330.10(a)(4)(iv). Consequently, they would not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active ingredient makes a contribution to claimed effects.
4. Botanical drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements. However, FDA intends to propose revisions to its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

This is a very significant change in the US FDA regulations and may represent a major opportunity for creating and capturing value in Chinese herbal medicines as single herbs. But under this guidance, only a relatively smaller number of Chinese herbal medicines can be qualified as botanical drugs by FDA, because most Chinese herbal medicines use multiple herbs.

## 2.2.3 Combination drugs

Most Chinese herbal medicines must meet the requirements of combination drugs before they can be approved by FDA as new drugs. This means that the efficacy and safety of each component or active ingredient must be individually demonstrated. This imposes the greatest difficulty for Chinese herbal medicines to be approved by FDA as new drugs because Chinese herbal medicines are based on a holistic theory. The ingredients are not simply mixtures of its parts, but are meant to constitute a new therapeutic system, a system in which 1+1 may be greater than 2.

Chinese herbal medicines prepared from smaller number of herbs may be more likely to be verified. *Fufang Danshen Diwan*, a Chinese herbal medicine prepared from *salvia*

*multiorrhiza (danshen)*, *panax notoginseng (sanqi)*, and *cinnamomum camphora (bingpian)* became the first Chinese herbal medicine gaining the FDA's IND approval to enter clinical trial in the US in 1997, although little progress has been obtained due to the inconsistent results on efficacy.

Some Chinese herbal medicines met the FDA's requirements for combination drugs, but the FDA's evaluation criteria are not suitable to assess the holistic therapeutic effects of most Chinese herbal formulas. Some Chinese pharmaceutical companies, such as the famous traditional Chinese herbal medicine manufacturer *Tong Ren Tang*, are actively exploring ways to bring Chinese herbal medicine to the world. One way is to spread the theory and philosophy of Chinese medicine, and at the same time attempt to find a suitable evaluation method to scientifically reflect the nature of Chinese herbal medicine.

## 2.2.4 Quality, standards and consistency - problems and improvements in producing Chinese herbal medicine

Chinese herbal medicine has long been known to have great variation and inconsistency from batch to batch and from producer to producer. To improve the standardization and quality control of Chinese herbal medicine, China has introduced Good Agriculture Practice (GAP), Good Laboratory Practice (GLP), Good clinical Practice (GCP), Good Manufacturing Practice (GMP), and Good Supply Practice (GSP) to regulate herbal medicine production.

Now, with the improved quality standards there are several Chinese herbal medicines that have obtained FDA's IND approval and are stepping into clinical trials. For example, Fuzheng Huayu Piece, manufactured by Shanghai Sundise Chinese Medicine Technology Development Co., Ltd, has obtained FDA's IND clearance in January 2007 to start phase II clinical trial in the US for the treatment of liver disease. The phase II clinical trial is planned to be finished by 2009, involving 120 patients. The table on the following page summarizes the progresses:

Drug	Manufacturer	Targeted disease	Progress or status
<i>Fufang Danshen Diwan</i>	Tasly Group	cardio-vascular disease	IND approval by FDA to enter clinical trials in the US in 1997.
<i>Kanglaite Injection</i>	Zhejiang Kanglaite Pharmaceutical	cancer of the pancreas	Drug registration certificate issued by the Health Ministry of Russia in December 2003.  IND approval by FDA to enter phase I clinical trials in the US in 2001. Enter phase II clinical trials in 2003.
SunRecome	Shanghai Green Valley Pharmaceutical	cancer	IND approval by FDA to enter phase I clinical trials in the US in 2005.



<i>Xuezhikuang</i>	Beijing WBL Peking University Biotech Co., Ltd.	cardio-vascular disease	IND approval by FDA to enter phase II clinical trials in the US.
<i>Fuzheng Huayu Piece</i>	Shanghai Sundise Chinese Medicine Technology Development Co., Ltd.	Liver disease	IND approval by FDA to enter phase II clinical trials in the US in January 2007
<i>Guizhi Fuling Jiaonang</i>	Jiangsu Kanion Pharmaceutical	Gyneco-pathy	IND approval by FDA to enter phase II clinical trials in the US in November 2006
<i>Yinxing Tongzhi</i>	Xingling Pharmaceutical	angina	IND approval by FDA to enter phase III clinical trials in the US.
<i>Weimaining</i>	Huahe Pharmaceutical	cancer	IND approval by FDA to enter phase II clinical trials in the US.

Despite the above very promising and significant inroad of Chinese herbal medicines toward the western mainstream market, no Chinese herbal medicines have yet obtained FDA's approval to be sold as new drugs in the US, because there are multiple problems from material preparation to pre-clinical research, from clinical trials to manufacturing of the herbal medicines. In short, there have been great improvements, but still a long way to go. In the following paragraphs, we look at the special challenges and potential solutions.

#### **2.2.4.1 Fingerprinting technology and material quality control**

This first basic issue is the quality of the herbal material. FDA requires that materials used by a drug must be traceable, under good quality control and consistent.

Most Chinese medicinal herbs are complex compounds of many ingredients. Further, herbs with the same name can display different level of therapeutic effects if they are grown in different places, collected in different periods, or processed by different procedures. Quality control and consistency maintenance of materials are more difficult for Chinese herbal medicines than for western chemical drugs. Lack of suitable measurement standards of medical herbs deteriorates the problem. Chinese Pharmacopoeia is the national code used to govern the quality of drugs. Chinese medical herbs and herbal pieces prepared for prepared Chinese medicine appeared in Chinese Pharmacopoeia (Volume I) in 1963 for the first time. The standards in this book describe the herbs and herbal medicines largely according to their appearances and other physical characteristics, apparently lack scientific methods to delineate quality requirements and ignored the issues of hazardous heavy metals and residual of pesticide, which have recently raised concerns among consumers of Chinese herbal medicine. The lacking of scientifically verifiable quality standards, for a long time, results in mixing of both high quality herbal and low quality materials, great variances in the prepared herbal medicines and inconsistent efficacy in the marketed herbal medicines. The current edition of Chinese Pharmacopoeia was issued in 2005, in accordance with the principles decided by

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the 8<sup>th</sup> Chinese Pharmacopoeia Commission. The new Pharmacopoeia takes into consideration of advanced technology and experimental methods widely adopted in China and abroad, and highlight the principle of “safety for use, reliability of therapeutic effect, feasibility of processes, controllability of manufacturing quality and perfection of specification.” Volume I of Chinese Pharmacopoeia 2005 contains monographs of Chinese material medica, including prepared slice, vegetable oil/fat and its extract, patented Chinese traditional medicines, and single ingredients of Chinese crude drug preparations. 1,146 monographs are included, with 154 new admissions and 453 revisions. New scientific methods, such as thin layer chromatography, high performance liquid chromatography (HPLC) and gas chromatography, are now used as standards of identity and content. The number of monographs adopting thin layer chromatography as a standard method to identify and quantify Chinese medicines reaches 1,523; the number of monographs adopting high performance liquid chromatography as a standard reaches 479; and the number of monographs adopting gas chromatography in the tests for identification and content reaches 47. Tests on 12 pesticides containing organic phosphorous and 3 pesticides containing pyrethroid are added for determination of pesticide residues. Atomic absorption spectrophotometry or inductively coupled plasma mass spectrometry is introduced to determine 6 kinds of heavy metals and deleterious elements, and the limits for lead, cadmium, mercury, arsenic and copper are stipulated for the first time.<sup>43</sup> Using the above scientific methods for quality assurance is now collectively called fingerprint technology. It offers significantly improved standards of quality verification.

Using fingerprints to identify and demonstrate the consistency of herbal materials and drugs now is accepted by FDA. Chinese SFDA plans to regulate herbal medicine by fingerprints of the material used, intermediate products and final drugs. Beginning in 2004, fingerprints of liquid injections have been compulsorily carried out. With the help of fingerprints obtained, the authentication and identification of medical herbs and herbal medicines can be conducted with reasonable accuracy. Because Chinese medical herbs and herbal medicines are complex compounds and may contain thousands of chemical ingredients, the amount and/or concentration of the chemically characteristic constituents reflected by fingerprints of different samples would not be exactly the same for different samples. To resolve this problem, fuzzy determination technology is now used to authenticate the “sameness” of Chinese medical herbs and herbal medicines, such as fuzzy cluster analysis method<sup>44</sup>. Some Chinese herbal medicines, such as *Fufang Danshen Diwan* and *Fuzheng Huayu* Pieces, have already come under stringent quality controls using fingerprints, the consistencies of the materials used in these medicinal formulas that are under the prospective clinical trials approved by the US FDA are thought to be under reasonable quality control and the variances are within acceptable ranges.

The second issue with regard to the quality control has to do with the findings that the

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<sup>43</sup> Preface of the Chinese Pharmacopoeia 2005

<sup>44</sup> Fingerprint of *Pogostemon cablin* by pyrolysis-gas chromatography and its fuzzy cluster analysis, Zhang Mingguang, et al., Chinese Traditional And Herbal Drugs, 2003 Vol.34 No.8 P.749-752

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therapeutic effects of herbs with the same name may vary significantly if they have different plant origins, growing conditions, harvest seasons, and drying processes. According to the concepts of Chinese medicine, Chinese medical herbs have four natures and five flavors. The four natures are "cold, cool, warm and hot." The five flavors are "sour, bitter, sweet, spicy/acrid and salty." Herbs with the same name but from different sources may vary in their nature and flavor, so they should be used differently. Simply comparing their fingerprints and selecting some commonness as quality control standards may not be proper in this case. Subdivision according to some determination factors and using fingerprints for each subdivision are being practiced to provide added quality control.

The use of fingerprints to identify and measure herbs and mixed formulas has gained significant footing in developing quality standards in this field and the technologies included in the fingerprints are proliferating as scientific researches progress. But the fingerprint technologies are facing major challenges. First of all, since Chinese medicinal herbs and mixed herbal medicines are holistic systems synergistically constituted by many ingredients, and many of which are of very low quantities. Even if several markers or pharmacologically active ingredients can be identified, the best therapeutic effects and properly controlled toxicity may be obtained only with the cooperation of those ingredients of very low quantities. So, using fingerprints to authenticate and identify Chinese medicinal herbs and herbal medicines requires more attention on the holism of the mixtures. In this aspect, multiple dimensions of fingerprints and fingerprints from technologies focusing more on the holism of the herbal mixtures and in-depth analysis of the fingerprints may be needed. Although fingerprints provide scientific aspects of Chinese herbs and herbal medicines, and may be used as standards to authenticate and identify different herbs and herbal medicines, the process could be very complex and holism is a very important consideration. In short, using fingerprints to improve the quality control and consistency of Chinese herbs and herbal medicines has just been around for a short time. Good quality and consistency have been obtained in some herbs and herbal medicines, but not in others. There is still a long way to develop a comprehensive and credible characterization fingerprinting for Chinese herbs and herbal medicines. On the Chinese regulator's side, the SFDA has taken steps to standardize procedures for medical material preparation. Good Agriculture Practice requirement and qualification standard was issued in November 2003 to regulate the production of medical herbal materials from perspectives of ecological environment, germplasm and breeding, cultivation, collection, transportation, packaging and quantitative administration. By monitoring and standardizing the basic process of Chinese herbal medicines, the quality of Chinese herbal medicine may improve gradually and steadily.

Those Chinese herbal medicines that have obtained FDA's IND approval to enter clinical trials, such as *Fufang Danshen Diwan*, *Kanglaite Injection*, *Fuzheng Huayu Piece* and *Guizhi Fuling Jiaonan*, have their materials provided by their own herbal planting bases or suppliers with GAP qualification and under standard operating procedures (SOP). But because a lot of investments will be needed to systemically update and standardize operations required by GAP and SOP, GAP qualification is not currently required by

Chinese SFDA for the time being, so relatively few Chinese pharmaceutical entities or medical herb planting entities have decided to obtain GAP qualification. Since 2004, only 46 entities with 39 kinds of herbs have obtained GAP qualification.<sup>45</sup> The following chart summarizes these herbal entities:

Time	No. of entities	Herbs
March 2004	8	<i>root of red-rooted salvia (danshen), panax notoginseng (sanqi), cornor (shanzhuyu), cordate houttuynia (yuxingcao), stigma croci (xihonghua), banlangen, gen-seng, panax</i>
December 2004	10	<i>dwarf lilyturf (maidong), gardenia (zhizi), Artemisia apiacea (qinghao), poppy shell (yingsuke), Chinese goldthread (huanglian), cornor (shanzhuyu) (two), panax, creat (chuanxinlian), erigeron breviscapus (dengzhancao)</i>
June 2005	8	<i>fleece-flower root (heshouwu), pseudostellaria root (taizishen), balloonflower (jiegeng), root of codonopsis pilosula (dangshen), coix seed (yiyiren), fiveleaf gynostemma herb (jiaogulan), officinal dendrobium stem (tiepi shihu), panax notoginseng (sanqi)</i>
February 2006	12	<i>tuber of elevated gastrodia (tianma), cornor (shanzhuyu), banlangen, catnip (jingjie), astragalus root (huangqi), cabline patchouli (guanghuoxiang), rhizome of Sichuan lovage (chuanxiong), oriental water plantain (zexie), dahurian angelica (baizhi), corydalis (kudiding), ginkgo leaf, pseudostellaria root (taizishen)</i>
December 2006	8	<i>rough gentian (longdan), figwort (xuanshen), glutinous rehmannia (dihuang), Chinese wam rhizome (shanyao), angelica (danggui), coltsfoot flower (kuandonghua), polygonum capilalum (touhualiao), bulb of ussuri fritillary (pingbeimu), panax (dihuang and shanyao are of one entity)</i>

#### 2.2.4.2 Pre-clinical research – toxicity and pharmacokinetics

FDA requires submitting data showing that the drug is reasonably safe for use in small-scale clinical trials. To meet the requirement, *in vitro* or animal studies need to be performed to collect non-clinical data about safety or submitting data obtained from previous clinical testing or marketing of the drug in US or other countries which have a population relevant to that of US.

Unlike western chemical drugs, which are highly targeted on a specific pathway underlying the disease process, Chinese herbal medicine focuses more on adjusting the holistic mechanism in the human body, which in turn resumes the body to a healthy

<sup>45</sup> Refer to the GAP statements of Chinese SFDA.

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condition. When Chinese medical practitioners use Chinese herbal medicines, they not only consider the disease condition of the patients, but also the total host conditions as well as social and psychological factors which may affect the holistic function of human body's defense system. Consequently, the results of pre-clinical researches of Chinese herbal medicine, *in vitro* or in animal models, may not reflect the holistic adjusting mechanism. For Chinese herbal medicines that aim at preventing chronic diseases or helping patients with systematic diseases, such as psoriasis, to resume healthy conditions, it is even harder to design proper *in vitro* or animal studies.

Various toxicity tests are an important part of pre-clinical research, but often are ignored in Chinese herbal medicines. Short test time, lacking of standard examination records, insufficient test index are common problems of toxicity tests of Chinese herbal medicine. When performing toxicity tests for Chinese herbal medicines, the measurement metrics are not easily standardized because the unique characteristics of formulation adjustments according to different syndromes and the cooperative effects among constituent components. By cooperation, the toxicity of one component may be reduced significantly, and the therapeutic power may be enhanced. To perform toxicity tests according to different syndromes of the same disease and on pairs or groups of components may be more suitable to Chinese herbal medicine. Further, the effective dosages of many Chinese herbal medicines are too great for administration into animals. This is another obstacle for pre-clinical research of Chinese herbal medicine. The newly developed micro-powder and ultra fine-powder technology, which breaks the herbal cell walls and helps release effective components, may help to greatly improve the utilization ratio of Chinese herbal medicines so as to reduce the effective dosage. Unlike western chemical drugs, which usually have only one action target, Chinese herbal medicines usually have multiple action targets. Toxicity may accumulate over a long-term use and may not be discoverable through acute toxicity tests. Therefore, toxicity tests of Chinese herbal medicines require more careful analysis. From various reports, an important cause of the toxicity problems of Chinese herbal medicines is improper use; many patients obtain herbal medicine preparations without consulting doctors because no medical prescription is required. General education on proper use of Chinese medicine would likely reduce these problems.

In terms of pharmacokinetics studies, the challenge is very obvious. Since Chinese herbal medicines usually contain many ingredients, many of which are still unknown, it is difficult for pharmacokinetics studies to obtain a complete understanding of Chinese herbal medicine. Currently, the serum-pharmacology of compounds provides a valuable academic base for pharmacokinetics studies of Chinese herbal medicines. Other new research methods are also under active exploration.

It is expected that as more pharmaceutical entities are GAP qualified, the quality and consistency of materials will improve greatly. Coupled with new methods and technologies, this will provide a solid base to control toxicity and pharmacokinetics studies for Chinese medicines. As part of the overall drug quality control efforts, in December 1997, Chinese SFDA issued Good Laboratory Practice for Non-Clinical Laboratory Studies (GLP) to regulate the non-clinical laboratory studies for all the drugs in China. After two revisions, the newest edition of GLP was issued in 2007, providing a system to regulate the design, operation, recording, report and data audits of non-clinical research. According to GLP, detailed standards are essential for each process that could

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affect the validity and integrity of the final result.

Since the regulation is relatively new, only very few institutions have applied and obtained GLP certification. The following are basic statistics:<sup>46</sup>

Year	2003	2004	2005	2006	2007	Total
No. of Entities (GCP Qualification)	4	7	4	8	3	26

With the improvement in material quality control and consistency, some pre-clinical researches of Chinese herbal medicines have met the requirements of FDA. Although these examples are scarce in number as statistics have provided in the previous sections, the overall trajectory of increased FDA compliance is very encouraging.

#### **2.2.4.3 Clinical trials – design and efficacy evaluation**

In 1985, regulations about clinical trials of Chinese herbal medicine appeared in China for the first time. In 1998, Good Clinical Practice for Drugs was issued, and herbal medicines were under the regulation. Chinese SFDA required that all institutions conducting clinical trials and medical institutions involved in drug clinical researches should obtain GCP qualification and perform their investigative duties, to effectively and responsively manage and coordinate clinical trials, to ensure that their researches are conducted in accordance with relevant laws and regulations, to ensure that the quality of drug clinical research and reliability of research data and protect the interests of testing subjects. By the end of 2005, 93 institutions obtained GCP qualifications. In 2006, 65 more institutions became GCP qualified<sup>47</sup>. Conducting thousands of active ongoing clinical trials in Chinese medicines, the 158 institutions with GCP qualification are by far in short supply. Conceivably, it is really difficult for these GCP qualified institutions to perform high quality and sufficient clinical trials under such a heavy workload.

How to design a scientific clinical trial for Chinese herbal medicines impose a big problem, for few practitioners who understand well the medicines to be tested have sufficient knowledge about scientific clinical trials, while those who know how to design and perform scientific clinical trials seldom understand the special characteristics of Chinese herbal medicine. For example, Chinese herbal medicines, which are aimed at restoring patients to healthy conditions through adjusting basic accommodation or compensatory mechanisms in the human body, usually have multiple action targets and may be suitable for several disease processes. As a consequence, the criteria for inclusion and exclusion are usually not as stringent. In terms of controls, clinical trials of Chinese herbal medicines often use other herbal medicines perceived to have positive effects as controls, rather than placebo. Since the perceived positive effects of the control medicine(s) used as controls lack solid confirmation or objective measurement criteria, false positive problem imposes a big issue for such trials and reduces the credibility and reliability of the results. As the preparations of Chinese medicines become miniaturized or formulations capsulated, it becomes possible to use placebo and this control issue in the trial design can be resolved. With regard to objective measurable endpoints in the

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<sup>46</sup> Refer to the GLP statements of Chinese SFDA.

<sup>47</sup> According to the GCP qualification statements issued by Chinese SFDA.

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clinical trials, scientifically verifiable standardized tests various well accepted scientific methods are becoming commonplace in clinical trials of Chinese herbal medicine, which help improve the quality and credibility of the trials. For example, in the clinical trials of *Fuzheng Huayu* Piece (Chinese medicine for liver disease) performed in China, Golden standard of liver biopsy was used to measure the endpoints and newest version of statistical analysis software suggested by FDA are used, which facilitate FDA to understand the documents about the trials and increase the reliability of the results.

From the US FDA's perspective, the biggest problem of clinical trials of Chinese herbal medicines is the evaluation and proof of efficacy. Current efficacy evaluation methods and standards generally accepted by FDA usually derive from research on western chemical drugs, focusing on the changes in pathology and physiology. Chinese herbal medicines act against a complex set of mechanisms with certain subjective syndromes rather than specific diseases, with the purpose of resuming patients to a healthy condition through multiple action targets, systematically adjusting and rebalancing various mechanisms in the human body. The process tends to be long, and the adjustment happens gradually. The advantage is that the efficacy effect usually continues for a longer time than that of western chemical drugs. To address this systematic difference of causal relationship and underlying mechanisms, on the one hand, companies are attempting to adjust formulations of Chinese herbal medicines to focus their direct actions on specific diseases so that the outcomes are more visible and verifiable in a relatively short period of time. For example, the clinical trials of *Kanglaite* Injection focus on testing its efficacy on cancer of pancreas although its original use is to act against multiple kinds of cancers. The clinical trials of *Fuzheng Huayu* Piece highlight its effects against liver fibrosis which is easy to measure through liver biopsy. On the other hand, new evaluation methods suitable to Chinese herbal medicine are being developed. These efforts focus on identifying some in-process indexes, such as immunological tests, to evaluate the efficacy of Chinese herbal medicines when they gradually improving the health condition of patients. Other evidences, such as changes of tongue and pulse, also play an important role in the therapeutic processes of Chinese medicine, but the significance of these data would translate very poorly across cultural boundaries, particularly for those people who do not have a good understanding of the theories of Chinese medicine. Although since 1997, there have been several kinds of Chinese herbal medicines that received FDA's IND approval to enter phase II clinical trials, a good sign of improvement of material quality control, no one has achieved substantial progress as of yet. Efficacy evaluation has been a major obstacle.

#### **2.2.4.4 Manufacturing quality control**

Since 1988, Chinese SFDA has been regulating drug manufacturing by Good Manufacturing Practice standards. SFDA requires that all pharmaceutical entities involved in herbal medicine manufacturing should obtain GMP qualification before January 1, 2008. But until now, only 355 entities in herbal medicine manufacturing have obtained the qualification while the total number of pharmaceutical entities registered in herbal medicine manufacturing is more than 1,100. Part of the reasons of the slow progress is lack of necessary financial resources to overhaul the current manufacturing facilities to conform the GMP standards. At this time, many herbal medicines manufactured by unqualified entities are on the market and competing with those medicines from GMP qualified manufacturers at low prices. The following is a time

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series chart that captures the incremental increase of numbers of GMP certified manufacturers.<sup>48</sup>

Year	No. of Entities (GMP Qualification)	No. of Entities (Herbal Medicine) (GMP Qualification)
1999	110	1
2000	596	2
2001	449	1
2002	684	4
2003	1180	28
2004	2700	74
2005	2165	91
2006	1610	97
2007	1029	57
Total	10523	355

In summary, the Chinese GMP requirements are likely to further raise the overall competence of manufacturers of Chinese herbal medicines toward FDA quality compliance. There has indeed been significant progress in this area and it is anticipated that by 2008, those manufacturers without GMP qualification will be forced out of the market.

## **2.2.5 Fingerprint technologies and quality control of Chinese herbal medicine**

Quality control of Chinese herbal medicine is more difficult than that of chemical drugs because there are multiple ingredients or compounds, many of which are still unknown. These ingredients are not simply mixed with each other, but synergistically constitute a therapeutic system.

Fingerprints can provide much important and relevant information about the characteristics of their constituent chemical compounds, such as its major components and properties. With the help of separation technology and various scientific analytical tools, fingerprints now play an important role in authentication, identification and quality control of herbal medicines. Most significantly, the US FDA has started to accept tests utilizing fingerprint-related technologies.

Common fingerprint related technologies include thin layer chromatography (TLC), gas chromatography (GC), high-performance liquid chromatography (HPLC), high performance capillary electrophoresis (HPCE), UV spectroscopy, infrared radiation (IR) spectroscopy, nuclear magnetic resonance, mass spectroscopy (MS), DNA fingerprint,

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<sup>48</sup> According to the GMP qualification statements issued by Chinese SFDA.



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and the list is growing. Hyphenation technologies, such as HPLC-MS, HPLC-NMR, and GC-MS, can be used to improve the analytical results. The following paragraphs highlight some of the major fingerprint methods.

Thin layer chromatography, a classic fingerprint technology, was used by Japanese researchers on analyzing herbal medicine in the 1960s. The advantages of TLC include high velocity, versatility, simple sample preparation and good reproducibility. With the help of image analysis and digitalized computer-aid technique, similarities between different samples can be evaluated.

Gas chromatography (GC) is very suitable to analyze volatile compounds of herbal medicines. The prominent advantage of GC is its high effectiveness and high sensitivity when detecting volatile chemical compounds. Besides that, its high selectivity of capillary columns enables separation of many volatile compounds simultaneously in short periods of times.

High-performance liquid chromatography (HPLC) is easy to learn and use, and is able to analyze almost all the known compounds in herbal medicines at high speed with high separation capability. So it becomes a very popular method of herbal medicine analysis.

UV spectroscopy can be used to measure the wavelength and intensity of absorption of ultraviolet and visible light by herbal medicines, but it is more suitable for single substances. When UV spectroscopy is used to test complex herbal compounds, the results should be backed up by HPLC.

The processes of using fingerprints as quality control for herbal medicine include fingerprint profile establishment, fingerprint analysis, and using standard fingerprints to control quality. The following paragraphs describe its general process.

The first step is to standardize the extraction process of Chinese herbal medicine to produce characteristic samples for fingerprint profile establishment. Then use chromatography and/or spectroscopy technologies to analyze the holistic extract, establish fingerprints and identify characteristic data. When standardizing the extraction process, various factors that affect the consistency of the herbs or the herbal medicines should be considered. To capture the holistic characteristics of Chinese herbal medicines, it is better to establish fingerprints that capture most ingredients, but as more ingredients are included, the more difficult to analyze the established fingerprint profiles. To partially resolve this issue, multi-dimensional fingerprints may be employed to provide a better view.

After the fingerprint for the holistic extract is established, the characteristic peaks of the extract should be analyzed, and then separated into multiple relatively simpler sub-systems. Sub-systems consisted of pairs or groups of ingredients may be more suitable to Chinese herbal medicines. Then as the relationship between each sub-system and characteristic peaks in fingerprint, the therapeutic effects of each sub-system and the relationship among sub-systems may be correlated and analyzed. Once the characteristics of sub-systems are identified, repeatability should be examined. Chinese medical theories should be referred to in analyzing the interrelationships between these sub-systems. When the above research is finished, the standardized fingerprint for holistic extract and the characteristics of sub-systems can be used to control the quality of the medical herbs or the preparation of herbal medicines in accordance with scientific comparability criteria.

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The first Chinese herbal medicine that obtained FDA's IND approval, *Fufang Danshen Diwan*, provides a good example of using fingerprints to improve the quality and consistency of Chinese herbal medicines. Three medical herbs are used to prepare the drug, which are *salvia miltiorrhiza* (*danshen*), *panax notoginseng* (*sanqi*), and *cinnamomum camphora* (*bingpian*). After fingerprint analysis, 10 water-soluble ingredients of *danshen*, 20 saponin ingredients of *sanqi* and their fingerprint characteristics are identified. Then multiple-fingerprint computation and analysis technology is used to control the material, the in-process extracts and the prepared medicine. The results are that the comparability of the materials provided by its GAP qualified planting base is controlled at levels higher than 95%, the comparability of the in-process extract and the comparability of the prepared medicines are controlled at levels higher than 90%. Quality and consistency of the medicines are greatly improved.<sup>49</sup>

In summary, the development and employment of various fingerprint technologies have provided new scientific ways to control the quality and navigate the properties of the whole plants or whole Chinese medicinal formulas. Different from the commonly used characterization methods to isolate and identify small molecule chemical entities, the fingerprinting technologies provide insights of the herbal medicines without breaking it down to many smaller molecules, making it possible to use fingerprints to characterize and control the properties of herbal medicines in a holistic fashion, consistent with the intrinsic philosophies of traditional Chinese medicine. With these new technologies, it is reasonable to foresee that more medicines based on Chinese herbal medicines and a wealth of accumulative empirical therapeutic medical formulas may be developed in much less expensive ways and in shorter periods of development times. This alternative pathway discussed in this thesis, that is, the mixed formula pathway for new drug development, may serve as a potential solution to today's escalating pharmaceutical costs, better treatments for hard-to-treat or chronic illnesses, prevention of diseases, improvement on human beings health status or quality of life and partially relieve pressure of the US health care "crisis."

## **2.3 Value Formation from Public Domain Knowledge to Private Property - Analysis of Literatures and Patents on Chinese Herbal Medicine**

### **2.3.1 Introduction**

The main hypothesis of this thesis is to postulate that there is significant latent value that has been accumulated about medicines and drugs (including Chinese herbal medicine) in China and around the world. Many successful drug developments based on Chinese herbs, including the three case studies in this thesis, have capitalized on the public domain knowledge in the form of published literature. The patents, in a market economy, are fundamental to economic value creation<sup>50</sup>. This situation is particularly true in the pharmaceutical industry. The following sections represent the author's research efforts to

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<sup>49</sup> Multiple-fingerprint tests for Fufang Danshen Diwan manufactured by Tasly Group

<sup>50</sup> Patent Statistics as Economic Indicators: A Survey, Zvi Griliches (1990)

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navigate, summarize and analyze the relevant data to substantiate, at a macro level, the existence of knowledge and value accumulation through the proliferation of scientific literatures and patents regarding Chinese herbal medicine. This public and private knowledge would form a new paradigm from which values may be created and captured.

Patent analysis is an important topic in the management of technology. Academics and corporations acquire information of technological development and competitive intelligence from patent database. The number of patents issued is often a surrogate indicator of technological R&D output. The simplest way to measure R&D productivity is to count the number of patents. Griliches (1990)<sup>51</sup> indicates additional insight into patents. Patents not only can measure inventive activities in the way of output but also as input. In other words, patent statistics can act as economic indicators. Furthermore, patent statistics are also technological indicators by improving patent information to judge technological change (Basberg, 1987)<sup>52</sup>. One can transfer patent data into valuable information or into intelligence by patent analysis. Usually, patent analysis has two purposes for general use: competitive analysis and technology trend analysis (Liu & Shyu, 1997)<sup>53</sup>.

A patent is a document, issued by an authorized governmental agency, granting the right to exclude anyone else from the production or use of a specific new entity, device, apparatus, or process for a stated number of years. The grant is issued to the inventor of this entity or process after an examination that focuses on both the novelty of the claimed item and its potential utility. The right embedded in the patent can be assigned by the inventor to somebody else, usually to his employer, a corporation, and/or sold to or licensed for use by somebody else. This right can be enforced only by the potential threat of or an actual suit in the courts for infringement damages. The stated purpose of the patent system is to encourage invention and technical progress both by providing a temporary monopoly for the inventor and by forcing the early disclosure of the information necessary for the production of this item or the operation of the new process.

Kuei-Kuei Lai, Mei-Lan Lin, and Shu-Min Chang (2006)<sup>54</sup> defines patent analysis as methods for analyzing patent data. The standard for patent analysis appears to be similar across the globe, all industries, and all companies. Basber (1987)<sup>55</sup> synthesizes earlier patent literature into three types. One type relates to the legislation and the functioning of the patent system. The other two are rationale of the system and patent as technical information. Regarding the third type, he also points out three groups of patent statistics as technology indicators. Patent analysis in strategic planning is dissected on the propensity of innovative activities, and the research trajectories between science and

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<sup>51</sup> Patent Statistics as Economic Indicators: A Survey, Zvi Griliches (1990)

<sup>52</sup> Patent and the measurement of technological change: a survey of the literature, Basberg, B.L. (1987)

<sup>53</sup> Strategic planning for technology development with patent analysis, Liu, S.J. and Shyu, J (1997)

<sup>54</sup> Research Trends on Patent Analysis: An Analysis of the Research Published in Library's Electronic Databases, Kuei-Kuei Lai, Mei-Lan Lin, Shu-Min Chang (2006)

<sup>55</sup> Patent and the measurement of technological change: a survey of the literature, Basberg, B.L. (1987)

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technology (Pavitt, 1985)<sup>56</sup>. Tsuji (2001)<sup>57</sup> systematically classifies literatures of patent analysis into three groups. The first group is international comparison. The others are econometric analysis and technology changes. In addition, using patent statistics as indicators of innovative activities are based on three perspectives of economics, bibliometrics, and descriptive comparisons for policy uses. Besides, Ernst (2003)<sup>58</sup> recommends the value of patent information for strategic planning, and he has built a conceptual framework showing patent function in technology management. Patent information is a useful source in five areas. Patent analysis can be employed in competition monitoring, assessing the attractiveness of technologies, technology portfolio management, the identification of external sources for knowledge generation, and human resource management. Similarly, many researches exemplify numerous methods of applying patent analysis, especially in technology competition analysis, investment evaluation, patent portfolio management, research management, product scope surveillance, corporate valuation, as well as mergers and acquisitions.<sup>59</sup> In the same way, the published literature could also be a source to analyze the accumulation of public domain knowledge, which, in turn, may be the sources to cultivate production of new patents.

For this thesis, I have collected and attempted to analyze literatures and patents that are related or possibly related to Chinese herbal medicine.

### **2.3.2 Methodology**

All data I used is from creditable sources.

The Chinese patent data is from SIPO database (<http://www.sipo.gov.cn>)

The world patent data is from LexisNexis (<https://www.lexisnexis.com>), the database is US Patents, European Patents, Patent Abstracts of Japan, PCT Patents, and UK.

The world patent data is also from Derwent innovations index (<http://portal.isiknowledge.com>), the database is Chemical--1963-present, Electrical and Electronic--1963-present, Engineering--1963-present.

The Chinese literature data is from CNKI (<http://www.edu.cnki.net>)

The worldwide literature data is from ISI Web of Knowledge /medicine (<http://portal.isiknowledge.com/>), the database is In-Process and MEDLINE--1950-present

Some data is from China Science & Technology statistics data book (<http://www.sts.org.cn/sjkl/kjtjdt/index.htm> )

Some data and analysis is from the literature that I cited, and I will explain in the

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<sup>56</sup> Patent statistics as indicators of innovative activities: possibilities and problems, Pavitt, K. (1985)

<sup>57</sup> A Methodological Study of Patent Statistics for Technoeconomic Analysis, Tsuji, Y.S. (2001)

<sup>58</sup> Patent information for strategic technology management, Ernst, H. (2003)

<sup>59</sup> Using patent information in technology business planning. Breitzman, A.F. and M.E. Mogee (2002). The many applications of patent analysis, Ashton, W.B. and Sen, R.K. (1988)

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paragraph why I use this data.

First, I will use the data to describe how many literatures or patents I found, and then I will compare different types of literatures or patents. Then, lay out the data along the time vector to see the change of numbers over time.

For literature analysis, similar keywords are used to search the literature by year. Keywords used are as following:

**CNKI:**

TS=医药 and 概况

TS=医药 and 提取

TS=医药 and 提纯

TS=医药 and 合成

TS=医药 and 制造

TS=医药 and 实验

TS=医药 and 动物实验

TS=医药 and 临床实验

TS=医药 and 化学配方

TS=医药 and 新化合物

TS=医药 and 分子结构

**ISI:**

TS=Drug or TS=medicine and TS=general

TS=Extractions

TS=Purification

TS=Synthesize

TS=Manufacturing

TS=Experiments

TS=Animal Experiments

TS=Human Clinical Trials

TS=New formulations

TS=Novel compounds

TS=Molecular mechanisms

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As we can see from the above keywords which may be potentially related to medicine or drugs, but may not be specifically related to Chinese herbal medicine. This is for two reasons, one, I found it to be hard to design keyword search profiles specifically for Chinese herbal medicine, two, I would rather characterize the overall innovative activity in drug development rather than just the Chinese herbal medicine, since most of the latter have been integrated into the overall scientific activities of drug development. It is relevant to this thesis to sense the level of activities and also the general ability to translate public domain knowledge into private intellectual properties and the implicit ability as an economy to capitalize on the latent knowledge value.

### **2.3.3 Analysis of literature statistics**

According to S&T papers of selected countries catalogued by SCI, EI and ISTP as a whole and by SCI, China ranks the 4<sup>th</sup> among all the countries in terms of the number of papers. The number of papers issued by SCI, EI and ISTP is 153,374. At the same time, the US ranks the 1<sup>st</sup> and the number of papers is 666,360. Papers from China may be close to the UK and Japan, but it is still a great gap to US.<sup>60</sup> From 2000 to 2006, literatures relevant to medicine published in China are increasing but the rate is far more behind those in the economically developed world. (CNKI database' update in 2006 is not yet complete at the time of search.) The data is tabulated and shown as attachment 1 of this thesis.

As the following charts will collectively show (most charts are for illustration purposes and self-evident; narrative explanations and units are omitted), although the literatures published in China about extractions is close to the total in the world, the major differences are in the later processes of drug development. In areas such as “purification,” “synthesization,” “manufacturing,” “experiments,” and “new formulations,” China is significantly and often by far behind the English-language world.

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<sup>60</sup> From: <http://www.sts.org.cn/sjkl/kjtjdt/data2006/2006-6.htm>

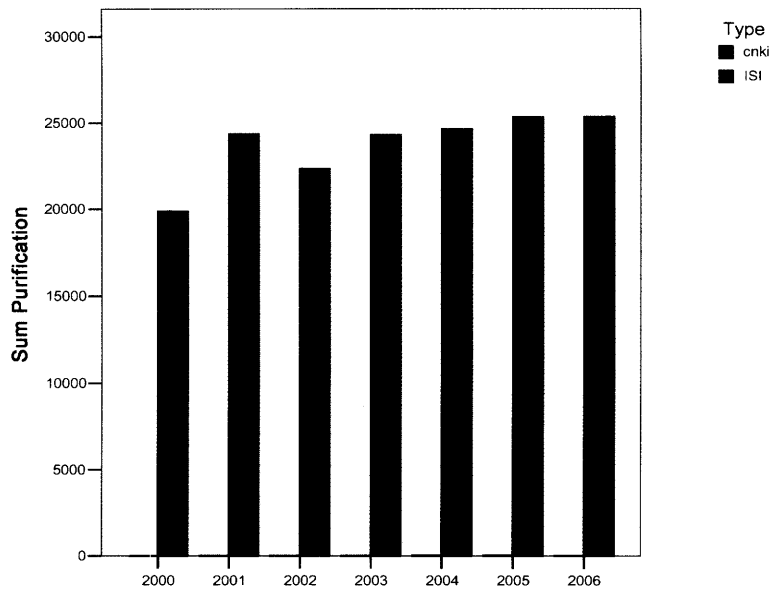


Figure 2.3.1: Search results of “purification” of CNKI and ISI

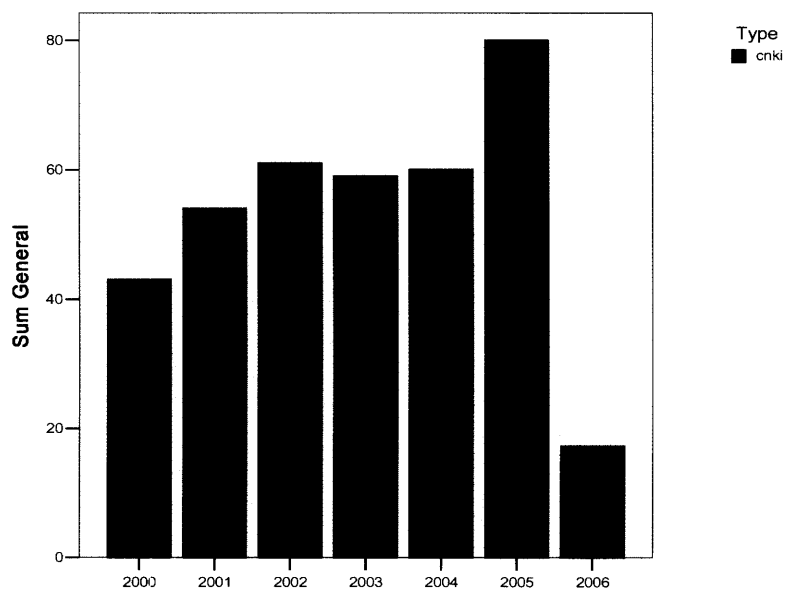


Figure 2.3.2: Search results of “medicine and general” of CNKI

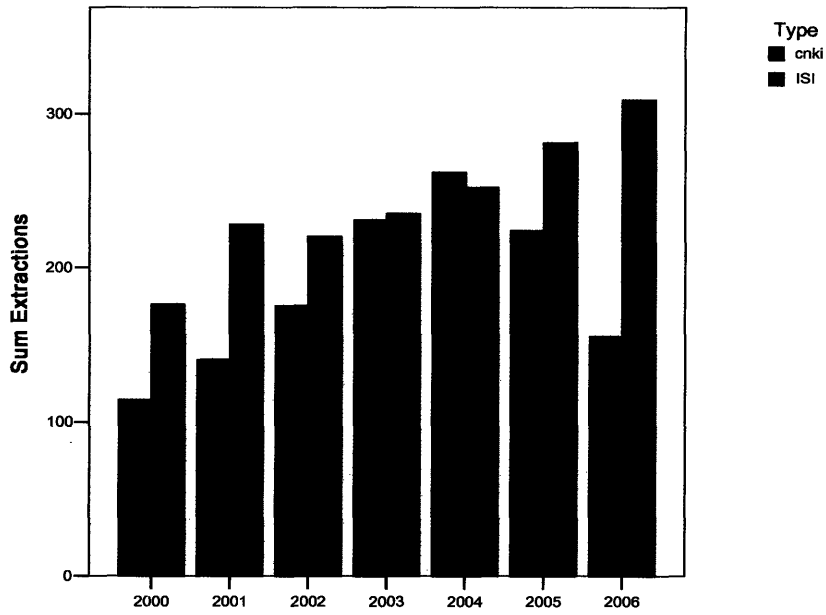


Figure 2.3.3: Search results of “extraction” of CNKI and ISI

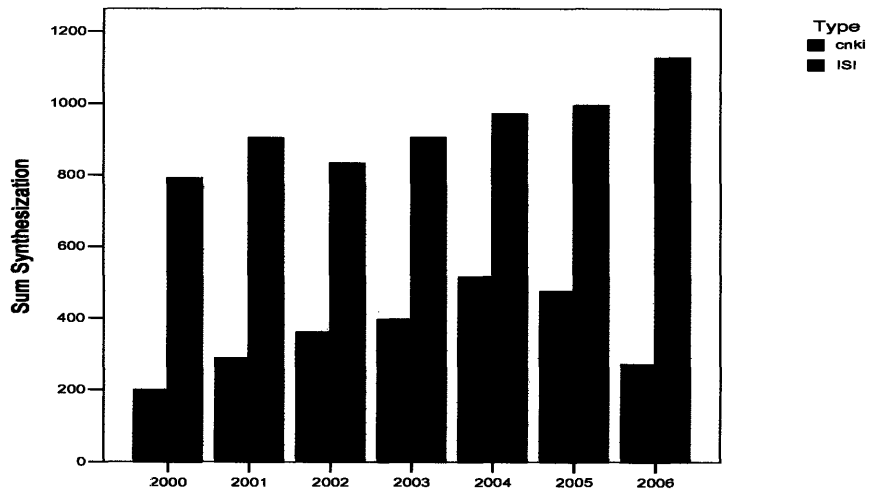


Figure 2.3.4: Search results of “synthesization” of CNKI and ISI



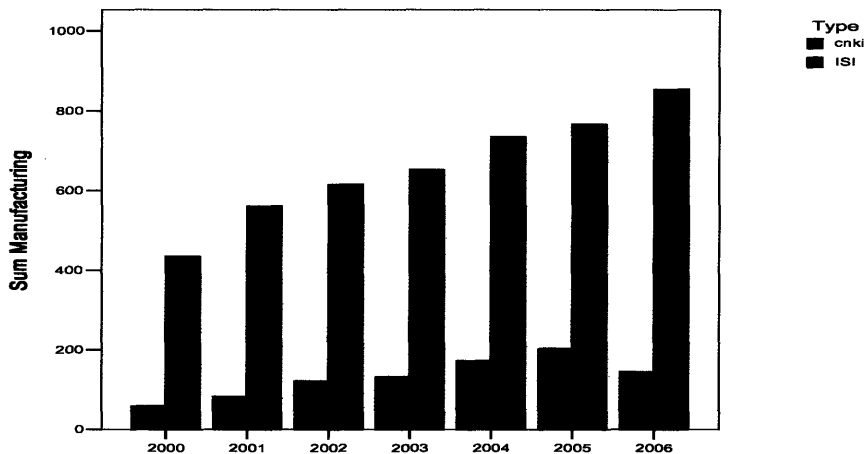


Figure 2.3.5: Search results of “manufacturing” of CNKI and ISI

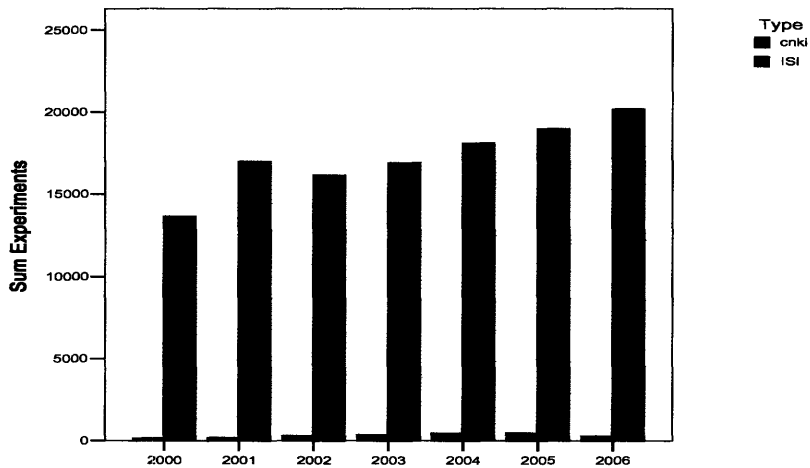


Figure 2.3.6: Search results of “experiments” of CNKI and ISI

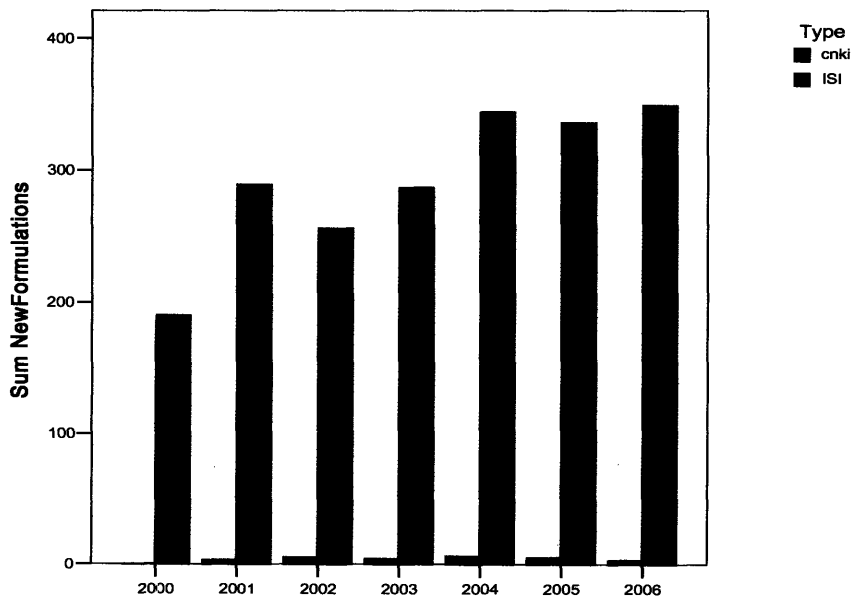


Figure 2.3.7: Search results of “new formulations” of CNKI and ISI

### 2.3.4 Patent statistics

As a general context, as shown in the figure 8 as follows, China’s R&D investments increase quickly in recent years, but are still far behind those in the US.

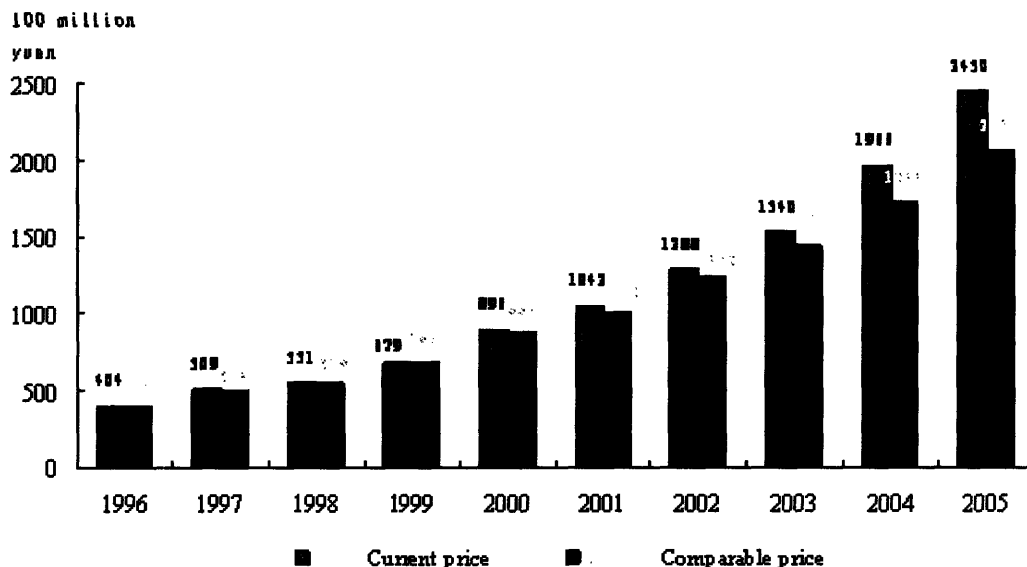


Figure 2.3.8: Gross Domestic Expenditure on R&D in China (2000~2005)<sup>61</sup>

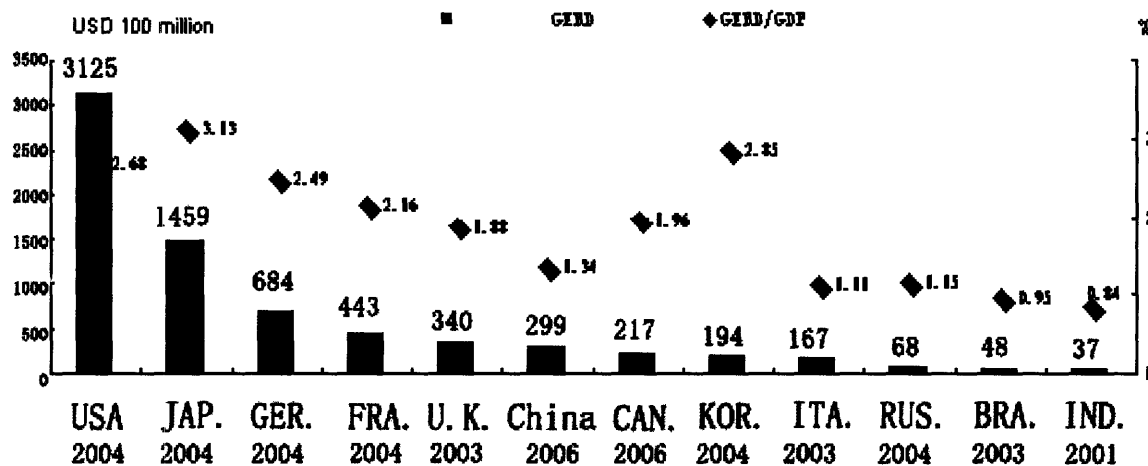


Figure 2.3.9: GERD in selected countries<sup>62</sup>

\* GERD Gross Domestic Expenditure on R&D

<sup>61</sup> From: <http://www.sts.org.cn/sjkl/kitjdt/data2006/2006-1.htm>

<sup>62</sup> From: <http://www.sts.org.cn/sjkl/kitjdt/data2006/2006-6.htm>

Both patent applications and patents granted related to medicines increased quickly from 1995 to 2003. (Please refer to Attachment 2 and 3 about the tabulated results of the searches.)

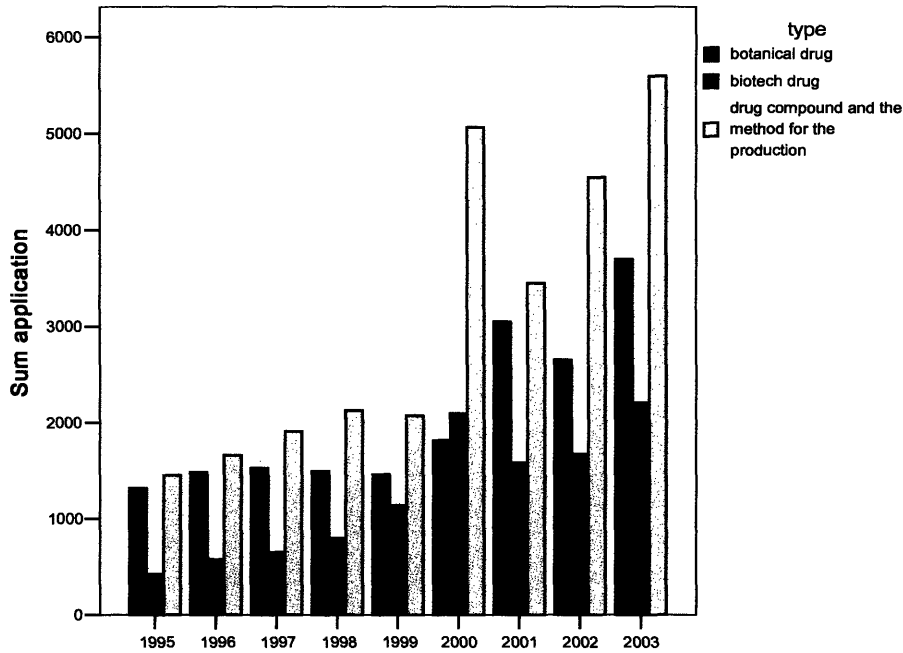


Figure 2.3.10: The three types of medicinal patent application from 1995-2003<sup>63</sup>

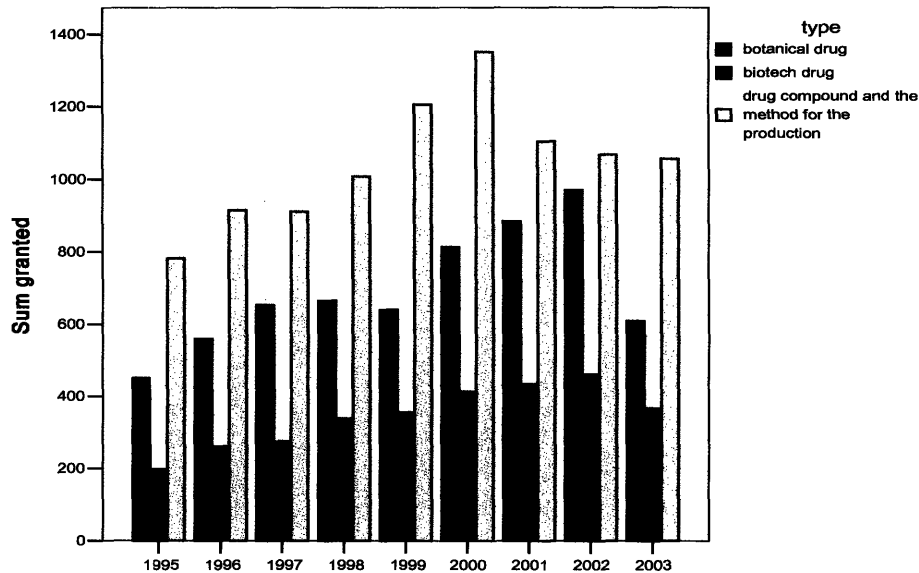


Figure 2.3.11: The three types of medicinal patent granted from 1995-2003<sup>64</sup>

<sup>63</sup> Chinese patent data, search results from SIPO database

<sup>64</sup> Chinese patent data, search results from SIPO database

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In the published articles, some authors argue that the contribution of patents to the GDP in China is not obvious in China, because of the absent of strong IP law or lack of enforcements for IP rights. But the effects of patents will likely increase as the legal and regulatory system in China becomes more mature in the future. In China, as the search data shows, nearly half of the medicinal patent applications were foreign applications. The applications of patents regarding botanic drugs (herbal medicines) and drug compounds as well as methods for production constitute the vast majority.

The above data, by and large in a qualitative fashion, demonstrates that there is a significant body of published knowledge and steadily growth of patent applications and issuance. The published Chinese language knowledge as scientific articles, in the keyword searches related directly and indirectly to medicines, is largely corresponding to the earlier and general categories of drug development rather than the keywords of “purification,” “synthesization,” “manufacturing,” “experiments,” and “new formulations” that are categorically corresponding to later stages of drug development pathways. In the patents filed in the Chinese patent agencies, a significant portion of applications and grants are those that originated in foreign countries. Many manufacturing and process patents are filed by Chinese domestic applicants. Taken altogether, the data supports the hypothesis that there is early formation and quick growth of scientific knowledge and IP, an indicator for latent valued to be realized and captured as time progresses.

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### 3. Case Studies

Among the singleton pathway and the alternative mixed formula pathway, the former is by far the most commonly used drug development trajectory from herb (plant) sources so far. In this section, I present three different case studies. The purpose of these case studies is to delineate the critical pathways, both from scientific and regulatory perspectives that the developers followed or are following. These cases are drugs targeting the anti-diabetic market and in different development stages, the drug Metformin (Glucophage) was derived from a plant known as *French Lilac*; the compound PGG and its derivatives are originated from the *banaba* plant (*lagerstroemia speciosa*), and some of the materials are from my personal communications with the developer, Professor Xiaozhuo Chen at Ohio University, who has graciously agreed to allow me to use the development story and data in this thesis. The development efforts are still underway, and the compound resveratrol, which was originally isolated from grape skin, is now known to exist in many plants. A new company founded by several Harvard Medical School professors is attempting to commercialize the compound and its derivatives as anti-diabetic drugs for FDA approval.

Common to all three cases, a wealth of empirical therapeutic evidence and published articles precedes the patenting and commercial development activities. In other words, the common trajectory appears to be a time series transformation from empirical experience into scientific research and publications and then into formation of private intellectual properties which further drive the commercialization. This common trajectory indirectly supports this thesis' hypothesis that value may be created from the accumulated knowledge in Chinese herbal medicine.

From the scientific perspective, all these three cases involve extraction and isolation of therapeutically effective compounds, molecular characterization, purification and modification, and sometimes synthesizations.

#### 3.1 Metformin

##### 3.1.1 Introduction

The reason of my selecting this case study for the thesis is the winding but successful road taken by innovative scientists and by several pharmaceutical companies in converting a plant with a long history of empirical evidence of therapeutic benefits into an ethical drug. The story delineates the processes of scientific discoveries and persistent efforts on the part of various pharmaceutical companies to satisfy FDA's rigorous requirements on controlling adverse effects caused by this herb-derived drug. This success story, as my data on the published literature and patent applications/grants, has sparked continued interests to further improve the existing drug or discover new drugs with fewer side effects.

Metformin is an oral anti-diabetic originally derived from the plant *French Lilac*, standing the test of time and continuing to be an important component in the management of diabetes. The following chart correlates the scientific discoveries about insulin and metformin with the major technological breakthroughs in history<sup>65</sup>. For example, the first

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<sup>65</sup> Understanding RTK signaling specificity: insulin versus IGFs, Pierre DeMeyts

insulin crystal was created in 1926 which coincides with Lindberg's cross-Atlantic flight, discovery of Metformin in 1957 which coincides with the launch of the Sputnik Satellite. These seemingly unrelated events may not be coincidental after all, because scientific values may not be realizable unless the human being has acquired enough body of knowledge and produced a high enough level of technological know-how.

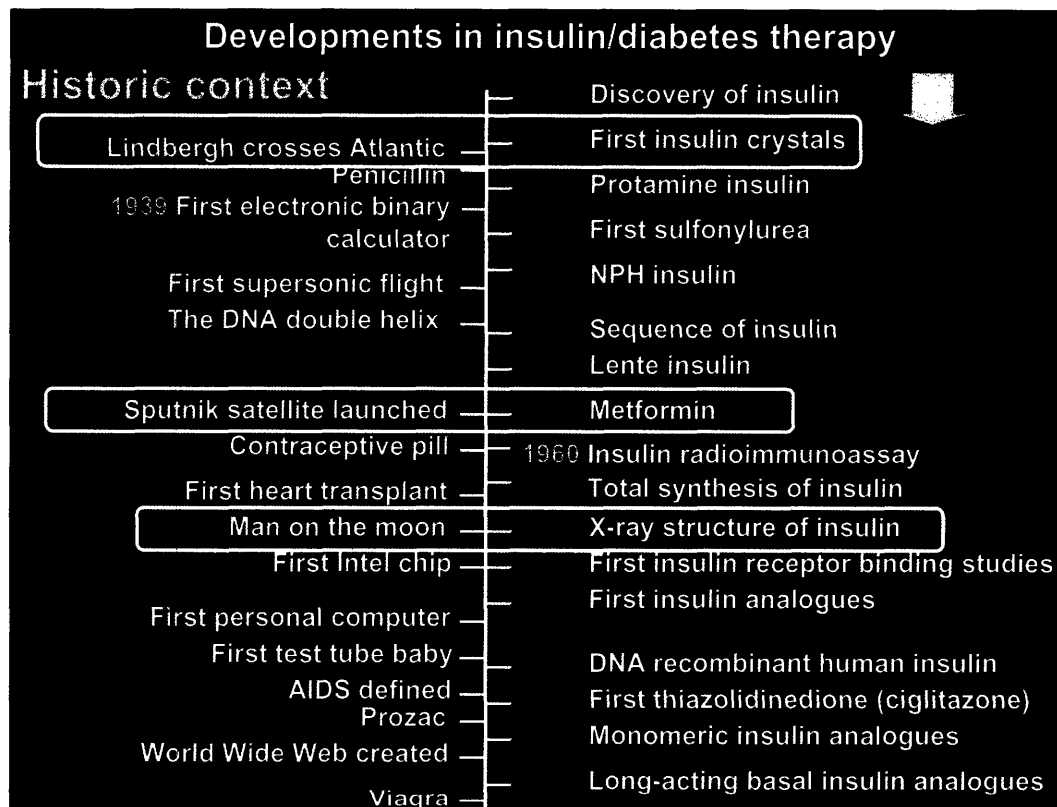


Figure 3.1.1 Scientific discoveries about insulin and metformin with the major technological breakthroughs in history<sup>66</sup>

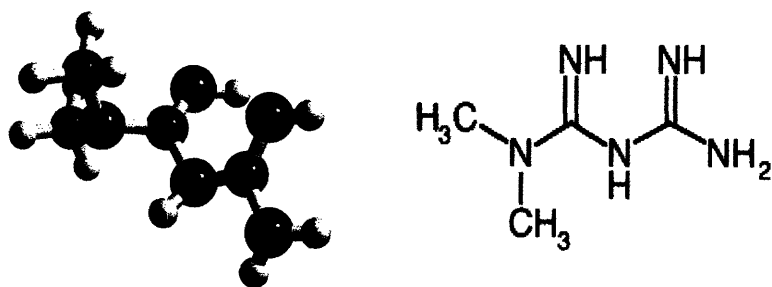


Figure 3.1.2 Chemical structure of Metformin<sup>67</sup>

<sup>66</sup> Understanding RTK signaling specificity: insulin versus IGFs, Pierre DeMeys

<sup>67</sup> www.3dchem.com & <http://pl.wikipedia.org/wiki/Metformina>

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Chemical formula of metformin is  $C_4H_{11}N_5$ . Metformin targets the liver, and has secondary effects on muscle and fat. The main actions of metformin include lower glucose production by the liver, increased number of insulin receptors on muscle and fat cells and lowers HbA1c by 1.5% to 2.0%. Main side effects include bloating, fullness, nausea, cramping, diarrhea, vitamin B12 deficiency, headache, metallic taste, agitation, and occasionally lactic acidosis.

Action mechanism of metformin is illustrated in the following diagram:

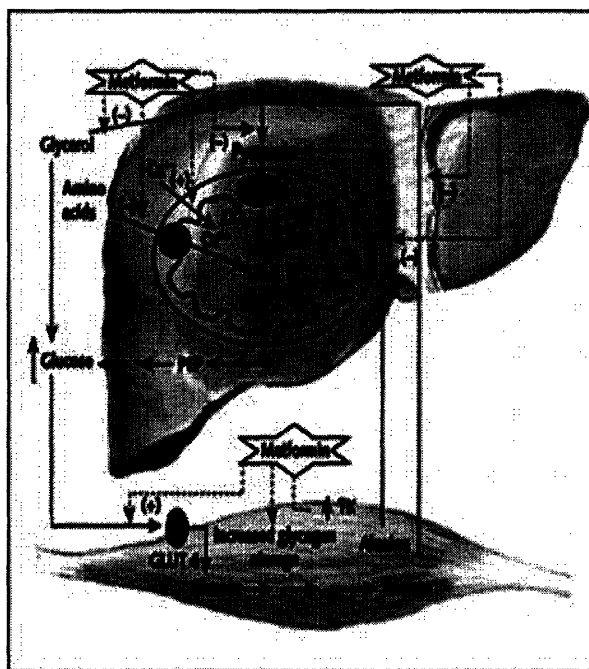


Figure 3.1.3 Mechanism of metformin<sup>68</sup>

Metformin is the only example of an approved anti-diabetic drug that was developed from an herbal source with a long history of use for diabetes. On March 3, 1995, Glucophage (active ingredient is metformin hydrochloride) obtained FDA approval (NDA 020357). In 1996 Glucophage became the largest selling oral anti-diabetic agent in the world. It is also the top-selling French drug in the US. Around eight million patients in more than 100 countries worldwide benefit from Glucophage (metformin).<sup>69</sup>

### 3.1.2 Development history of metformin

Metformin is derived from *French lilac* plant, which was noted in the early 1900's to lower blood sugar. Diabetes has been a mysterious disease for very long period of time. It took centuries to identify its mellitus form and its ties to insulin came to be known even much later. The ultimate acceptance of the biguanides and the understanding of their mechanism of action is part of contemporary history. Prior to the availability of insulin and

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<sup>68</sup> <http://musik.myweb.uga.edu/antidiab2.htm>

<sup>69</sup> <http://www.ezeediabetes.co.za/cogowelglucstory.asp>

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anti-diabetic medicines, hypoglycemic plants (400+) were extensively used throughout the world.<sup>70</sup> The most interesting one was *galega officinalis* (also known as *goat's rue*, *French lilac*, *Italian fitch* or *professor-weed*), a plant from the Galega genus of the Faboideae, found to yield alkaloid galegine.



Figure 3.1.4 The plant *French lilac*<sup>71</sup>

The therapeutic effects of *French lilac* have been known in the folk population for a long time. In medieval times, a prescription of *French lilac* was able to relieve the intense urination accompanying the disease that later known as diabetes mellitus. *French lilac* was also given during plague epidemics to promote perspiration and has been used as a galactogogue in cows. The active ingredient in the *French lilac* that produced the hypoglycaemic effects was shown to be galegine or isoamylene guanidine. A curious chapter in the history of guanidine-based hypoglycemic agents arose from the mistaken notion that the tetany of hypoparathyroidism was due to over production of guanidine following parathyroidectomy, leading to the demonstration that an infusion of guanidine produced lowering of blood glucose.<sup>72</sup>

In the early 1900's, the pharmacological and therapeutic properties of *French lilac* led to the use of guanidine derivatives in the treatment of diabetes mellitus. Galegine was isolated as an active anti-hyperglycemic agent from the plant *galega officinalis* L, which became the template for the synthesis of metformin and the synthesis of other biguanidine-type anti-diabetic drugs.

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<sup>70</sup> The Story of Glucophage

<sup>71</sup> The blooming of the French lilac & <http://commons.wikimedia.org>

<sup>72</sup> The blooming of the French lilac



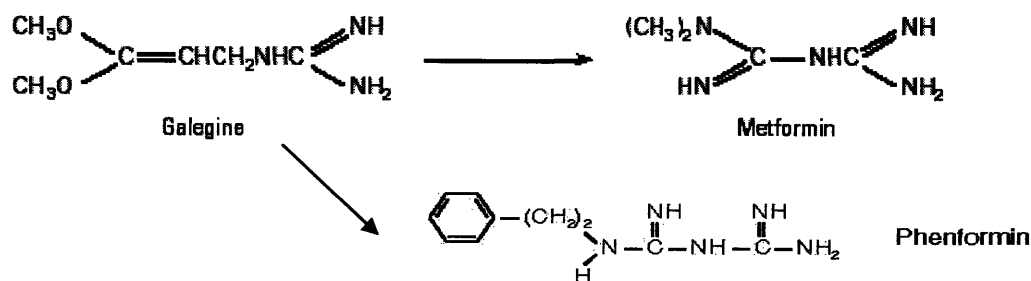


Figure 3.1.5 The synthesis of metformin and other biguanidine-type anti-diabetic drugs<sup>73</sup>

Watanabe first noted the hypoglycemic effects of guanidines at the beginning of this century. Since guanidine was quite toxic, substituted guanidines (synthalin A and B) were synthesized around 1928 and utilized, which turned out to be very toxic as well. This led to the synthesis of biguanides in 1929. However, some initial investigators believed even the most active of these biguanides (N1, N1-dimethylbiguanide or metformin) to be not indicated for use as an insulin substitute in humans. Phenformin (phenylethylbiguanide) was synthesized in 1956.<sup>74</sup> The breakthrough of metformin, a dimethylbiguanide, was made possible by Jean Sterne (1919-1997), a French physician and pharmacologist, in the mid-1950s.<sup>75</sup>

In 1955, Hollunger and Creutzfeld pinpointed the mechanism of action of the guanidines through pharmacological and pathological studies. Dr. Jean Sterne and his colleague Denis Duval of Aron Laboratories near Paris, screened hypoglycaemic actions and degrees of toxicity of different biguanide compounds in 1956, and eventually chose metformin (dimethyl-biguanide hydrochloride) since it showed the greatest efficacy for the lowest toxicity. Their metformin preparation was branded "Glucophage." The first clinical trials using Glucophage were conducted in 1957. The clinical trials showed that the effectiveness of Glucophage increased with age and degree of obesity and the product was "surprisingly safe." By the end of 1965 in France, Aron Laboratories' factory produced about 12 tons per year. In 1982, Jan Aron sold 75% of his company to Lipha, who provided the necessary additional capital, technical tools and marketing capacity required. The Aron takeover by Lipha and research into the complexity of insulin resistance ushered in a new era for metformin. Metformin made its final breakthrough when clinical research studies established the link between hyperinsulinism (elevated insulin levels) and obesity. Lipha grew to become Groupe Lipha in 1987. In 1973, metformin was approved to be sold in the German market. For the US market, the story is very winding, among the two drugs from the biguanide class, metformin and phenformin, the drug phenformin was introduced in the US market first under the names D.B.I., Meltrol-50 capsules in 1970, but phenformin was associated with a life-threatening side

<sup>73</sup> The Value of Plants Used in Traditional Medicine for Drug Discovery, Daniel S. Fabricant and Norman R. Farnsworth, *Environ Health Perspect* 109(suppl 1):69-75 (2001).

<sup>74</sup> Medical Officer Safety Review, Epidemiology & Clinical Trials Branch, Metformin

<sup>75</sup> Metformin: The Long Path to Success

effect of lactic acidosis, and was withdrawn from the US market on November 15, 1978.<sup>76</sup> When this risk surfaced, phenformin was pulled from drugstore shelves worldwide. Metformin was eventually found to be 20 times less likely to cause lactic acidosis, but it was tainted by the history of its cousin. It was not cleared for use in type 2 diabetes in the US until 1994.<sup>77</sup> Lipha's application file to the FDA to market metformin in the US market is the "thickest" file ever presented in the US: 412 volumes of about 400 pages each – a total of 165,000 pages. The file contained a full thirty-five years of European toxicology and therapeutic experience including 2,000 publications and the summaries of 100 clinical studies. It cost Lipha over \$60 million. Lipha subsequently selected Bristol-Myers Squibb (BMS) as their American partner.<sup>78</sup> On March 3, 1995, BMS' Glucophage (active ingredient is metformin hydrochloride) received FDA approval (NDA 020357).

The approval history for Glucophage (NDA 020357) is summarized as follows:<sup>79</sup>

Action Date	Supplement Number	Approval Type
03/03/1995	000	Approval
09/13/1995	002	Package Change
04/30/1996	003	Control Supplement
07/26/1996	004	Manufacturing Change or Addition
06/06/1997	005	Manufacturing Change or Addition
11/06/1997	006	Labeling Revision
02/10/1998	008	Labeling Revision
05/15/1998	007	Manufacturing Change or Addition
07/02/1998	009	Manufacturing Change or Addition
10/22/1998	010	New or Modified Indication
11/05/1998	011	Formulation Revision
11/18/1998	013	Manufacturing Change or Addition
12/04/1998	014	Control Supplement
03/12/1999	016	Manufacturing Change or Addition
06/01/1999	015	Manufacturing Change or Addition
06/07/1999	018	Control Supplement
09/22/1999	017	Efficacy Supplement with Supporting Clinical Data
08/04/2000	021	Manufacturing Change or Addition

<sup>76</sup> Controlling Diabetes with Class, David Mendosa,

<sup>77</sup> [http://www.diabetesnet.com/diabetes\\_treatments/metformin.php](http://www.diabetesnet.com/diabetes_treatments/metformin.php)

<sup>78</sup> The Story of Glucophage

<sup>79</sup> Drugs@FDA

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12/15/2000	019	Patient Population Altered
02/08/2001	022	Labeling Revision
04/19/2001	020	Efficacy Supplement with Supporting Clinical Data
01/08/2002	024	Labeling Revision
03/19/2004	026	Labeling Revision
03/19/2004	027	Labeling Revision
11/01/2006	030	Labeling Revision

### **3.1.3 Initial success, new insights and continued research**

Success stories always ignite people's interests to further navigate the underlying mechanisms and look for new insights, which may lead to discovery of other new or improved drugs. The side effects of Metformin have also been a source of academic and commercial interests.

The drug metformin is an effective treatment for NIDDM (non-insulin dependent diabetes mellitus) which accounts for 90-95% of the total number of patients with diabetes mellitus. An estimated 12 million people in the United States have NIDDM. Patients with NIDDM nearly always have both insulin resistance and abnormal pancreatic beta-cell function. Metformin has increased glucose disposal in most studies using hyperinsulinemic-, euglycemic-, and hyperglycemic-clamp procedures in patients with NIDDM, with muscle implicated as its main site of action.

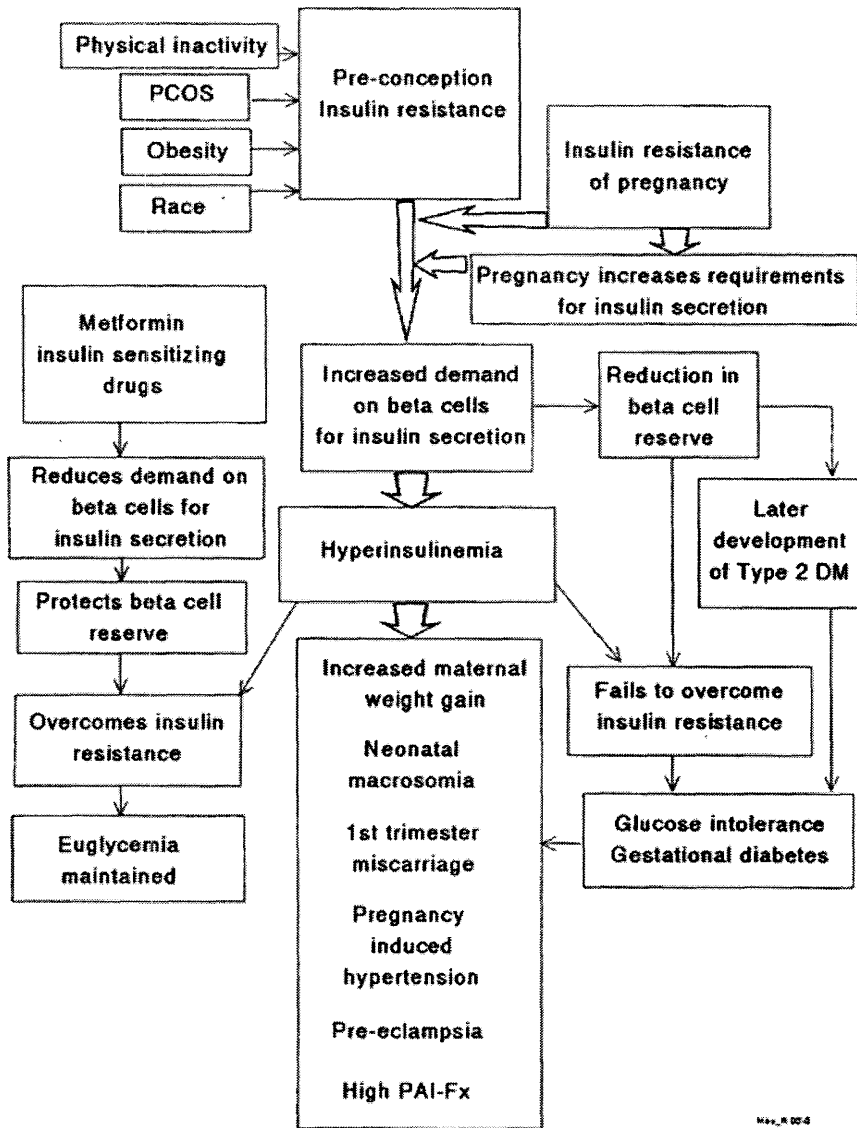


Figure 3.1.6 Dynamic mechanisms of NIDDM and of the drug metformin<sup>80</sup>

Table 3.1.1: Pharmacokinetic Aspects of Metformin<sup>81</sup>

VARIABLE	COMMENT
Bioavailability	50-60 percent; absorbed mainly from the small intestine; estimated absorption half-life, 0.9 to 2.6 hours
Plasma concentration	Maximal, 1 to 2 µg per milliliter (approximately 10 <sup>-5</sup> M) 1 to 2 hours after an oral dose of 500 to 1000 mg, negligible binding to plasma proteins

<sup>80</sup> [http://www.jewishhospitalcincinnati.com/cholesterol/images/current\\_diabetes\\_reports-GD\\_figure.gif](http://www.jewishhospitalcincinnati.com/cholesterol/images/current_diabetes_reports-GD_figure.gif)

<sup>81</sup> Metformin, Clifford J. Bailey, Ph.D., M.R.C.Path., and Robert C. Turner, M.D.

Plasma half-life	Estimated at 1.5 to 4.9 hours
Metabolism	Not measurably metabolized
Elimination	About 90 percent is eliminated in urine in 12 hours; multi-exponential pattern involving glomerular filtration and tubular secretion
Tissue distribution	Distributed most tissues at concentrations similar to those in peripheral plasma; higher concentrations in liver and kidney; highest concentrations in salivary glands and intestinal wall

Table 3.1.2: Mechanisms of the Antihyperglycemic Effect of Metformin<sup>82</sup>

MECHANISM	COMMENT
Suppression of hepatic glucose output	Contributes post-absorptive and postprandial plasma glucose -lowering effect
Increased insulin-mediated glucose disposal	Demonstrated by glucose -clamp procedures; due at least in part to a reduction in blood glucose concentrations
Increased intestinal glucose use	Shown only in studies in animals
Decreased fatty-acid oxidation	--

Table 3.1.3: Clinical Use of Metformin<sup>83</sup>

VARIABLE	COMMENT
Type of therapy	Monotherapy; combination therapy with a sulfonylurea
Indications	After failure of dietary therapy in NIDDM, especially in over weight patients; after failure to achieve acceptable glycemic control with sulfonylurea therapy
Tablet sizes	500 mg; 850 mg
Treatment schedule	Should be taken with meals; dose should be increased slowly; maximal dose, 2,550 mg daily
Contraindications	Renal and hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; use of intravenous radiographic contrast agents; pregnancy

<sup>82</sup> Metformin, Clifford J. Bailey, Ph.D., M.R.C.Path., and Robert C. Turner, M.D.

<sup>83</sup> Metformin, Clifford J. Bailey, Ph.D., M.R.C.Path., and Robert C. Turner, M.D.

Side effects	Gastrointestinal symptoms (diarrhea, nausea, abdominal discomfort, anorexia) and metallic taste, which improve with dose reduction; may impair absorption of vitamin B <sub>12</sub> and folic acid
Adverse reactions	A risk of lactic acidosis in patients with any of the listed contraindications; hypoglycemia if taken with a sulfonylurea or in the presence of alcohol abuse
Precautions	Medical history should be checked for contraindications; hemoglobin and plasma creatinine concentrations should be checked periodically; should be administered with caution in patients receiving concomitant cimetidine therapy (may reduce renal tubular secretion of metformin)

Table 3.1.4: Exclusion Criteria for the Use of Metformin<sup>84</sup>

Renal impairment: plasma creatinine values $\geq 1.5$ mg per deciliter (132 $\mu$ mol per liter) for men and $\geq 1.4$ mg per deciliter (124 $\mu$ mol per liter) for women
Cardiac or respiratory insufficiency that is likely to cause central hypoxia or reduced peripheral perfusion
History of lactic acidosis
Severe infection that could lead to decreased tissue perfusion
Liver disease, including alcoholic liver disease, as demonstrated by abnormal liver-function tests
Alcohol abuse with binge drinking sufficient to cause acute hepatic toxicity
Use of intravenous radiographic contrast agents

Metformin achieved great success in commercialization. In 1996 Glucophage became the largest selling oral anti-diabetic agent in the world. Today, around eight million patients in more than 100 countries worldwide benefit from Glucophage. Metformin stands the test of time. According to the literature published and patents filed in recent years, it is still an important research object and has value to be discovered. The following is a summary of literature search I performed on metformin from 1999 to 2006:

Year	ISI Record Counts	CNKI Record Counts
1999	187	12
2000	190	21
2001	219	22

<sup>84</sup> Metformin, Clifford J. Bailey, Ph.D., M.R.C.Path., and Robert C. Turner, M.D.

2002	323	35
2003	364	78
2004	390	101
2005	452	140
2006	508	165

(Source: Chinese literature source comes from CNKI (<http://www.edu.cnki.net>), and the worldwide literature source comes from ISI Web of Knowledge (<http://portal.isiknowledge.com>.)

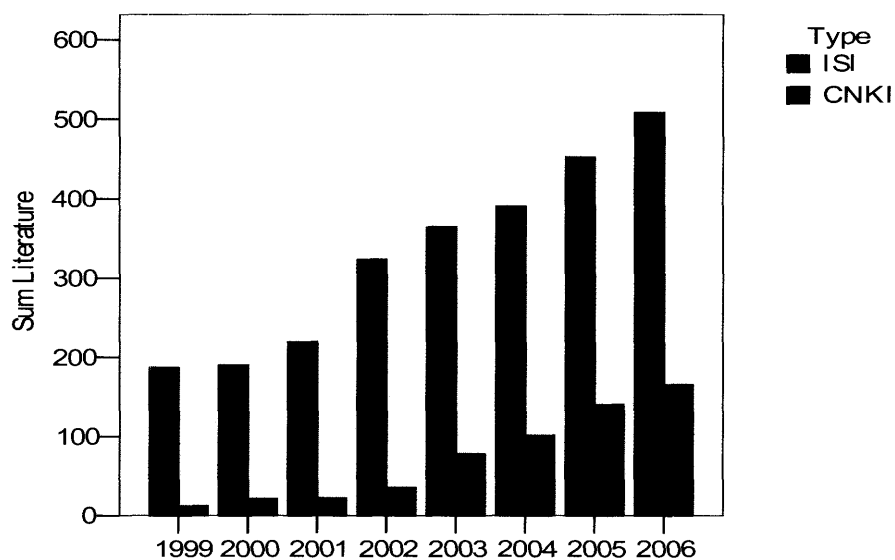


Figure 3.1.7 Search results of metformin from ISI and CNKI

The above chart is a graphic illustration of publications in English ISI database and Chinese CNKI database.

Below is a time series layout of patent applications related to metformin from different sources:

Year	SIPO	Derwent	LexisNexis
1999	4	6	5
2000	7	15	12
2001	5	19	22
2002	11	22	36
2003	7	34	55
2004	16	39	39
2005	11	51	41
2006	5	42	29

(Source: SIPO: the Chinese patent (<http://www.sipo.gov.cn>), and The Derwent innovations index (ISI Web of knowledge): US, WO, EP, DE patent (<http://isiknowledge.com>).

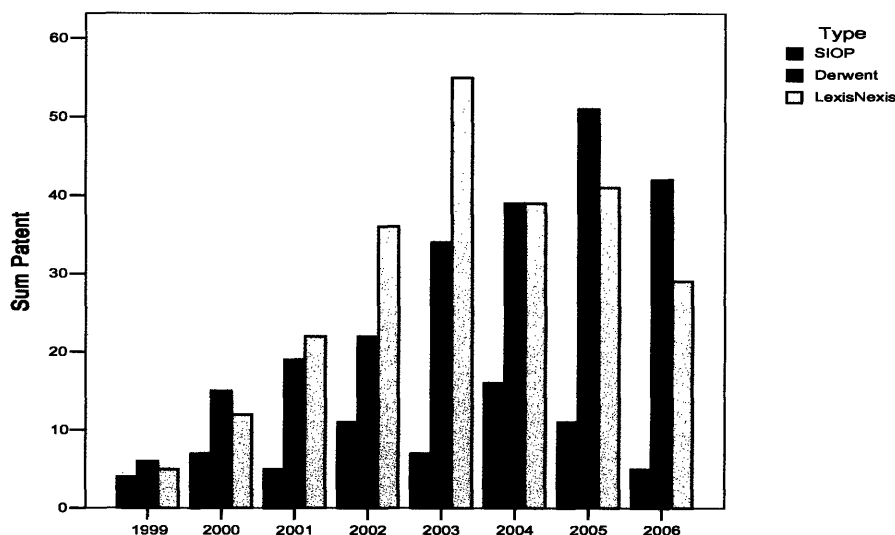


Figure 3.1.8 Summary of search results of metformin-related patents from SIPO, Derwent and LexisNexis

## 3.2 PGG Derived from *Lagerstroemia Speciosa* (Banaba)

### 3.2.1 Introduction

The reasons of my selecting this case study are in two folds. First, the principal investigator, Professor Xiaozhuo Chen, is a long-term personal acquaintance who received education both in China (Tsinghua University) and the US (University of Ohio) and has intimate knowledge about Chinese herbal medicines and modern chemical technology and molecular biology. A person of this cross-border background, I believe, is particularly suited to capitalize on the accumulated knowledge in herbal medicine and capture value through converting the herbal medicines into food supplements, nutraceutical medicines (herbal formula) or ethical drugs. Secondly, Professor Chen and his colleagues overturned a well established and widely published understanding that corosolic acid, rather than tannic acid PGG as he discovered, is the most potent therapeutic component in the herb *banaba*. This case illustrates that the current scientific understanding of herbal medicines, even for the ones that have been intensively researched over many decades, is far from complete, a statement that supports the general hypothesis in this thesis that there is substantial untapped value vested in the Chinese herbal medicines.

The source of this case study is from both the published articles and private communications with the innovator and leading researcher of these herbal compounds, Professor Xiaozhuo Chen, who has given me express permission to disclose the technical aspects of the innovation and his unpublished data. The technical innovations in this thesis have been properly filed for patent protection.

*Lagerstroemia speciosa* (*banaba*) is a type of tree, more commonly known as *banaba*, which grows in Thailand and most of Southeast Asia like the Philippines and Malaysia.



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*Banaba* is a deciduous, tropical, flowering tree that can grow to 18 m in height, with a 9 to 12 m spread. The large, oblong, dark-green, leathery leaves measure 5 to 10 cm wide by 12 to 30 cm long. The leaves turn an orange-red color in the fall. The flowers are pink to purple in color, giving way to oval, nut-like fruits. The bark of the tree is thin, mottled, and peeling.<sup>85</sup>



Figure 3.2.1 Pictures of *banaba*.<sup>86</sup>

*Banaba* is a popular medicine plant in the Philippines, consumed in various forms by Filipinos for treatment of diabetes and kidney related diseases. For example, banaba tea has been a traditional health drink in the Philippines since ancient times. It was found to have therapeutic effects on various ailments such as diabetes, kidney and other urinary problems. In the countryside, the leaf decoctions were also used for its diuretic and purgative action and root parts for stomach ailments.

### 3.2.2 Research history on banaba

Gradually, the popularity of this herbal medicine began to attract scientists worldwide. After doing numerous *in vitro* and *in vivo* studies that consistently confirmed the anti-diabetic activity of *banaba*, scientists have identified different components of *banaba* to be responsible for its activity. One reason may be that *banaba* extracts prepared from *banaba* leaves from different sources may have different chemical compositions, leading to different experimental results. In 1940, Garcia F. researched the hypoglycemic effect of decoction of *lagerstroemia speciosa* leaf administered orally (from the J of Philippine Medical Association)<sup>87</sup>. In 1993, researchers in Japan (Murakami et al) isolated corosolic acid from the methanol extract of *lagerstroemia speciosa* leaf.<sup>88</sup> Their research found that corosolic acid has a significant glucose transport-stimulating activity at a concentration of 1 $\mu$ M. Corosolic acid activates the transport of glucose across cell membranes, resulting in blood sugar reductions. Corosolic

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<sup>85</sup> [www.drugs.com](http://www.drugs.com)

<sup>86</sup> <http://www.stuartxchange.org/Banaba.html>

<sup>87</sup> On the hypoglycemic effect of decoction of *Lagerstroemia speciosa* leaves (banaba) administered orally, Garcia F. (1940); J Phil Med Assoc 20:: 395–402.

<sup>88</sup> Screening of plant constituents for effect on glucose transport activity in Ehrlich Ascites tumor cells, Murakami C, Myoga K, Kasai R, Ohtani K, Kurokawa T, Ishibashi S, et al. (1993); Chem Pharm Bull 41::12 2129–31.

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acid (2 $\alpha$ -hydroxyursolic acid) was the first identified as the effective compound of *banaba* extract. Corosolic acid also shows a memory effect of blood glucose lowering even after the treatment is stopped.

In 1996, Kakuda et al<sup>89</sup> studied the hypoglycemic effect of *lagerstroemia speciosa* in animals and *in vitro* studies. They found that when genetically diabetic mice (Type II) were fed a diet containing hot water extract from *lagerstroemia speciosa* for 5 weeks, their elevated blood glucose was significantly suppressed. In 1999, Suzuki et al<sup>90</sup> found that when obese diabetic rats were fed a diet containing extract from *lagerstroemia speciosa* for 12 weeks, their blood glucose levels were not suppressed, but their body weights were lowered significantly. In 2001, Liu et al<sup>91</sup> found that an extract of *lagerstroemia speciosa* leaf has insulin-like glucose uptake - stimulatory and adipocyte differentiation - inhibitory activities in 3T3-L1 cells. The plant extract may be useful for prevention and treatment of hyperglycemia and obesity in type II diabetics. In 2002, William V. Judy et al studied the antidiabetic activity of a standardized extract (from *lagerstroemia speciosa* leaf in a dose-dependence study.<sup>92</sup>) In 2004, a group of researchers found that glucose transporter 4 (GLUT4) translocation from the intracellular microsomal membrane to the plasma membrane was significantly increased in the muscle cells of mice treated orally with corosolic acid ( $p < 0.05$ ).<sup>93</sup> This result is both interesting and puzzling. The GLUT4 membrane translocation mechanism initiated by corosolic acid as described must be independent of the insulin receptor mediated signaling pathway since corosolic acid does not use this pathway for its activity. In 2006, these researchers found that corosolic acid significantly reduces blood glucose levels and plasma insulin levels in KK-Ay diabetic mice.<sup>94</sup> The mean blood glucose levels of mice at various time intervals after a single oral administration of corosolic acid 2 mg/kg lowered blood glucose levels 4 hours after administration ( $p < 0.05$ ). Corosolic acid 10 mg/kg-treated mice showed a significant decrease in plasma glucose levels 4 and 7 h compared with the control values ( $p < 0.01$ ).

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<sup>89</sup> Hypoglycemic effect of extracts from *Lagerstroemia speciosa* L. leaves in genetically diabetic KK-Ay mice, Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H, Kuroyanagi M. ( 1996;), *Biosci Biotechnol Biochem* 60::2 204–8.

<sup>90</sup> Antiobesity activity of extracts from *Lagerstroemia speciosa* L. leaves on female KK-Ay mice, Suzuki Y, Unno T, Ushitani M, Hayashi K, Kakuda T. ( 1999;), *J Nutr Sci Vitaminol* 45::6 791–5 (Tokyo).

<sup>91</sup> An extract of *Lagerstroemia speciosa* L. has insulin-like glucose uptake-stimulatory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells, Liu F, Kim J, Li Y, Liu X, Li J, Chen X. ( 2001;), *J Nutr* 131::9 2242–7

<sup>92</sup> <http://www.acu-pro.com/diabet1.htm.gb>

<sup>93</sup> Corosolic acid induces GLUT4 translocation in genetically type 2 diabetic mice, Miura T, Itoh Y, Kaneko T, Ueda N, Ishida T, Fukushima M, et al. ( 2004;), *Biol Pharm Bull* 27::7 1103–5.

<sup>94</sup> Antidiabetic effects of corosolic acid in KK-Ay diabetic mice, Miura T, Ueda N, Yamada K, Fukushima M, Ishida T, Kaneko T, et al. ( 2006;), *Biol Pharm Bull* 29::3 585–7.

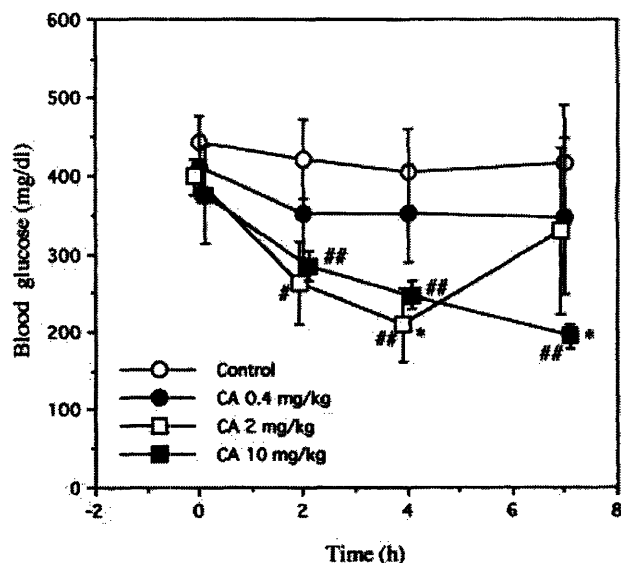


Figure 3.2.2 Effects of a Single Dose of CA on Blood Glucose in KK-Ay Mice<sup>95</sup>

In a different approach, using 3T3-L1 adipocytes as a cell model and a glucose uptake assay as the functional screening method, Chen (with whom I had continuous communications) et al showed that the *banaba* water extract exhibited an insulin-like glucose transport inducing activity. Penta-o-galloyl-glucopyranose (PGG) was identified as the most potent gallotannin. A comparison of published data with results obtained for PGG indicates that PGG has a significantly higher glucose transport stimulatory activity than lagerstroemin. Chen et al have also shown that PGG exhibits anti-adipogenic properties in addition to stimulating the glucose uptake in adipocytes. The combination of glucose uptake and anti-adipogenesis activity is not found in the current insulin mimetic drugs and may indicate a great therapeutic potential of PGG.<sup>96</sup>

### 3.2.3 Development and commercialization of PGG

#### Turning point of scientific research - identification of PGG

To confirm the effect of corosolic acids, the first step was to isolate them from other components in the extract, such as tannins, which comprise up to 40% of the extract material. But a surprise result emerged. When tannins were removed from the material, glucose transport stimulatory couldn't be found. Then, it was concluded that the glucose transport activity of the *banaba* extract was caused by the tannin component, rather than corosolic acid. This was indeed a turning point of scientific research.

<sup>95</sup> Antidiabetic effects of corosolic acid in KK-Ay diabetic mice, Miura T, Ueda N, Yamada K, Fukushima M, Ishida T, Kaneko T, et al. (2006); Biol Pharm Bull 29::3 585-7.

<sup>96</sup> Antidiabetes and Anti-obesity Activity of Lagerstroemia speciosa, Chen et al, eCAM Advance Access published online on March 14, 2007

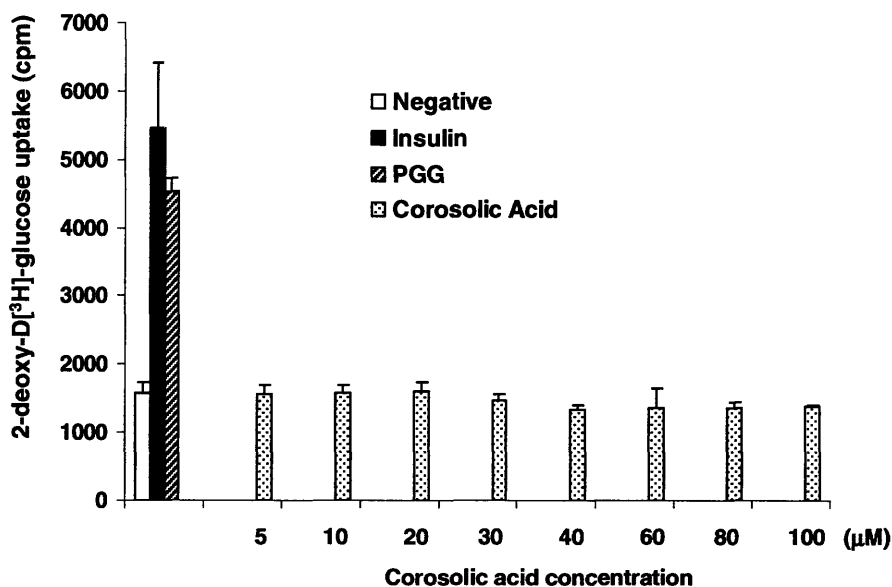


Figure 3.2.3: Absence of glucose transport stimulatory activity of corosolic acid in adipocytes.<sup>97</sup>

Although tannins were identified to be responsible for the glucose transport stimulatory activity of *banaba* extract, they comprise a wide range of polyphenolic compounds. Which are the real active components of the extract? Tannic acid, which is also a constituent of red wine and shows the effects on various health beneficial activities, provides a further research direction for researchers. The main components of tannic acid are gallotannins, a sub-class of the tannins usually consisting of a glucose core connected to many galloyl groups via ester bonds.<sup>98</sup> Then, it was confirmed that tannic acid was much more potent and effective. So the research shifted to focus on tannic acid.

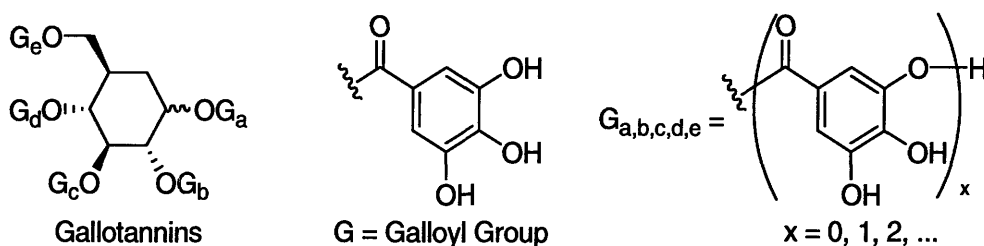


Figure 3.2.4 Chemical structures of gallotannins.<sup>99</sup>

Further research by Chen et al separated components of tannic acid by HPLC, and identified penta-o-galloyl-glucopyranose (PGG) as the most potent component of gallotannins with a glucose uptake assay in 3T3-L1 adipocytes. PGG exist in two anomeric

<sup>97</sup> Antidiabetes and Anti-obesity Activity of *Lagerstroemia speciosa*, Chen et al, eCAM Advance Access published online on March 14, 2007

<sup>98</sup> Antidiabetes and Anti-obesity Activity of *Lagerstroemia speciosa*, Chen et al, eCAM Advance Access published online on March 14, 2007

<sup>99</sup> Antidiabetes and Anti-obesity Activity of *Lagerstroemia speciosa*, Chen et al, eCAM Advance Access published online on March 14, 2007

forms. The  $\alpha$ -anomer was found to be slightly more active than the  $\beta$ -form in its glucose transport stimulatory activity, while  $\beta$ -PGG is much more prevalent than  $\alpha$ -PGG.<sup>100</sup>

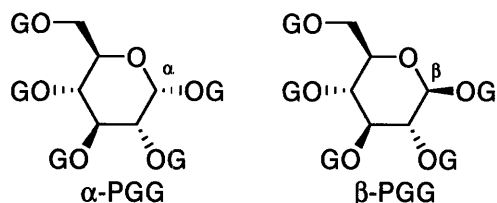


Figure 3.2.5 PGG exist in two anomeric forms.<sup>101</sup>

After that, comparison between lagerstroemin and PGG was made. Lagerstroemin was shown to exhibit glucose transport stimulation at  $40\mu\text{M}$  with an  $\text{EC}_{50}$  of  $80\mu\text{M}$ . In comparison,  $\alpha$ -PGG and  $\beta$ -PGG exhibit activity at a concentration as low as  $10\mu\text{M}$  with  $\text{EC}_{50}$  of  $17\mu\text{M}$  and  $18\mu\text{M}$ , respectively. In other words,  $\alpha$ -PGG and  $\beta$ -PGG are about five times more potent than lagerstroemin in stimulating glucose transport. Chen's study also showed that its glucose transport inducing activity is about 54% of that of insulin (22). In comparison,  $\alpha$ -PGG and  $\beta$ -PGG showed about 60-70 % of insulin's glucose transport inducing activity. Thus,  $\alpha$ -PGG and  $\beta$ -PGG are at least 30% more effective than lagerstroemin.<sup>102</sup>

When PGG was identified, more information about it was obtained and analyzed. It was found that PGG is widely distributed in many other different plants of different genera, including *euphorbia*, *acer* (maple), *quercus* (oak), *betula* (birch), and *rhodiola*. PGG was found in different parts of woody medicinal plants including the leaves, roots or rhizomes, bark, fruits and flowers. Many of these plants have been used clinically to treat diseases. Some of the PGG-containing plants are edible, either for medical purposes or for human nutrition, suggesting that PGG is relatively non-toxic to human.

Other researches studying the multiple health beneficial properties of PGG found that it showed anti-cancer, radical scavenging, anti-virus, anti-diabetes and anti-obesity, as well as neuronal cell protection activities in cultured cells, animals, and even in humans.

The development of new drugs based on the optimization of small molecular weight gallotannins, in general, and PGG in particular seems to have a promising outlook. But PGG has many isomers. Although the molecular weights of all the isomers of PGG are the same, the chemical properties, such as susceptibility to hydrolysis and chromatographic behavior, and the biochemical properties, such as the ability to precipitate protein, are structure-dependent.<sup>103</sup> On the other hand, PGG interacts with different proteins with relatively high affinity to exhibit different bioactivities. Thus, PGG

<sup>100</sup> Distribution, Bioactivities and Therapeutical Potentials of Natural Compound Pentagalloylglucopyranose, by Yulin Ren, Xiaozhuo Chen, Current Bioactive Compounds, Vol. 3, No. 2. (June 2007), pp. 81-89.

<sup>101</sup> Antidiabetes and Anti-obesity Activity of Lagerstroemia speciosa, Chen et al, eCAM Advance Access published online on March 14, 2007

<sup>102</sup> Antidiabetes and Anti-obesity Activity of Lagerstroemia speciosa, Chen et al, eCAM Advance Access published online on March 14, 2007

<sup>103</sup> Tannin handbook, www.users.muohio.edu/

itself has relatively low selectivity for protein targets. This weakness suggests that PGG has to be chemically modified for each specific activity to enhance the activity in study and reduce other “interfering” activities. This may also have significant implications on their potential toxicity properties. Chen’s study on modifications and enhancements of PGG indicates the possibility. The compounds with selected activity can be chemically generated. These characteristics indicate that PGG is a lead molecule in the biomedical and biological research of gallotannins and in their development into new therapeutics.

### Commercialization

As PGG was found to have great medical potential value, a series of patents filed and a corporation was established to realize the potential medicinal value, through the control of patents and licenses related to research findings about *banaba* extract and further developed products. Although *banaba* extract and PGG have multiple beneficial effects, this firm focuses on their value for diabetes and obesity therapies.

The World Health Organization (WHO) estimates over 180 million people worldwide has diabetes. This number is likely to double to 360 million by 2030.<sup>104</sup> The company plans to offer a dietary supplement solution derived from *banaba* extract, for example, *banaba* leaf extracts from a Philippine forest. Then a natural agent name C-5, closely related to the effective agent found in *banaba* and later a chemically purified to crystals for oral supplement.

*Banaba* extract produced by this method has similar glucose uptake profiles to insulin. It even has an advantage over insulin because insulin cannot be orally administered while *banaba* extract and its derivatives can.

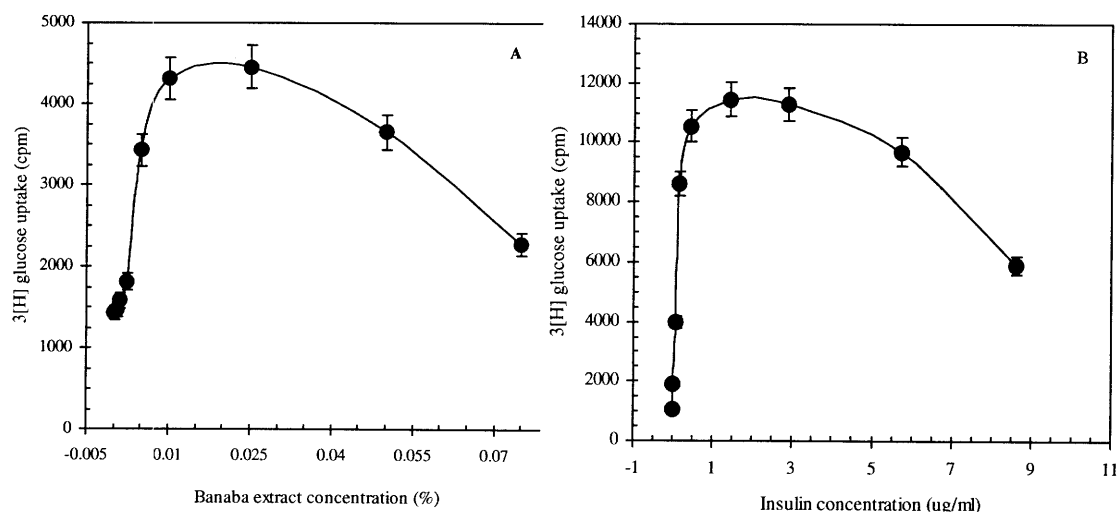


Figure 3.2.6 *banaba* extract and insulin: Similar Glucose Uptake Profiles<sup>105</sup>

<sup>104</sup> Thesis author’s private communication with Xiaozhuo Chen.

<sup>105</sup> Thesis author’s private communication with Xiaozhuo Chen.

The chemical product C-5 also shows therapy effects on diabetic mice and obese mice

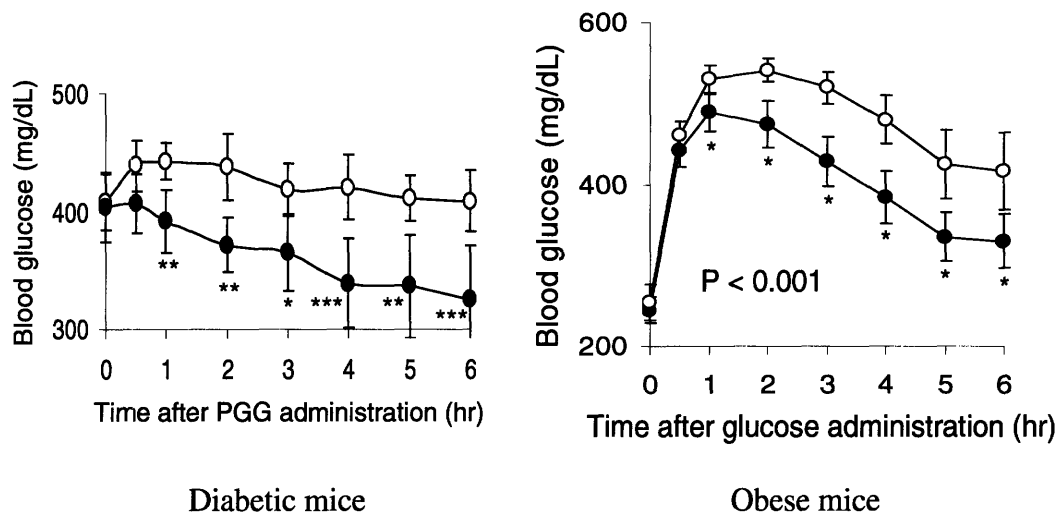


Figure 3.2.7 C-5 single dose oral administration reduces blood glucose.<sup>106</sup>

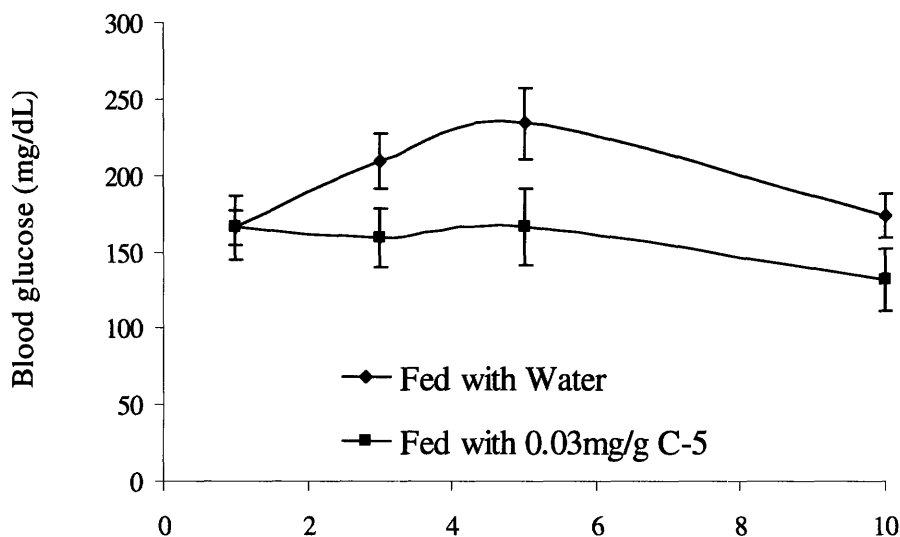


Figure 3.2.8 Feeding C-5 supplement maintains steady glucose levels in genetically obese mice.<sup>107</sup>

C-5 keeps pre-fat cells in their existing state, but more importantly is that in the presence of insulin C-5 still prevents fat formation.

<sup>106</sup> Thesis author's private communication with Xiaozhuo Chen.

<sup>107</sup> Thesis author's private communication with Xiaozhuo Chen.

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## Inspiration on drug development from Chinese medical herbs

The development of PGG provides a good example of how to utilize the experience about medicinal uses of plant to derive molecule products which has the potential to develop into official drugs. It is a feasible direction for modern development of drugs from past experiences of medical plants. While Chinese medicine has accumulated experience about many effective uses of herbs in medical practice, it has great potential value to be discovered and realized.

Note that, corosolic acid, rather than PGG, has been identified and widely believed as the effective component for many years. It requires rigorous and persistent research efforts to challenge the existing discoveries and assumptions, and it may be a long and winding road before the herb-derived molecules could pass through the FDA regulatory hurdle. The significance of this case study, however, is the potential feasibility to commercialize and capture value on earlier raw products such as *banaba* tannic acid extracts and modified PGG C-5, not as small molecule drugs, but food supplement and herbal medicines.

## 3.3 Grapes, Red Wine and Resveratrol

### 3.3.1 Introduction

The reasons of my selecting this case study are that, firstly, although resveratrol was first isolated from *grape*, the Chinese plant *polygonium cuspidatum (hu zhang)* has shown to have 10 times more concentrated resveratrol content; secondly, the published articles in Chinese journals have proliferated so fast that many clinical trials have already been conducted to demonstrate the therapeutic benefits of resveratrol; and thirdly, a Boston-based company co-founded by Dr. Sinclair at Harvard Medical School, Sirtris Pharmaceuticals, Inc., has swiftly captured the commercial opportunity to convert resveratrol into an ethical anti-diabetic drug and successfully raised over \$100 million from venture capital and IPO. This is another ongoing case to demonstrate the vast potential in herbal plants that can be captured once the accumulative empirical knowledge is coupled with the modern molecular sciences.

The national diet of France includes a lot of high-fat, high-cholesterol foods, such as butter, cream, meat, and so on, which is suspected to be bad for the heart. Yet the rate of coronary heart disease mortality in France is lower than those observed in other industrialized countries with a similar risk factor profile. This well-known fact is called French Paradox. For hundreds of years, this phenomenon has been studied by many researchers and it was suggested that the French are somehow protected from cardiovascular disease because they drink a lot red wine.

As early as the 1920's Dr. Johanna Brandt wrote a book proclaiming that *grapes* cured her of cancer. Since then it has been known that there are several beneficial substances in *grapes* (wine as well) that assist in lowering cholesterol, reduce the risk of heart disease and have antioxidant abilities. Further researches focused on the ingredients of red wine, which led to the discovery of resveratrol. This may be at least partly responsible for the beneficial effect of red wine. Resveratrol, also known as 3,4',5 trihydroxystilbene and 3,4',5-stilbenetriol, is a compound found largely in the skins of red grapes. It is a naturally



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occurring phytoalexin produced by some plants in response to injury or fungal infection. Chemical formula of resveratrol is  $C_{14}H_{12}O_3$  and the molecular weight is 228.25 daltons.

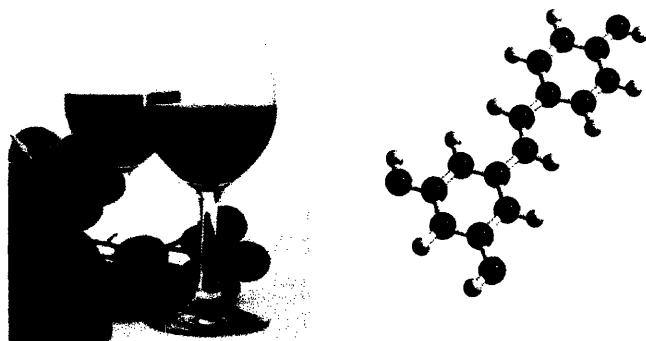


Figure 3.3.1 Grape, red wine and resveratrol<sup>108</sup>

Physical-chemical properties of resveratrol are as following:<sup>109</sup>

Property	Information
Physical State	Solid, powder
Color	Off white
Melting Point (°C)	253-255
Octanol-Water Partition Coefficient (LogP)	3.139±0.343
pKa (of the most acidic H-donor)	9.14±0.20
Solubility in Water (mol/L)	<0.01

Resveratrol is abundant in *vitis vinifera*, *labrusca*, and *muscadine grapes* and exist at a very high concentration (10 times more concentrated than in grape skin) in the dried roots and stems of the plant *polygonium cuspidatum* (also known as “*hu zhang*” in Chinese, used in traditional Chinese and Japanese medicine as a circulatory tonic). Other sources of resveratrol include *peanuts* and *mulberries*.

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<sup>108</sup> <http://www.safealternativemedicine.co.uk/ReservatrolHealthGrapes.html> & <http://www.3dchem.com/molecules.asp?ID=277>

<sup>109</sup> trans-Resveratrol [501-36-0]: Review of Toxicological Literature, Prepared for Scott Masten, Ph.D., National Institute of Environmental Health Sciences, by Karen E. Haneke, M.S., Integrated Laboratory Systems, March 2002

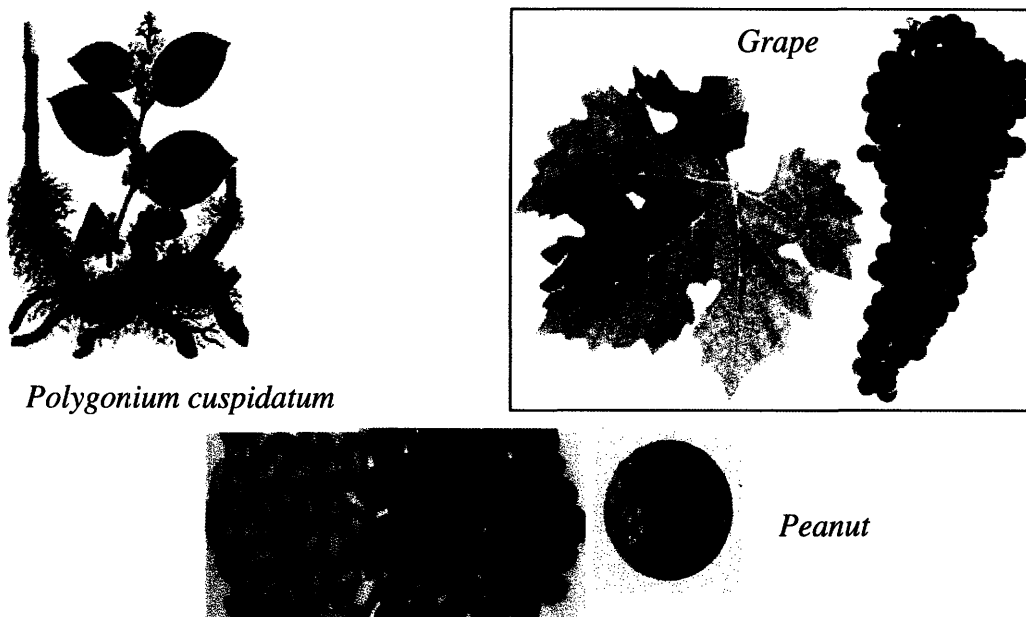


Figure 3.3.2 Some plants that contain resveratrol.<sup>110</sup>

Resveratrol is the parent molecule of a family of polymers called viniferins. Cis- and trans-resveratrol occur naturally as do their glucosides. The stereoisomer of resveratrol found in grapes and peanuts is the trans-form. Both cis- and trans-resveratrol are found in *Polygonium cuspidatum*.

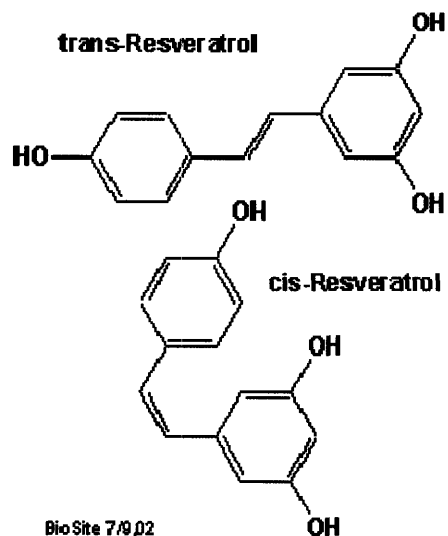


Figure 3.3.3 Cis- and trans-resveratrol.<sup>111</sup>

<sup>110</sup> Pictures are searched from internet.

<sup>111</sup> <http://www.longevinex.com/article.asp?story=Imitations>

### 3.3.2 Research about resveratrol's beneficial effects

Various test demonstrated that resveratrol may help prevent cardiovascular disease and cancer. Additionally, a growing number of published reports have appeared both on Chinese and English-language journals on resveratrol's therapeutic effects on cancer and various inflammatory diseases. Recent researches of Dr. David Sinclair at Harvard Medical School and other researchers suggested that resveratrol may even have life-extending effects.

#### Life-extending effects

Long time studies on longevity confirm that caloric restriction can extend lifespan in numerous species. A calorically restricted diet includes all necessary nutrients but has some 30 percent fewer calories than usual. The diet extends the life span of rodents by 30 to 50 percent, but the prospect of a near-starvation diet is obviously a difficult idea to market to human populations. Dr. Sinclair and his chief co-author, Dr. Konrad T. Howitz, of Biomol Research Laboratories in Plymouth Meeting, Pa., claims they have succeeded in finding a class of drugs that mimic caloric restriction in two standard laboratory organisms - yeast and fruit flies. It's resveratrol. Other studies show life-extending effects of resveratrol on other species.







PROGRESSION OF SUCCESSFUL LONGEVITY EXPERIMENTS IN INCREASINGLY HIGHER LIFE FORMS USING RESVERATROL					
2003	2004	2004	2006	2006?	1992
					
<b>Yeast Cells</b> <i>Saccharomyces cerevisiae</i>	<b>Fruit fly</b> <i>Drosophila melanogaster</i>	<b>Roundworm</b> <i>Caenorhabditis elegans</i>	<b>Killifish</b> (vertebrate) <i>Nothobranchius furzeri</i>	<b>Rodents</b> Study in final stages	<b>Humans</b> Red wine
David Sinclair, colleagues, Harvard	S L Helfand, colleagues, Univ. Connecticut	David Sinclair, colleagues, Harvard	L Domenici, colleagues, Italy	David Sinclair, Harvard	Serge Renaud, Michel de Lorgeril, France
Nature 425:191-6, 2003	Proc Natl Acad Sci 101:12980-5, 2004	Nature 430:686, 2004	Current Biology 16: 296-300, 2006	—	Novartis Fnd Sym 216: 208, 1998
Increased Lifespan <b>60%</b>	Increased Lifespan <b>29%</b>	Increased Lifespan <b>15%</b>	Increased Lifespan <b>27-59%</b>	Increased Lifespan	Increased Lifespan <b>?</b>

Figure 3.3.4 Life-extending effects of resveratrol on some species.<sup>112</sup>

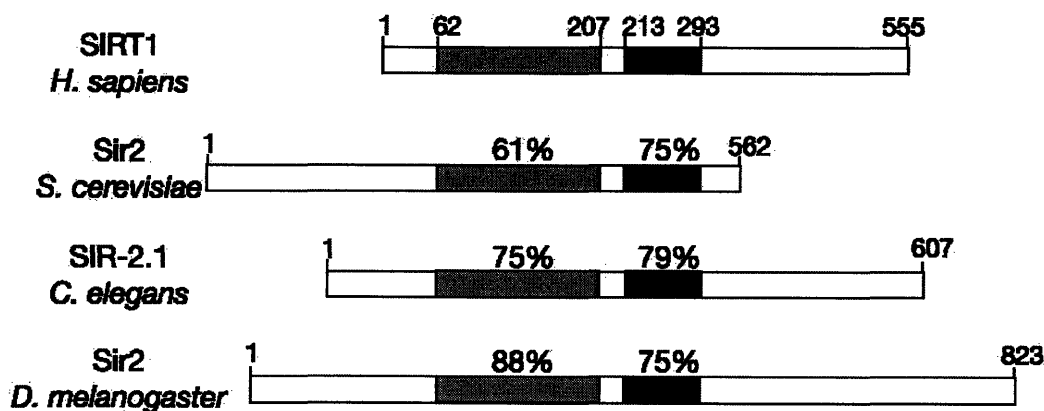
Dr. Sinclair finds a survival gene that can be "switched on" to become a longevity gene. The gene increases the production of an enzyme that prolongs the time a living cell has to

<sup>112</sup> [http://www.longevinex.com/images/resveratrol\\_experiments\\_full.jpg](http://www.longevinex.com/images/resveratrol_experiments_full.jpg)

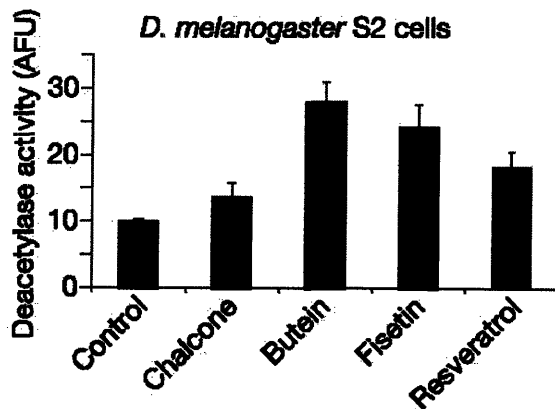
repair its DNA genetic material. This enzyme is normally produced when the survival of living cells is threatened by starvation, exposure to germs or bombardment by solar ultraviolet radiation. No longer would humans have to starve themselves to prolong life. Scientists involved in the research say that human life spans could be extended by 30 percent if humans respond to the chemicals in the same way as rats and mice do to low calories. Even someone who started at age 50 to take one of the new chemicals could expect to gain an extra 10 years of life, said Dr. Leonard Guarente of the Massachusetts Institute of Technology, one of the pioneers of the new research.

Sir2-like proteins (sirtuins) are a family of NAD<sup>+</sup>-dependent deacetylases conserved from *Escherichia coli* to humans that play important roles in gene silencing, DNA repair, rDNA recombination and ageing in model organisms. A caloric restricted diet has life-extending effects in diverse species, suggesting that there is a conserved mechanism for nutrient regulation of ageing. In budding yeast, extra copies of SIR2 extend lifespan by 30%, apparently by mimicking caloric restriction.<sup>113</sup> The following figures show the effect of polyphenolic STACs on sirtuins:

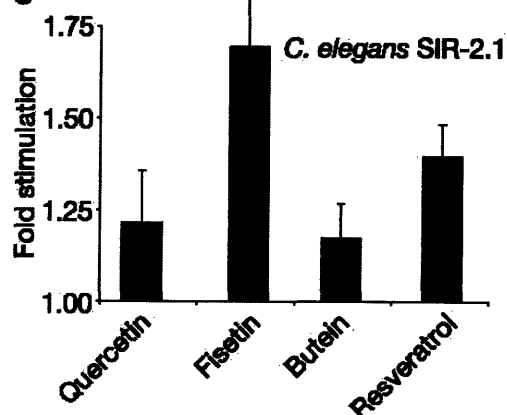
**a**



**b**



**c**



<sup>113</sup> Sirtuin activators mimic caloric restriction and delay ageing in metazoans, Jason G. Wood, Blanka Rogina, Siva Lavu, Konrad Howitz, Stephen L. Helfand, Marc Tatar & David Sinclair, *Nature*, August, 2004, VOL 430, 5

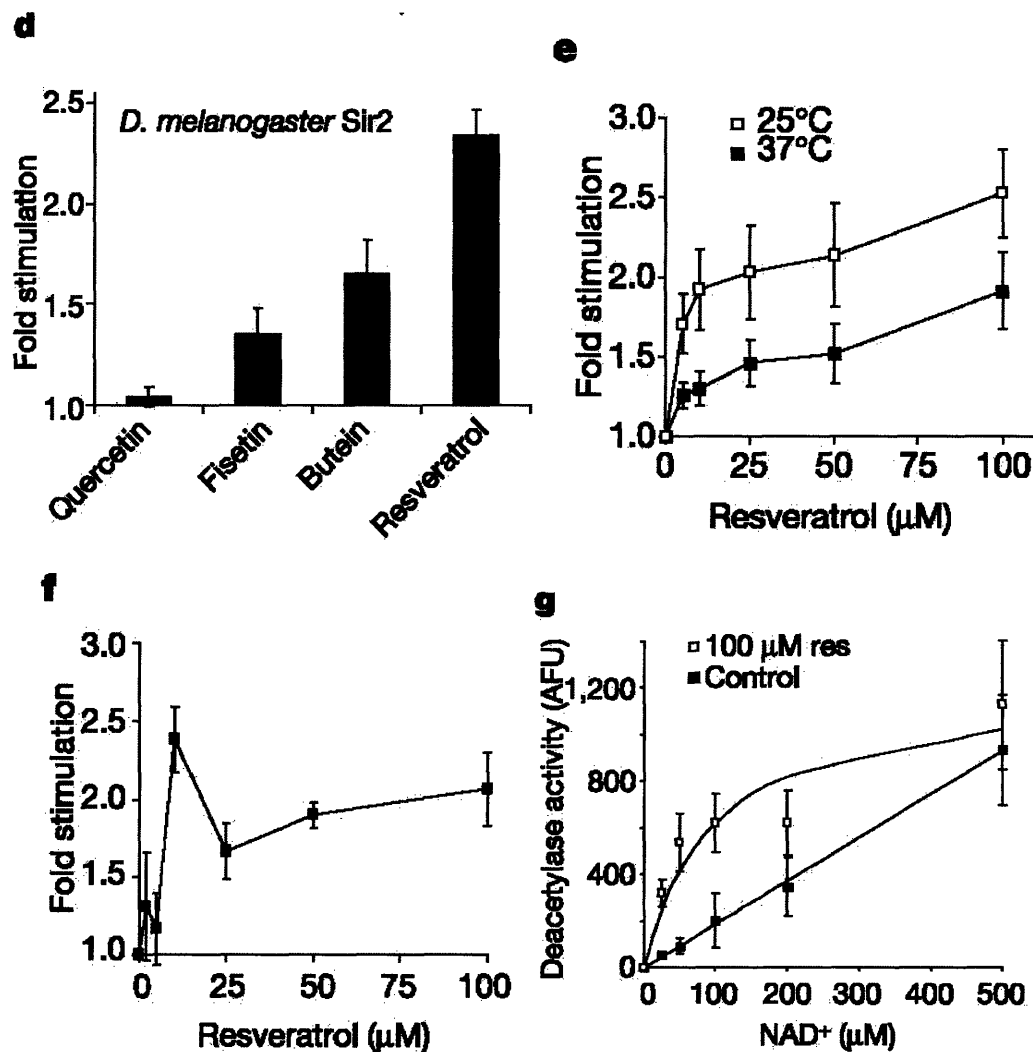


Figure 3.3.5 Effect of polyphenolic STACs on sirtuins (a-g).<sup>114</sup>

Recently, 18 small molecules from plants were identified that can increase human SIRT1 activity *in vitro* and *in vivo*, including resveratrol, butein, and piceatannol. The compound with the greatest stimulatory activity was resveratrol.<sup>115</sup> Although laboratory tests have clearly demonstrated that resveratrol may help prevent cardiovascular disease and cancer, there are several reasons why recommending a population-wide usage would be premature. First of all, little is known about the absorption and clearance of resveratrol, the identities of its metabolic products, or its effects on the liver. A study in rats showed that resveratrol is absorbed in the gut and has a high affinity for the heart and liver. Secondly, the research on resveratrol has focused on its short-term effects and has been dominated by *in vitro* studies on non-human models. Thirdly, its role as a potentiator of

<sup>114</sup> Sirtuin activators mimic caloric restriction and delay ageing in metazoans, Jason G. Wood, Blanka Rogina, Siva Lavu, Konrad Howitz, Stephen L. Helfand, Marc Tatar & David Sinclair, *Nature*, August, 2004, VOL 430, 5

<sup>115</sup> Toward a unified theory of caloric restriction and longevity regulation, David A. Sinclair, Available online 11 May 2005, [www.sciencedirect.com](http://www.sciencedirect.com)

breast carcinomas may significantly limit its use, even for its "proven" benefits. Finally, its main dietary source is red wine. Not only is its concentration in wine extremely variable, but recommending increased consumption of red wine to boost resveratrol intake could certainly do more harm than good. In spite of any beneficial aspects, red wine and other alcoholic beverages pose health risks that include liver damage and physical addiction.

### 3.3.3 Anti-diabetic drug development

As resveratrol has demonstrated so many health beneficial effects, there is great market potential for related products. It is estimated that there are 200 million people around world using resveratrol related products, with an annual increase of 50 million. The market for resveratrol related products will increase quickly in recent years. When I did a patent search, 185 patents are found in law@LexisNexis database, using resveratrol as the keyword. As shown on the following pie chart, more than half are related to applications.

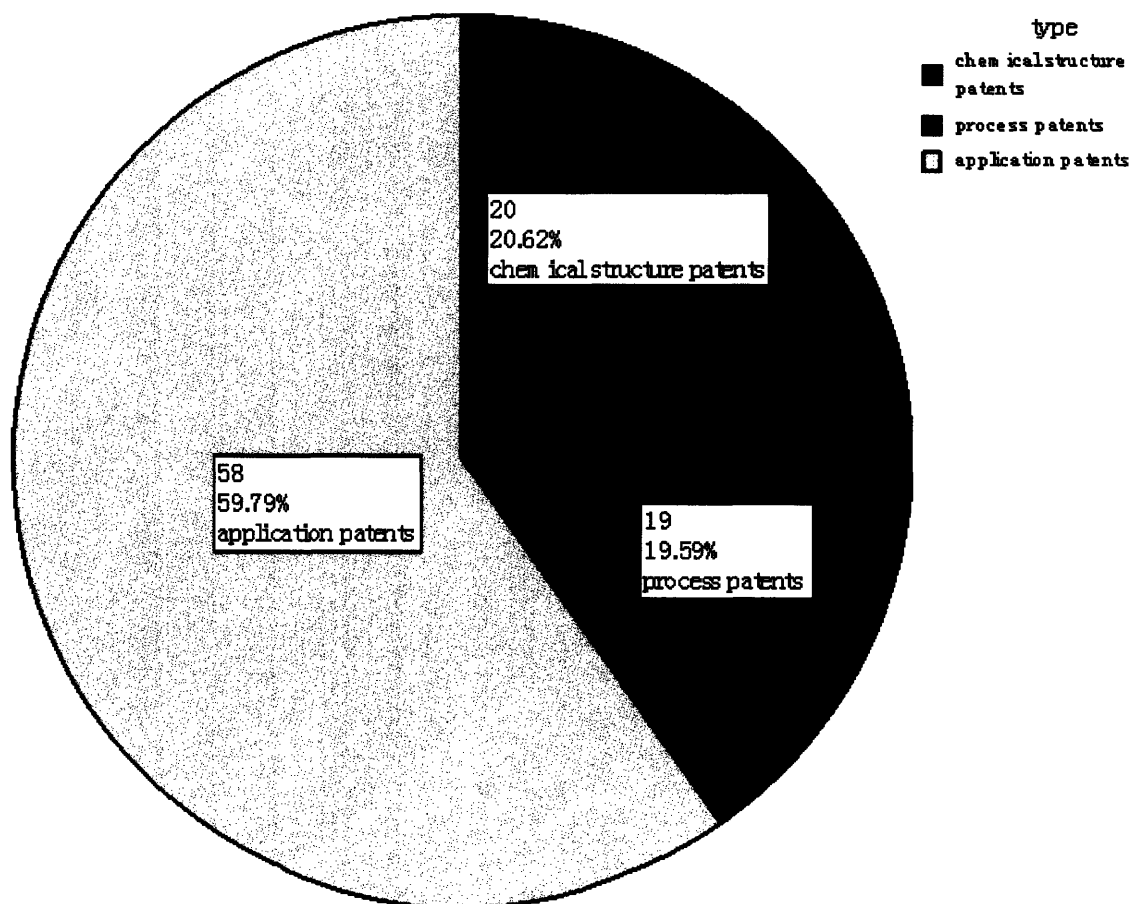


Figure 3.3.6 Summary of Resveratrol-related patent search results from LexisNexis

Several methods have been used to extract resveratrol and related compounds from wine and to isolate the trans- and cis- isomers of resveratrol, including high-performance liquid chromatography (HPLC), liquid chromatography (LC), gas chromatography (GC), gas

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chromatography-mass spectrometry (GC-MS), and capillary electrophoresis (CE). Most of the resveratrol-containing supplements which are marketed in the US contain extracts of the root of *polygonum cuspidatum*.<sup>116</sup> High-speed counter-current chromatography—with the solvents chloroform, methanol, and water—was found to be an effective method for separating resveratrol from *polygonum cuspidatum*, yielding greater than 98% purity (as measured by HPLC). It is very interesting to see that most of the technologies used to extract resveratrol are the same as the fingerprint technologies as I described in this thesis.

Sirtris Pharmaceuticals, Inc., of which Dr. Sinclair is a cofounder, started clinically testing its first medicine, a resveratrol-based drug that promises to help keep diabetic patients' blood sugar under control. Venture capitalists have shown great interest in this early stage biotech company. According to its website, it has raised over \$80 million in the first two years since the founding of the new company and it successfully IPO's in early 2007.<sup>117</sup>

Drug development basing on resveratrol also means great opportunity of operation between entities in China and outside China. In China, there are a lot of resources of the material, such as *grape* and *polygonum cuspidatum*. Advanced extracting methods already have been applied in the production. One kilogram of resveratrol only costs RMB 5,000 (\$600). Some Chinese researchers have done extensive researches on various beneficial effects of resveratrol, including clinical trials for cancer and heart failure treatments. For example, Fei Hongxin et al (2006) studied the effects of resveratrol against human hepatoma cell line HepG2 cells<sup>118</sup>. Combining the inexpensive and abundant material resources in China and western molecule research technology, we could certainly expect a great business opportunity.

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<sup>116</sup> Resveratrol, <http://www.pdrhealth.com>

<sup>117</sup> [http://money.cnn.com/2007/01/18/magazines/fortune/Live\\_forever.fortune/index.htm](http://money.cnn.com/2007/01/18/magazines/fortune/Live_forever.fortune/index.htm)

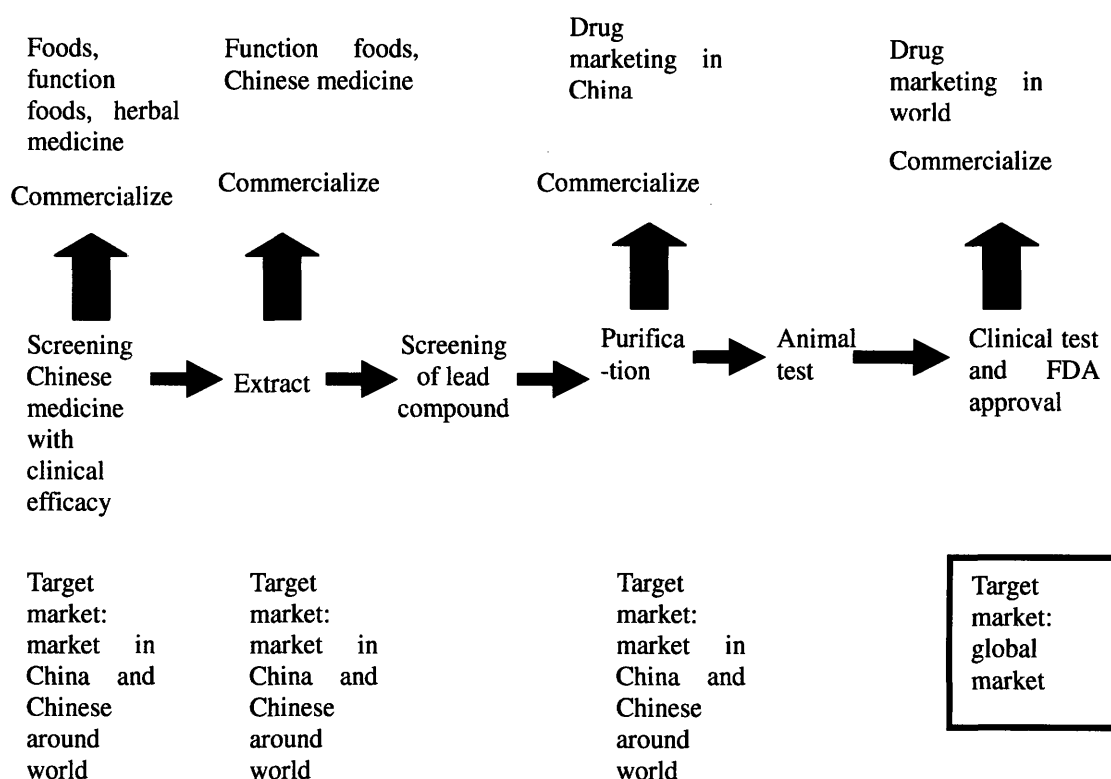
<sup>118</sup> Depressant effect of resveratrol on human hepatoma cell line HepG2 cells, Fei Hongxin, et al, Heilongjiang Medicine and Pharmacy, Aug, 2006, Vol 29, No.4, pp 30-31

## 4. Discussion

The preceding sections of this thesis has described and defined various aspects of critical paths to modernize and realize value in Chinese herbal medicine. In the following section, I propose a few conceptualized value-creation platforms and models.

### 4.1 Value-Realization Platforms and Models

The following schematic shows a platform that, with the use of scientific technologies for quality control and material consistency, multiple levels of commercial values may be created along the trajectory to convert herbs into ethical drugs.

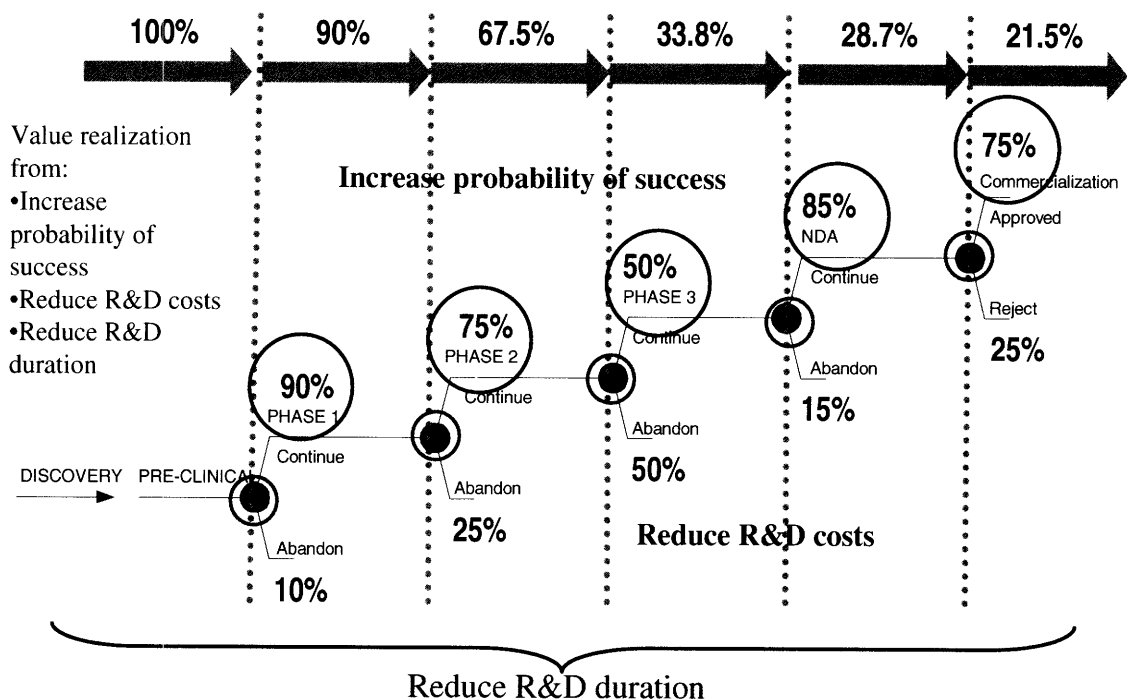


### 4.2 “Bridge” Opportunities

As discussed at the beginning sections of this thesis about the “bridge” opportunities of joint drug development from Chinese herbal medicine under the globalization context, a cross-border virtual platform between China and the US may bring additional value from three aspects: (1) because the starting point of drug development is often based on clinically validated Chinese medicines or mixed formulas, such as the case studies have repeatedly shown, the probability of successful drug development may be increased relative to the current chemical drug screening processes; (2) a significant amount of



R&D work and clinical tests may be performed in China, where costs of material and patient recruiting costs are much lower than those in the US or other western countries, and (3) potentially reduced overall R&D duration. The following is a simplified conceptual model.



Taking the findings in this thesis altogether, it becomes apparent that the herb-derived drug development pathways could be constructed in a rationally designed fast-track trajectory. For example, from the empirical efficacy the extract of individual herbs may be firstly tested on a number of well established animal disease models to generate leads. Once the leads show evidences of efficacy, the minimally required effective components may be developed through various technologies such as HPLC, such components then may be characterized by fingerprint technologies as described in this thesis and tested for animal toxicity, pharmacokinetics, *in vitro* and *in vivo* molecular mechanism and efficacy. Once herb-derived extracts survive the above development funnel and show overall promise, they are positioned to undergo further developmental and official regulatory processes.

## 5. Conclusion

This thesis supports the hypothesis that significant values are embedded in Chinese herbal medicine and such value may be created and captured through modernizing Chinese medicine by current scientific methods and technologies. Both ethical singleton (chemical) herb-derived drugs and mixed formula herb-derived drugs may be created. The trend of globalization facilitates and enhances such a value proposition.

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## Attachments

### Attachment 1: Literature Search Results of CNKI and ISI Relating to the Medical Industry

	year	General	Extraction	Purification	Synthesiza- tion	Manu- facturing	Experi- ments	Animal Experiments	Human Clinical Trials	New Formu- lations	Novel Com- pounds	Molecular Mechanisms
CNKI	2000	43	114	7	199	58	146	24	42	0	18	13
	2001	54	140	11	287	81	171	29	40	3	36	32
	2002	61	175	18	359	121	281	65	82	5	34	50
	2003	59	231	17	395	132	352	78	74	4	48	74
	2004	60	262	37	514	172	457	71	108	6	71	134
	2005	80	224	31	474	203	467	69	105	5	57	119
	2006	37	155	22	270	144	286	37	70	3	48	55
ISI	2000	.	176	19873	790	434	13623	1328	1263	190	1506	4319
	2001	.	228	24355	903	561	16970	1676	1566	289	2123	5273
	2002	.	220	22324	832	615	16138	1639	1686	256	2132	5635
	2003	.	235	24297	904	652	16889	1684	1918	287	2501	6117
	2004	.	252	24632	970	735	18076	1728	1884	344	2645	6872
	2005	.	281	25330	993	766	18962	1807	1884	336	2952	7392
	2006	.	309	25351	1125	854	20166	1824	1860	349	2997	7931

\* About the missing data: the search results are more than 100,000, so are to be ignored

\* All of the results of CNKI in 2006 are obviously decreasing; the most likely reason is that the CNKI database is not updated in a timely manner. So we can ignore the results of CNKI in 2006.

**Attachment 2: Total Applications for Three Types of Patents Received from China and Abroad<sup>119</sup>**

April 1985 - February 2007

		Total		Invention		Utility Model		Design	
		Number	%	Number	%	Number	%	Number	%
Total	Sub-total	3429723	100.0%	1126053	100.0%	1315644	100.0%	988026	100.0%
	Service	1670505	48.7%	853491	75.8%	379828	28.9%	437186	44.2%
	Non-service	1759218	51.3%	272562	24.2%	935816	71.1%	550840	55.8%
Domestic	Sub-total	2805715	100/81.8	586676	100/52.1	1306160	100/99.3	912879	100/92.4
	Service	1072774	38.2%	334803	57.1%	372679	28.5%	365292	40.0%
	Non-service	1732941	61.8%	251873	42.9%	933481	71.5%	547587	60.0%
Foreign	Sub-total	624008	100/18.2	539377	100/47.9	9484	100/0.7	75147	100/7.6
	Service	597731	95.8%	518688	96.2%	7149	75.4%	71894	95.7%
	Non-service	26277	4.2%	20689	3.8%	2335	24.6%	3253	4.3%

2007-03-23

<sup>119</sup> From: [http://www.sipo.gov.cn/sipo\\_English/statistics/szslzljfb/200703/t20070323\\_147084.htm](http://www.sipo.gov.cn/sipo_English/statistics/szslzljfb/200703/t20070323_147084.htm)



**Attachment 3: Total Grants for Three Types of Patents Received from China and Overseas<sup>120</sup>**

April 1985 - February 2007

		Total		Invention		Utility Model		Design	
		Number	%	Number	%	Number	%	Number	%
Total	Sub-total	1793786	100.0%	307592	100.0%	860020	100.0%	626174	100.0%
	Service	843742	47.0%	260384	84.7%	276671	32.2%	306687	49.0%
	Non-service	950044	53.0%	47208	15.3%	583349	67.8%	319487	51.0%
Domestic	Sub-total	1536697	100/85.7	117567	100/38.2	853178	100/99.2	565952	100/90.4
	Service	597769	38.9%	77401	65.8%	271458	31.8%	248910	44.0%
	Non-service	938928	61.1%	40166	34.2%	581720	68.2%	317042	56.0%
Foreign	Sub-total	257089	100/14.3	190025	100/61.8	6842	100/0.8	60222	100/9.6
	Service	245973	95.7%	182983	96.3%	5213	76.2%	57777	95.9%
	Non-service	11116	4.3%	7042	3.7%	1629	23.8%	2445	4.1%

2007-03-23

<sup>120</sup> From: [http://www.sipo.gov.cn/sipo\\_English/statistics/gnwsqb/200703/t20070323\\_147089.htm](http://www.sipo.gov.cn/sipo_English/statistics/gnwsqb/200703/t20070323_147089.htm)

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**Attachment 4: Three Types of Medicinal Patent Applications and Grants 1995~2004<sup>121</sup>**

		Botanical drug	Biotech drug	Drug compound and the method for the production
1995	Application	1322	424	1455
	Grant	451	198	782
1996	Application	1485	577	1659
	Grant	559	261	915
1997	Application	1527	649	1910
	Grant	653	275	911
1998	Application	1493	796	2127
	Grant	665	338	1008
1999	Application	1460	1136	2074
	Grant	640	355	1206
2000	Application	1815	2092	5064
	Grant	813	413	1351
2001	Application	3045	1578	3447
	Grant	884	434	1104
2002	Application	2653	1673	4546
	Grant	970	461	1068
2003	Application	3698	2207	5598
	Grant	609	367	1056
2004	Application	3356	1576	3739
	Grant	48	120	372

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<sup>121</sup> Statistics on the Patents of Medicinal Invention from 1995 to 2004 in China