

## Update on US FDA Regulations on Chinese Traditional Medicine

Patrick Yang



**About the author:** Dr. Patrick Yang is currently a Staff Scientist at Sunesis Pharmaceuticals Inc. He worked at Millennium Pharmaceuticals, Inc. and Nektar Therapeutics Inc. for several years before joined Sunesis. He graduated from Nanjing University, and obtained his Ph. D. in pharmaceutical sciences from University of the Pacific, USA. He has several years' working experience in analytical field and management in China. His major research interests include analytical development, method transfer/validation, preformulation/formulation, and controlled release of drug. He can be reached at peiyangusa@yahoo.com.

### Abstract

Chinese Traditional Medicine (CTM) is one of the oldest medicines. It works well for many diseases, and has been enjoyed for centuries throughout the world. Its increasing use in recent years is evidence of a public interest in having alternatives to conventional medicine. The West's narrow scientific approach used to miss the point of such ancient practices, which attempt to treat the body as a complex whole instead of trying to heal a specific illness. The Federal Government regulates CTM through the Food and Drug Administration (FDA) as foods rather than as drugs per old regulations, which have some limitations and are not appropriate. In order to meet the special properties of CTM, protect the customers, provide the incentive to the research on the CTM-based drug development, and benefit the public health, FDA released a new guidance on botanical drug and approved the first botanical drug recently. The significant impact in drug industry by this change is far reaching. It is expected to have more botanical drugs and tighter competition in the near future. CTM will certainly play a more important role and make greater contributions to healthcare of human being. This paper overviewed the history of CTM acceptance process in Western mainstream, introduced the current status of CTM in USA, reported successful cases of CTM, summarized the research and clinical trials on CTM, explained the FDA's old regulations on drug, analyzed the limitations of the regulations to CTM, compared CTM with Western medicine, and elucidated the new guidance on botanical drugs.

---

There have been many changes and new information since my previous paper on Chinese Traditional Medicine (CTM) published in 2005<sup>1</sup>. This paper is the follow-up on the update status of CTM and its new FDA regulations in USA.

### Overview of CTM in Europe

Chinese Traditional Medicine has developed into a mature system for more than three thousand years. Today about 60% worldwide population depend on herb medicine. The traditional medicine exports from China are worth more than \$500 million a year to meet the apparent growing interest in alternative therapies globally<sup>2</sup>. It was predicted that the potential market volume of Chinese Herb Medicine would be \$400 billion in 2010.

The vast majority of Asians believe in CTM, and many use it loyally. For decades, however, this seemingly blind faith has sparked deep suspicion among Western scientists. It took time for Westerners to accept CTM. European gets to accept CTM earlier than American. Acupuncture is popular in the continent for a century, and herbs are regarded as drugs and prescribed by physicians. In most European counties, the acupuncture and herbal therapy are conducted mainly by Western medical doctors. By so far, German and France are in advance in this field. Both countries have established their

own complete effective regulatory systems specific for CTM. In these systems, several standards are different from those of conventional drugs. For example, multiple components in CTM are permitted, while the main component has to be strictly scrutinized. Besides, CTM has to be prescribed by European physicians, making the market and management standardized and controllable. Currently about three fourth French has tried herbs or other alternative medicines at least one time in all life. In 2004, the governments of Italy and China signed agreements to intensify co-operation in the development and marketing of traditional Chinese medicine, which faces difficulties entering the global market due to the lack of scientific evidence as to its safety and efficacy<sup>3</sup>. The investments were increased in clinical studies and personnel exchanges to make CTM acceptable to public organizations and more patients in the West. In the same year, the European Union has formed a new government panel to investigate the safety of herbal medicines<sup>4</sup>. The Committee on Herbal Medicinal Products held its meeting every two months under new EU legislation designed to protect consumers. One of the goals of the panel is to harmonize regulation of the herbal product industry across the European Union.

### Overview of CTM in America

In USA, CTM is taken as Complementary and Alternative Medicine (CAM). The U.S. Government's National Institutes of Health (NIH) established the National Center for Complementary and Alternative Medicine (NCCAM). As defined by the center, CAM is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine<sup>5</sup>. It can also be loosely defined as treatments and practices not commonly taught in medical schools, not generally used in hospitals, or covered by insurance companies. Alternative medical systems are built upon complete systems of theory and practice, and have often evolved apart from and earlier than the conventional medicine that is practiced in the United States. Another new term, Integrative Medicine, is the medicine or system that combines CAM and conventional medicine and applies it to clinical therapy.

Until 1970s did American begin to believe a portion of CTM especially acupuncture. CTM experienced renewed popularity as part of the back-to-the-earth and natural foods movements. The consumption of herbal teas has steadily increased. In 1984, faced questions about herb safety, Canada established an advisory committee to review the available information on herbs and make recommendations<sup>6</sup>. A report in 1993 in the *New England Journal of Medicine* suggested that, for the first time in modern history, annual visits to alternative practitioners may exceed those to primary care physicians<sup>7</sup>. Another report

in 1998 in the *Journal of the American Medical Association (JAMA)* indicated that 42% of Americans have tried some sort of alternative medicine, from megavitamins to energy healing, up from 34% in 1990<sup>8</sup>. Right now about 50% of American population is under the treatment of alternative therapies despite a lack of rigorous evidence for whether or not they work. As many as 70% cancer patients seek some form of alternative therapy<sup>9</sup>. About 15% doctors are applying alternative treatment including CTM, homeopathy, energy healing, etc<sup>10</sup>. By so far, forty-one states permit licensed acupuncturist. According to Dr. Subhuti Dharmananda, the founder and director of the Institute for Traditional Medicine and Preventive Health Care, Inc. (ITM), over 16,000 acupuncture licenses are currently registered by those states<sup>11</sup>. Just in New York City, the number of licensed acupuncturists has been up to 2000<sup>12</sup>, and the number got to be 5600 in California<sup>11</sup>. A national survey recently conducted by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) indicated that, one out of ten adults in America has been treated by acupuncture, and 21% among them got CTM and massage in the same time. In addition, about 60% American expressed their willingness to take acupuncture as an option<sup>13</sup>.

In a 1995 Gallop survey, more than 28 million Americans reported taking herbal supplements<sup>7</sup>. In 1997, Americans spent \$27 billion on unproven remedies. St. John's Wort, an herb taken for depression, alone racked up an estimated \$400 million in U.S. sales in 1999<sup>14</sup>. Herbal and other alternative medicaments clocked up a stunning \$40 billion in sales in 2001<sup>15</sup>. Approximately 1500 botanicals are sold as dietary supplements or ethnic traditional medicines<sup>16</sup>. People take supplements for many reasons. A scientific study on this topic published in 2002 reported the supplements used by over 2,500 Americans and the reasons to use them<sup>17</sup>. The major reasons based on their responses are: health/good for you, dietary supplement, arthritis, memory improvement, energy, immune booster, sleep aid, etc.

It has been somewhat surprising in this era of triumph for modern medicine to see the rapid growth of alternative/complementary medicine. There is a growing tendency among physicians to acknowledge and even embrace certain forms of CAM. Fueled by popular interest, alternative medicine is gaining ground at scores of universities; now it was brought into the curriculum. Since 1990s, more than 70 U.S. universities, including some famous medical schools have offered some sort of alternative medicine program, such as Harvard, Yale, Stanford, Cornell, Columbia, Duke, and several branches of the University of California, etc<sup>18</sup>. Some universities even established alternative medicine center, such as Harvard (by David Eisenberg), the state University of New York at Stony Brook (by Samuel Benjamin), and University of Arizona (by

Andrew Weil, perhaps the best known champion of alternative medicine). Up to now, there are more than 50 schools specializing in acupuncture or Asian remedies, including eight schools in New York States.

Changes in the use of the terms “alternative” and “complementary” suggest the shape of this shift. At first, it was called simply “alternative medicine”, reflecting dissatisfaction with regular medicine as well as a cultural rebellion against the biomedical community. In more recent years, several studies indicate that there has been a shift from “alternative” therapies to “complementary” therapies, adopted not in opposition to regular medicine, but in alliance with it<sup>19</sup>.

This change indicates that more and more people like to get a more moderate and less aggressive therapy<sup>20</sup>. However, CTM has still been the subject of controversy in U.S. since their introduction into the mainstream marketplace three decades ago. The fight never stops between skeptical scientists and powerful supporters of alternative therapy. In the point view of the former people, alternative therapy is associated with witchcraft, charlatan, or quackery; while the latter people criticize the funding for alternative research “woefully inadequate”. In 1992, the Office of Alternative Medicine (OAM) was ear-marketed into existence. In 1997, former presidential science adviser D. Allan Bromley and others urged Congress to abolish the office. Instead, Senator Tom Harkin, a die-hard fan of alternative medicine, kept boosting its budget, from an initial \$2 million to nearly \$70 million in 2000. And in 1998, he succeeded in elevating the office (OAM) to a full-fledged center, NCCAM, with its own authority to award research grants<sup>18</sup>. Now NCCAM enjoys autonomy similar to that of NIH’s 18 existing institutes and centers<sup>21</sup>. Over the past two and half year, representative Burton, another hard-nosed supporter of alternative medicine, has held at least 10 hearings to urge NIH to examine alternative remedies. In November of 1997, a consensus panel convened by the NIH concluded that there is clear evidence that acupuncture is effective for relieving pain in a variety of situations, including postoperative and chemotherapy nausea and vomiting, probably for the nausea of pregnancy, and postoperative dental pain<sup>6</sup>. Due to this conclusion, many used-to-be-stubborn medical insurance companies changed their policy and began to accept the co-payment for above treatments by acupuncture. On the other hands, there was also different voice from anesthesiology field, suggesting that NIH consensus statement on acupuncture “should not prompt physicians to use acupuncture or to refer patients to acupuncturist”<sup>22</sup>. In 2000, President Bill Clinton set up the White House Commission on Complementary and Alternative Medicine Policy, but the panel has failed to reach agreement on the awkward question of how to deal with alternative medicine<sup>23</sup>. The majority called for the health

department to establish a powerful new office to coordinate research and information on “alternative” treatments such as homeopathy and acupuncture. Its report calls for the government to increase its support for research into alternative medicine. The report adds that “safe and effective” alternatives should be paid for by federal health programs, and that the government should provide incentives for private companies to research natural therapies that cannot be patented. But a minority of members has written a statement of dissent. The divided opinions will be remaining for more years.

### The Successful Cases of CTM

As the Father of modern medical sciences, Hippocrates, said, “The power of nature is the greatest regime of healing”. Originated from nature, CTM treated many diseases effectively.

One of the most successful examples is a non-quinine-based drug called artemisinin in treating advanced cerebral malaria. Artemisinin is the biotech world’s moniker for qing haosu, a crystalline compound extracted from sweet wormwood, a weedy plant indigenous to China. The curative powers of such plants are the basis of Chinese traditional medicine. During China’s brief war with Vietnam in 1979, the Chinese government gave its soldiers a crudely distilled antimalaria pill based on artemisinin – and it worked<sup>15</sup>. Today, scientists at the Shanghai Institute of Materia Medica, where artemisinin was first isolated, have further refined the compound into what is now simply the most effective antimalarial drug we’ve ever had<sup>24</sup>. However, although artemisinin has been used as an herbal remedy in China for 2000 years, it hasn’t yet been approved for clinical use in Western countries. One member of this family, a water-soluble form called artesunate, got trapped in a regulatory cul-de-sac. Although Chinese researchers had published safety and efficacy data, Western authorities looked askance at their research methods. The World Health Organization (WHO), for instance, declined to launch major clinical trials of artesunate in the 1980s, after some of its advisers expressed concerns about neurotoxic effects seen in animal studies. It was suspected that the biggest roadblock was that artesunate “came from the wrong place”.

In 1994, as local parasites through Thailand are becoming resistant to all forms of quinine, the once miraculous antimalaria agent, the WHO decided to support trials of artesunate with a quinine-based drug mefloquine as the last line of defense. It was then reported that this oral therapy yielded efficacy of “nearly 100%”<sup>25</sup>. Moreover, after a five-year delay caused in part by skepticism that a drug based on a Chinese herbal remedy could be effective, the WHO recently gave official backing for the distribution of an artemisinin-based medicine

in Africa<sup>15</sup>. Now the WHO plans to submit a drug application to the Food and Drug Administration (FDA) to obtain a license to develop the rectocap, a rectal suppository formulation based on artesunate, in collaboration with a European manufacturer.

Recently, the promise of artemisinin looks richer than ever. Henry Lai, a bioengineering professor at the University of Washington, recently published a paper detailing experiments in which artemisinin killed virtually all breast cancer cells exposed to it within 16 hours, while having no impact on normal cells<sup>26, 27</sup>. Not only does it appear to be highly effective, but it's very selective<sup>28, 29</sup>. In tests at other universities in the U.S. and Germany, artemisinin has also shown early promise in combating disease like leukemia and bone cancer. In 2004, the Bill & Melinda Gates Foundation awards \$42.6 million to OneWorld Health for development of artemisinin through synthetic biology. OneWorld Health partners with UC Berkeley and Amyris Biotechnologies with the goal of providing unlimited, affordable supplies of first-line antimalarial ingredient using synthetic biology<sup>30</sup>. Other supports for the fight against malaria come from public-sector organizations, philanthropic foundations, and "in-kind" industry contributions such as GlaxoSmithKline's new malaria and tuberculosis drug-discovery unit<sup>31</sup>.

Another successful example of the traditional medicine-based drug is Xue Bao ("blood treasure"), which is derived from yellow root, a purple flowering plant<sup>14</sup>. It is probably the farthest down the testing road. Chemist T.S. Jiang in Taiwan is running a trial of the drug. Xue Bao reduces the side effects of chemotherapy on cancer patients, so that appetite improves, normal sleep patterns resume, and hair grows back. Critically, Xue Bao has produced no side effects, unlike the two Western drugs G-CSF and EPO, which are most widely used in conjunction with chemotherapy. So far the drug has been tested on 500 patients in Taiwan and mainland China with encouraging results. It still has to pass the third and final trial stages.

### Research and Clinical Trial

CTM has a potential to play a more and more important role in modern life. Diseases like anthrax and smallpox progress too rapidly for our immune system's natural ability to control them. Simply stated, these diseases can kill us before our immune system can rally to defend against them. Many CTM practices do have a place in treating similar conditions, especially in relieving symptoms, and in improving one's quality of life. However, in the case of bioterrorism, there is no CTM practice that has been shown to sufficiently stimulate the immune system to fight these deadly diseases<sup>32</sup>. Nor do any

dietary supplements or other CTM products have the potency to eliminate highly lethal microorganisms and toxins, once they have entered our systems. The potential on CTM on treating epidemic diseases shed a slight light early in 2003 on SARS, a kind of coronavirus. Normally it takes at least two years to find the vaccine based on the estimation of Dr. David Ho, the inventor of cocktail treatment on HIV. However, CTM bypassed this duration. This was proved by the death rates of SARS patients in different countries. During the peak time of SARS, the death rate was 6% in mainland China, but about 12.4% in Taiwan, Canada, and Singapore. The reason for the half-fold lower rate in mainland China was believed to attribute to the application of CTM treatment<sup>33</sup>. A number of tests carried out at King's College at London have found that traditional remedies from around the world are effective at treating many ailments, according to researchers<sup>34</sup>. The herbal-based products are produced by many manufacturers in USA, such as Aller 24 by Confidence, which is very effective in treating flower allergy.

The wealth of opportunities provided by traditional medicines offers particular promise for developing capacity for drug research and development. Chinese built up TCM based on natural products, which are a reservoir containing abundant chemical novelty and diversity. A handful of past and current "miracle drugs" are originated from plants – from quinine to Taxol, from aspirin to the birth control pill (see Table 1 for a listing of additional compounds)<sup>35</sup>. Among the 520 new drugs approved between 1983 and 1994, 157 were natural products or derived from natural products. A landmark survey from 2003 published in the *Journal of Natural Products* showed that a whopping 61% of 877 small-molecule new chemical entities (NCEs) introduced worldwide from 1981 to 2002 can be traced to natural products. In addition, 74% of anticancer drugs and 78% of antibacterials are either natural products or inspired by a natural product model, reported by Frank Peterson, head of Novartis Pharma natural products research<sup>36</sup>. In 1999, nine of the best-selling non-protein drugs were either derived from or developed as the results of leads generated from natural products. Natural products and their derivatives comprised about 35% of the total pharmaceuticals market volume of 230 billion US dollars in 1996. However, about 40% of the chemical scaffolds of the published natural products are unique and have not been made by synthetic chemistry. Given the history of success that natural products have had as drug compounds, the logic of mining the natural world for candidates is obvious. The drug discovery by the aid of TCM has a great space to further explore.

The active ingredient(s) in many herbs and herbal supplements are not known. There may be dozens, even hundreds, of such compounds in an herbal supplement. Using sophisticated

**Table 1. Some Representative Plant-Derived Medicinal Compounds**

Type	Compound	Source	Disease treated/use
Alkaloid	Camptothecin	<i>Camptotheca acuminata</i>	Breast, colon cancer, etc.
	Colchine	<i>Colchicum autumnale</i>	Antitumor agent, gout
	Irinotecan	<i>Camptotheca acuminata</i>	Anticancer, antitumor
	Quinine	<i>Cinchona ledgeriana</i>	Antimalarial, antipyretic
	Reserpine	<i>Rauwolfia serpentina</i>	Antihypertensive, tranquilizer
	Theobromine	<i>Theobroma cacao</i>	Diuretic
Glycoside	Etoposide	<i>Podophyllum peltatum</i>	Antitumor agent
	Digitalin	<i>Digitalis purpurea</i>	Cardiotonic
Terpenoid	Docetaxel (Taxotere)	<i>Taxus sp.</i>	Antitumor agent
	Artemisinin	<i>Artemisia annua</i>	Antimalarial
	Paclitaxel (Taxol)	<i>Taxus sp.</i>	Breast, colon cancer, etc.

technology, scientists are currently working to identify these ingredients, analyze products, and understand how herbs affect the body.

In the past few years, a quite but historic campaign has been under way to subject traditional Asian treatments to rigorous scientific scrutiny. Government in China, Singapore, Taiwan and Hong Kong are pouring money into hard research on long-accepted cures. The NIH also spent \$220 million on research and training in alternative medicines in 2001, a chunk of which will go toward the study of Asian remedies. Every year, NIH spent \$120 million on research in mechanism of TCM treatment. The NCCAM

currently contains more than 6,200 clinical studies sponsored by NIH, other Federal agencies, and the pharmaceutical industry in over 69,000 locations worldwide<sup>37</sup>. NCCAM is funding studies on a variety of CAM treatments. A few examples include acupuncture; herbs such as *Ginkgo biloba*; dietary supplements such as glucosamine, chondroitin, saw palmetto, and soy; and massage. Examples of diseases and conditions for which these CAM therapies are being studied include arthritis, neurological disorders, cardiovascular disease, and cancer. Some of these studies involve

partnerships with other institutes at NIH. Institutions outside

**Table 2. Major Clinical Trials Funded by NCCAM**

Study	Institute	No. of Patients	Length (years)	Cost (millions)
<i>Ginkgo biloba</i> to prevent dementia	University of Pittsburgh School of Medicine	3000	6	\$15
Glucosamine and chondroitin sulfate for knee arthritis	University of Utah School of Medicine	1000	4	\$6.6
St. John's Wort for depression	Duke University	330	3	\$4.3
Acupuncture for knee arthritis	University of Maryland School of Medicine	570	4	\$2.5
Saw palmetto extract in benign prostatic hyperplasia	Veterans Affairs Medical Center, San Francisco	224	3	\$1.8
Shark cartilage for lung cancer	M.D. Anderson Cancer Center	500	5	\$2.5
Gonzalez Protocol for pancreatic cancer*	Columbia-Presbyterian	90	5	\$1.4

\* This study is only randomized trial. All other studies in the table were double-blind-placebo-randomized trial.

the Federal government are conducting studies as well. For example, the Integrative Medical Center at Memorial Sloan-Kettering Cancer Center is investigating *Rhizoma Coptidis* for cancer patients<sup>12</sup>. One of the herbal products is co-developed with a US botanical company, Harmonex, and Shanghai Longhua Hospital. The phase I clinical trial has been approved by FDA. Table 2 lists some major clinical trials funded by NCCAM, most of which were co-funded by other institutes, such as Office of Dietary Supplements (ODS), National Cancer Institute (NCI), etc.

As with all trials, the odds are heavily stacked against success. But if just one of these drugs makes it to the pharmacy shelves alongside artemisinin, the world's medicine chest, compartmentalized for centuries, will have grown immeasurably richer. The two approaches (traditional and conventional therapies) are getting to join hands in recently. In 2004, the first International Integrative Oncology Conference was held in New York. Researchers from many prestigious oncology centers, such as Memorial Sloan-Kettering Cancer Center, the University of Texas MD Anderson Center, and Dana-Farber Cancer Institute discussed the topics about the role of acupuncture and herbs on oncology. It will be another sign that what once seemed like two fundamentally opposed approaches to healing have finally begun to work in tandem.

### **FDA Regulations on CTM as Food and Supplements**

Even when an herbal prescription has centuries of use behind it, and when its production and sale are closely supervised by government agencies, things can go horribly wrong. Several dozen Japanese died in the late 1990s after taking a popular liver tonic called *shosikoto*, which the national health insurance program had certified<sup>15</sup>. In USA, the Consumer Reports, published in May 2004, listed 12 dangerous supplements. Two TCM products from China are categorized as "absolutely dangerous" due to the content of aristolochic acid. It was said that taking these two supplements may incur cancer, renal disease or even death. This journal suggested the customers not to use these supplements. *Consumer Reports* is a prestigious journal with 3.3 million subscribers. It has a high reputation and great influence on consumers. In order to be fair and objective, this journal never published any advertisements for any commercial organization. Every year, it spends almost one hundred thousand dollars to make survey among the readers, and invests huge money on purchasing, testing and evaluating the quality and price of various products.

Herbal supplements can act in the same way as drugs. Therefore, they can cause medical problems if not used correctly or if taken in large amounts. In some cases, people have experienced negative effects even though they followed the instructions on a supplement label.

While many CTM treatments have already been in use for a long time (sometimes for centuries), there is not the kind of scientific knowledge available about them that has been gained from studies of conventional medicine. Many people are already using CTM, and without this scientific knowledge, they may be at risk—for example, for serious effects from taking the wrong dose, using the treatment in the wrong way, or using it with another treatment with which it interacts.

Actually the alternative medicine is getting positive remarks. Among the advocates are many famous people, such as Charles, the British prince. The WHO affirmed that alternative medicine should establish its deserved role in modern medical field. Considering the alternative medicine gets to be the victim of the misuse by its zealots and the ignorance from its skeptics, the WHO has issued new guidelines in 2004 aimed at educating people about the proper uses of alternative medicines. The move is in response to the increasing number of people who do not inform their physicians they are using the medications and then suffer adverse reactions. Topics covered in the guidelines include acupuncture, herbal medicines and food supplements<sup>38</sup>.

In fact, the FDA cannot restrict the use of supplements unless substantial harm has been proven. It is highly imperative to have regulations for CTM or supplement. In the United States, herbal and other dietary supplements are regulated as foods or nutraceuticals rather than drugs by the FDA<sup>39</sup>. Nutraceutical is defined as any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. This means that CTM does not have to meet the same standards as drugs and over-the-counter medications for proof of safety, effectiveness, and what the FDA calls Good Manufacturing Practices (GMPs). Given that, a recommendation by a 1997 presidential commission called for FDA to convene an expert committee to review the wealth of information that already exists on botanicals and then inform consumers and manufacturers about unsafe preparations<sup>40</sup>.

FDA regulation of herbs falls into a somewhat gray area between food and drugs. Depending on their intended use, herbs and other products, such as vitamins and diet aids, might sometimes be considered foods, sometimes drugs, and sometimes both. But for centuries, herbs and herbal teas have been used for medicinal purposes. Many of today's most potent medicines, such as digitalis, morphine and opium, are derived from herbs. If an herbal tea makes a claim to prevent or cure a disease, FDA considers it to be a drug and regulates it as such. This means the tea must be approved by FDA as safe and effective for its intended use<sup>6</sup>.

In general, the laws about putting foods (including supplements) on the market and keeping them on the market are less strict than the laws for drugs<sup>41</sup>. This can be demonstrated in two aspects specifically. First, research studies in people to prove a supplement's **safety** are not required before the supplement is marketed, unlike for drugs. Second, the manufacturer does not have to prove that the supplement is **effective**, unlike for drugs. The manufacturer **can** say that the product addresses a nutrient deficiency, supports health, or reduces the risk of developing a health problem, if that is true. If the manufacturer does make a claim, it must be followed by the statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Moreover, the manufacturer does not have to prove supplement **quality**. The FDA does not analyze the content of dietary supplements. At this time, supplement manufacturers must meet the requirements of the FDA's GMPs for foods. GMPs describe conditions under which products must be prepared, packed, and stored. Food GMPs do not always cover all issues of supplement quality. Some manufacturers voluntarily follow the FDA's GMPs for drugs, which are stricter. Some manufacturers use the term "standardized" to describe efforts to make their products consistent. However, U.S. law does not define standardization. Therefore, the use of this term (or similar terms such as "verified" or "certified") does not guarantee product quality or consistency. If the FDA finds a supplement to be unsafe once it is on the market, only then can it take action against the manufacturer and/or distributor, such as by issuing a warning or requiring the product to be removed from the marketplace.

In March 2003, the FDA published new proposed guidelines for supplements that would require manufacturers to avoid contaminating their products with other herbs, pesticides, heavy metals, or prescription drugs. The guidelines also require supplement labels to be accurate. The Federal Government also regulates supplement advertising, through the Federal Trade Commission. It requires that all information about supplements be truthful and not mislead consumers.

For a CTM product that is sold over the counter (without a prescription), such as a dietary supplement, safety can also depend on a number of things: the components or ingredients that make up the product, where the components or ingredients come from, the quality of the manufacturing process (for example, how well the manufacturer is able to avoid contamination)<sup>42</sup>.

The manufacturer of a dietary supplement is responsible for ensuring the safety and effectiveness of the product before

it is sold. The FDA cannot require testing of dietary supplements prior to marketing. However, while manufacturers are prohibited from selling dangerous products, the FDA can remove a product from the marketplace if the product is dangerous to the health of Americans. Furthermore, if in the labeling or marketing of a dietary supplement a claim is made that the product can diagnose, treat, cure, or prevent disease, such as "cures cancer," the product is said to be an unapproved new drug and is, therefore, being sold illegally. Such claims must have scientific proof.

### **Limitations of the FDA Regulations, and Comparison of CTM and Conventional Medicine**

There is mounting evidence that the efforts to unlock the secrets of Asian remedies could produce tangible benefits for sufferers of diseases that have confounded both Western and Eastern schools of medicine—everyone from menopausal women to cancer patients.

It ought to be easy: take drug combinations that have been used for thousands of years and apply strict scientific tests to them to find out what makes them work. Then distill the active compound and make a pill. But life isn't that simple. The very fact that traditional remedies have been used successfully for centuries—precisely what should make them invaluable signposts to researchers—means that drugs developed from those formulas can't be patented. That, in turn, means that no international drug behemoth is driving this research.

Another daunting challenge used to lie in getting approval from the notoriously strict U.S. regulatory agency, the FDA. Before recently, the FDA required proving how a certain medicine affects the body. That's easy with Western medicine but traditional Chinese medicine is like a recipe: you can't prove to the FDA what each ingredient does. A Chinese herbal formula is a carefully balanced recipe of several different herbs. Each herb has its own specific functions. An herbal formula is even tailor-made to suit a particular patient. Under many circumstances, even the same kind of herb has different efficacy due to different places of product. The herb has unique shape and odor, and it is very difficult to design a suitable placebo for a controlled study.

Pharmaceutical companies start with the herb and extract the "active ingredients," but alternative practitioners maintain that the whole herb is more therapeutic than its isolated ingredients and is less likely to result in side effects. Research indicated that the nontoxic natural products are actually more safe and effective than their patented, FDA-approved counterparts, for the very reason that they can't be patented: they are found naturally in living things<sup>7</sup>. Despite such obstacles, a few

pharmaceutical titans, including Roche and Merck, do maintain small research projects in China. They are testing some plant ingredients to see how they affect the body<sup>15</sup>.

There are theoretical hurdles too. Western scientists can't figure out what makes some of the most effective traditional methods work. Take acupuncture. While there is no longer any serious doubt in Western scientific circles that it works in alleviating pain and even lowering blood pressure, there is no convincing explanation of how it does so. As advocates of traditional Asian medicine see it, the West's narrow scientific approach missed the point of such ancient practices, which attempt to treat the body as a complex whole instead of trying to heal a specific illness. The quest for precision leads scientists to disassemble complex formulas in the hope of isolating a single compound that could cure one specific disease. That's anathema to Asian healers.

Western medicine approaches diseases in a "direct and unilateral way". Even when it works, it fails to take into account the human body's complexity. By contrast, traditional cures are effective in combating chronic diseases caused by a variety of factors. Traditional medicine doesn't analyze or attach the disease directly but it tries to return the body to balance, to its normal state. This principle is agreeable to that in homeopathy, another alternative therapy developed by a German doctor and pharmacist in 18th century, and further proved by a French scientist, Jacques Benveniste, and a British pharmacologist, Madeleine Ennis<sup>10</sup>.

Comparing the efficacy of an herbal medicine with a chemical medicine is risky. Chemicals are like sharp knives: if you use them properly they will do their jobs perfectly, but if you miss your target, they might cause serious side effects. Herbs are like dull knives -- they are not as swift, but they have fewer side effects.

The basic principle of Chinese medicine is to readjust and balance the elements in human body back to a normal and healthy level. Western medicine is like a key to a lock. The mechanism and the compound are very clear, and the target is hit precisely by "a deadly bomb". But traditional Chinese medicine is nonspecific. The "shotgun" scans a lot of targets and the chance to hit the right target is quite high. It also explains why traditional cures are better for disease prevention and treatment of chronic conditions that are usually caused by a combination of factors, not a single virus or bacterium.

There are several blind areas in Western medicine, which might be solved by alternative medicine, such as: filterable virus, most chronic degenerative diseases (diabetes, hypertension, and kidney failure), most mental diseases (depression),

most self-immune and allergy diseases (asthma, rheumatoid and leukemia), and most kinds of cancer and stubborn dermal diseases. Chinese medicine offers cost-effective approaches to managing and preventing complex chronic illness.

### FDA's New Regulations on CTM as Drug, and First Approved CTM Drug

For too long, the natural health products industry has kept its distance from medical research and from clinical medical practice, focusing instead on the short-term marketing advantages derived from keeping herbal and nutritional remedies exempt from any FDA review of efficacy. A wiser approach should be for the natural products industry to work with medical research, including the FDA, so that consumers and medical practitioners could be warned about potential harm and assured that the claimed health benefits were really there. The public needs good science to sort the worthless and dangerous from the potentially helpful. Many scientists support the efforts to investigate alternative therapies "provided that the research is held to rigorous scientific standards, is suitably peer-reviewed, and is fairly administered", as expressed by Nobel laureates Paul Berg, a Stanford University biochemist, and Jerome Friedman, a Massachusetts Institute of Technology physicist<sup>9</sup>.

However, Western pharmacology studies focused on identifying single compounds to treat diseases. The FDA's old regulations require developers to identify exactly what kind of herbal ingredients can cure, and proved its effectiveness. Otherwise, the products are not allowed to enter the pharmacy sales. Due to the complex nature of a typical herbal drug and the lack of knowledge of its active constituent(s), the requirements by old regulations are not appropriate. FDA was urged to follow up Europe's advanced strategies and take them as reference into consideration for readjusting regulation systems. With the upcoming demand, FDA was under the pressure to regulate the CTM as drugs rather than as foods. This would not only protect the customers, but also provide the incentive to the research on the CTM-based drug development, and hence benefit the public health.

In order to meet the special properties of CTM, FDA lowered the hurdle by setting a new regulation specifically valid for botanical drug products including CTM. A **Botanical Product** is a finished, labeled product that contains vegetable matter, which may include plant materials, algae, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic. Only when a botanical product is intended for use in diagnosing, mitigating, treating, curing, or preventing disease, it is taken as **Botanical Drug Product** or **Botanical Drug**,

and is subject to the new regulation as a drug. Another term, **Botanical Drug Substance**, is a drug substance derived from one or more plants, algae, or macroscopic fungi. It can be made from one or more botanical raw materials. A botanical drug substance does not include a highly purified or chemically modified substance derived from natural sources.

Ten years ago, FDA started the drafting of Guidance for Industry: Botanical Drug Products. The final version was released in June of 2004. Currently, there are several botanical drugs, including cascara, psyllium, and senna, that are included in the OTC drug review. On October 31 2006, just about two years after the release of its new regulation, FDA approved the first ever submitted New Drug Application (NDA) for botanical drug product, Polyphenon® E Ointment. The approval for Polyphenon E Ointment has been made out to the name Veregen™. The product is developed by a Germany biotech company MediGene AG, and is indicated for the treatment of external and perianal genital warts<sup>43</sup>.

Orally administered green tea, catechins or catechin-rich green tea extracts were reported to have several health benefits including anti-oxidative, chemo-preventive, anti-tumor, and other health protective activities. Although tea was considered a panacea for some, as a *Materia Medica* in TCM, tea is known to have side effects. Overdose of tea could cause sleeplessness or insomnia. MediGene AG tried a new way of using green tea. The clinical trial indicated that Veregen showed high and sustained efficacy with very few adverse events in the treatment of genital warts. The results come from an international phase III trial with more than 1,000 patients in 15 countries medicated with Veregen. For the purpose of FDA approval, the safety and efficacy of Veregen were studied in two randomized, double-blind clinical studies on nearly 400 adults with external genital and anal warts.

The significance of this approval is that the active substance in Veregen is an extract from green tea leaves. Veregen is a relatively simple botanical derived from a single part of a single plant (green tea leaves), containing a class of well-studied chemical entities as the major active ingredients (catechins). Because of the unique nature of botanicals, FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic, semisynthetic, or otherwise highly purified or chemically modified drugs. The major change in the new policy is that, for those who want to develop prescribed drug from plant extracts, they only need to extract one effective material, and this extracted material may contain hundreds of compounds. There is no longer a need to indicate the effect of each single compound.

The implementation of the new policy brought in a substan-

tial growth in NDA submission of herbal drug products so that FDA even set up a special office to receive such applications. The FDA hired experts to enrich the education sector, and have the new “Botanicals review team” (BTR) to perform the pharmaceutical assessment. The team includes Dr. Shaw T. Chen (MD and Ph.D., team leader), Dr. Jinhui Dou (pharmacologist and team reviewer, graduated from the Beijing University of Traditional Chinese Medicine) and other experts. The BTR review covers the following areas<sup>44</sup>:

- i) Biology of the medicinal plants-identification, potential misuse of related species;
- ii) Pharmacology of the botanical product-activity/toxicology in old documents and new testings;
- iii) Prior human experiences with the botanical product-past clinical use and relevance to current setting.

Now many companies submitted applications of botanical drug product to the FDA, and some drugs are into clinical stage. Currently about 250 Botanicals have been approved into clinical trials. Most drugs are based on traditional Chinese medicine.

There are many differences in policy between botanical drug and chemical drug. The major differences and related policy issues are summarized as follows based on Botanical Guidance and its Q&A section<sup>45</sup>:

**Purification and identification:** Botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. A new botanical drug (containing multiple chemical constituents) may qualify as a new chemical entity. Both purification and identification of the active ingredients in botanicals are optional and not required. In the initial stage of clinical studies of a botanical drug, it is generally not necessary to identify the active constituents or other biological markers or to have a chemical identification and assay for a particular constituent or marker. Identification by spectroscopic and/or chromatographic fingerprinting and strength by dry weight (weight minus water or solvents) can be acceptable alternatives.

**Test and control:** Because of the complex nature of a typical botanical drug and the lack of knowledge of its active constituent(s), FDA may rely on a combination of tests and controls to ensure the identity, purity, quality, strength, potency, and consistency of botanical drugs. These tests and controls include (1) multiple tests for drug substance and drug product (e.g., spectroscopic and/or chromatographic fingerprints, chemical assay of characteristic markers, and biological assay), (2) raw material and process controls (e.g., strict quality

controls for the botanical raw materials and adequate in-process controls), and (3) process validation (especially for the drug substance).

**Raw material and environmental issue:** Because the botanical drug products are allowed to remain as complex mixtures, quality consistency is a more complicated issue than that of non-botanicals. Plant materials used in the production of botanical drug products often are not completely characterized and defined or are prone to contamination, deterioration, and variation in composition and properties. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, in contrast to the situation with synthetic or highly purified drug products, it may be difficult to ensure the quality of a botanical drug by controlling only the corresponding drug substance and drug product. To ensure that a botanical drug product used in clinical trials is of consistently good quality, and that sufficient information exists to meet the requirements, the sponsor should have, in addition to final product testing, appropriate quality controls for the botanical raw materials. It became necessary to extend the control of botanical drug substance and product to that of botanical raw material, and in some cases, to the agricultural aspects of growing/harvesting medicinal plants by following Good Agricultural and Good Collection Practice (GAP and GCP) for starting materials of herbal origin. FDA encourages early consultation with the Agency on environment-related aspects of a requested action, especially one that involves harvesting a wild species, to ensure that planning and decisions reflect environmental values, avoid delays later in the process, and avoid potential conflicts.

**Bioavailability:** Because there could be more than one active constituent in a botanical drug or the active constituent may not be identified, it could be difficult or impossible to perform standard *in vivo* bioavailability and pharmacokinetic studies. If this is not possible, the bioavailability of a botanical drug could be based on clinical effects observed in well-controlled clinical trials. FDA may, for good cause, waive or defer the *in vivo* bioavailability study requirement if a waiver or deferral is compatible with the protection of the public health.

**IND:** FDA does not require that all studies submitted in an NDA be conducted under an Investigational New Drug Application (IND). Clinical studies need not necessarily be conducted under an IND (i.e., if they are carried out abroad). The clinical data generated from these studies conducted without an IND can be used to support an NDA if the studies were adequately designed and conducted under good clinical practices. However, although an IND is not required by law in all cases, the sponsor is encouraged to go through the IND process.

**Individualized treatments:** In many cases, botanical therapies are highly individualized with variations in relative contents of multiple plant ingredients tailored for each patient. A sponsor may not submit a separate IND for every change in composition, if similar patients are being treated for the same indication. Studies can be designed to take into account individualized treatments. Multiple formulations can be included in one IND if they are being studied under a single clinical trial. It is important that the IND provide the rationale for using multiple formulations and the criteria used to assign patients to different treatment regimens.

**Toxicity:** Many medicinal plants with therapeutical potential are quite toxic. Well-known examples of safety issues concerning botanicals include the nephrotoxicity associated with herbal preparations containing aristolochic acid and the hepatotoxicity associated with comfrey products containing pyrrolizidine alkaloid. Other examples include the cardiovascular and central nervous system effects associated with yohimbe and the hepatotoxicity associated with germander and chaparral. When the potential benefit of an investigational drug outweighs its risk in the intended patient population, clinical trials may be allowed to proceed under an IND.

**Prior human experience:** The Guidance also stipulates that because many botanicals have been used as medicine in alternative medical systems for long time, the prior human experiences may substitute for animal toxicology studies in the preliminary safety evaluation of IND studies. How these human data, mostly not of modern scientific quality, can be useful to support an NDA application was not clearly described in the Guidance. The Agency recognizes that prior human experience with a botanical product can be documented in many different forms and sources, some of which may not meet the quality standards of modern scientific testing. The sponsor is encouraged to provide as much data as possible, and the review team for the botanical drug IND generally will accept all available information for regulatory consideration. FDA will assess the quality of the submitted data on a case-by-case basis. It should be emphasized that, in reviewing botanical drugs, the Agency does not lower or raise the safety and efficacy standards for marketing approval that apply to purified chemical drugs.

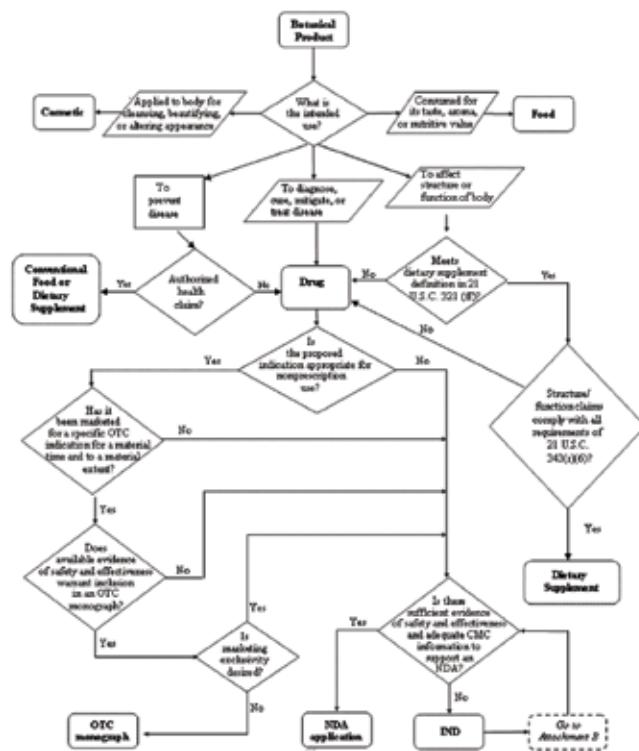
**Priority:** FDA treats botanical and purified chemical drugs the same. FDA will assign the same level of priority to botanical drug products as to other drugs with respect to meeting with IND sponsors and NDA applicants. For clinical data to support marketing approval, there should be no difference between botanical and non-botanical drugs.

The Guidance also provides two flow charts for: 1) the

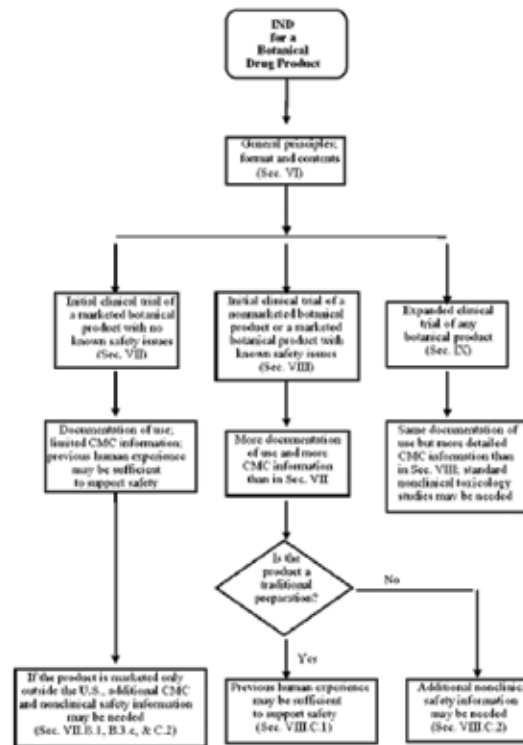
regulatory approaches for marketing botanical drug products, and 2) the information to be provided in an IND for a botanical drug. The two flow charts are attached in this paper also to elucidate the process of the new policy.

With the release of the FDA new guidance and approval of first botanical drug, more and more botanical drugs are predicted to be developed and get into the approval process. In the near future, the botanical drugs will be accepted by mainstream medical field as a big family in drug chest. The competition in drug industry will be tighter.

**Attachment A: Regulatory approaches for marketing botanical drug products**



**Attachment B: Information to be provided in an IND for a botanical drug**



**Conclusions**

Chinese Traditional Medicines work well for centuries. The interest in using them is growing, and the research on them is increasing. The West's narrow scientific approach used to miss the point of the ancient practices, and hurdles the CTM acceptable in mainstream. The FDA's old regulations on drug have some limitations and are not appropriate to regulate CTM as drugs. The FDA's recent release of new guidance and approval of first botanical drug brings a significant impact in drug industry. More botanical drugs and tighter competition are expected. There is a potential role for some complementary medicine and natural health products in preparing us to meet the challenges of the 21<sup>st</sup> century.

**Acknowledgement**

A great gratitude is to Alex Wu for his valuable discussion and nice share of his knowledge.

**References**

1. Yang, P. Chinese Traditional Medicine: the Status and FDA Regulations in USA. *Trend in BioPharm. Ind.* 1:19-25, 2005.

2. Financial Times 6/2/04
3. China Daily 8/31/04
4. Reuters 9/23/04
5. <http://nccam.nih.gov/health/whatisacam>
6. <http://w.fda.gov/bbs/topic/CONSUMER>
7. Walker, L.P. and Brown, E.H. *The Alternative Pharmacy*. Paramus, NJ, Prentice Hall, 1998. pp 3-12.
8. Eisenberg, D. M. J. *Am. Med. Assoc.* 280, 1569-1567, 1998.
9. Vogel, G. Senate hears testimony supporting OAM. *Science* 278: 378, 1997.
10. Fang, H. From Homeopathy to Eastern Medicine. *The New Era Weekly Magazine*, Issue 12, 2007.
11. Website of the Institute for Traditional Medicine and Preventive Health Care, Inc. (ITM): <http://www.itmonline.org/>
12. [http://www7.chinesenewsnet.com/gb/MainNews/Soc-Digest/Health/2004\\_10\\_21\\_11\\_14\\_12\\_958.html](http://www7.chinesenewsnet.com/gb/MainNews/Soc-Digest/Health/2004_10_21_11_14_12_958.html)
13. Website of the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) <http://www.nccaom.org/home.htm>
14. Stokstad, E. Stephen Straus's impossible job. *Science* 288: 1568-1570, 2000.
15. Simon Elegant. Herbal Healing. *Time*, 159 (22)7, 2002.
16. <http://ntp-server.niehs.nih.gov>
17. Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *Journal of the American Medical Association.* 2002; 287(3):337-344.
18. Marshall, E. Bastions of traditional adapt to alternative medicine. *Science* 288:1571-1572, 2000.
19. Koop, C. E. The future of medicine. *Science* 295: 233, 2002.
20. Greenwald, J. A new breed of healers. *Time*, 157(16), 8, 2001.
21. Couzin, J. Beefed-up NIH center probes unconventional therapies. *Science* 282: 2175-2176, 1998.
22. Taub, A. Thumbs down on acupuncture. *Science* 279: 5348, 1998.
23. Check, E. Alternative therapies leave US commission divided. *Nature* 416: 355, 2002.
24. Jiande Gu, Kaixian Chen, Hualiang Jiang, Jezzy Leszczynski. The Radical Transformation in Artemisinin: A DFT Study. *J. Phys. Chem. A.* 1999, 103.
25. Marshall, E. Reinventing an ancient cure for malaria. *Science* 290:437-439, 2000.
26. Lai, H. and Singh, N.P. Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. *Cancer Letters* 91:41-46, 1995.
27. Moore, J.C., Lai, H., Li, J.R., Ren, R.L., McDougall, J.A., Singh, N.P. and Chou, C.K. Oral administrations of dihydroartemisinin and ferrous sulfate retarded growth of implanted fibrosarcoma in the rat. *Cancer Letters* 98:83-87, 1995.
28. Singh, N.P. and Lai, H. Selective toxicity of dehydroartemisinin and holotransferrin on human breast cancer cells. *Life Sciences* 70:49-56, 2001.
29. Singh N.P. and Lai, H. Selective toxicity of artemisinin on human breast cancer cells in culture. *Third World Conference on Breast Cancer*. June 4-8, 2002, Victoria, B.C., Canada.
30. <http://www.oneworldhealth.org/media/details.php?prID=161>.
31. Panos, C. P. Winning the drugs war. *Nature* 430: 942-943, 2002.
32. <http://nccam.nih.gov/health/alerts/bioterrorism/>.
33. KTSF Channel 26 TV interview with Professor Qi Wu (American College of Traditional Chinese Medicine) at 17:00 on 11/15/2003.
34. BBC 9/29/04
35. Lesney, M. Nature's pharmaceuticals. *Today's Chemist at Work* 7:27-32, 2004.
36. Peterson, F. Natural product scaffolds as starting points for drug discovery. 2004 ACS symposium.
37. <http://nccam.nih.gov/clinicaltrials/factsheet/index.htm>.
38. BBC 6/23/04
39. <http://www.nccam.nih.gov/health/supplement-safety/>.
40. Greensfelder, L. Herbal product linked to cancer. *Science* 288: 1946, 2000.
41. <http://www.nccam.nih.gov/health/bottle/>.
42. <http://nccam.nih.gov/health/decisions/index.htm>.
43. Wall Street Journal, 3/10/2007.
44. Botanical Drug Review on application number 21-902 by Center for Drug Evaluation and Research. 9/15/2006.
45. Botanical Drug Products, Guidance for Industry. June 2004.