Botanical Drugs: The Next New New Thing?

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Abstract

While herbal medicines hold great promises for treating diseases, they also have serious limitation in their current forms. Currently the regulatory scheme for herbal medicines in the United States is inadequate and it undercuts the incentives for American industry to develop drug products from herbal medicines. This paper argues that FDA should develop a drug model for herbal medicines. This will help both to mainstream herbal medicines in the United States, and to alleviate the production crisis that the American pharmaceutical industry is facing. This paper also assesses FDA's new Draft Guidance for Botanical Drug Products for its incentivizing effects on the industry.

Introduction

In the past few years, herbal medicines have attracted strong attention in the United States and worldwide, as part of a larger fascination with natural products. This paper explores the future of herbal medicines in the United States and seeks to make the case that botanical drugs, as a new drug model for herbal medicines, will lend much-needed arsenal in the perennial fight against human diseases.

The current regulatory state of affair regarding herbal medicines is sub-optimal as it fails to spur rigorous research and development efforts into herbal medicines. Due to the unfavorable regulatory climate, few US companies are engaged in developing drug products from herbal medicines. FDA ought to promote industry efforts in exploring herbal medicines by approving botanical drugs with substantially lower standard. Such policy will benefit both consumers and the pharmaceutical industry suffering a "dry spell" in conventional drug development.

The first section of this paper illustrates the huge market potential for herbal medicines within the United States and globally. It points out that this market potential could be curtailed by lack of standardization and scientific validation for many herbal medicines. The second section examines the crisis the American pharmaceutical industry is facing and the limitation of the conventional "silver bullet" approach in drug development. The third section contends that developing botanical drugs from herbal medicines can bring the better of the two worlds together. It promises to alleviate the "dry spell" the pharmaceutical industry is facing, and bring more effective medicines to patients at faster rate. The fourth section examines the current regulatory climate and points to the disincentive effect of the current regulations. Rationales for adopting a lower standard for botanical drug approval are discussed. The last section assesses The Draft Guidance for the Industry: Botanical Drug Products (Hereinafter "Draft Guidance"), released by FDA in August 2000, for its incentives on industry efforts in the field of developing drug models for herbal medicines. Finally, this paper proposes further changes to be adopted in the final Guidance.

I.

The Market: US and Worldwide

The projected market size for herbal medicine in the market worldwide is staggering. One study estimates the global market at about 18 to 20 billion US dollars in 1997.[2] Among these, Asia dominates as the largest market at about 40% share, Europe follows at 35%, and North America accounts for about 17%.[3]

The America market is equally promising. Partially fueled by the passage of the Dietary Supplement Health and Education Act (DSHEA), the US market has seen a rise in the sales of herbal products in the form of dietary supplements from 3.3 billion to 6.5 billion between 1990 and 1996.[4] The rise in the sale of these products can be directly attributed to the increase of people using herbs. Within a short span of seven years from 1991 to 1998, the percentage of the American population using herbs increased from a bare 4% to a significant 30-35% in 1998.[5]

In spite of the staggering growth, the US market still has plenty of room to grow. As America is late to catch the trend of consuming herbal products, other nations' consumption patterns may shed light on the direction of the US market. For instance, over 60% of the population in Germany, and 80-90% of the population in China and uses herbs regularly.[6] By inference, the US market is still capable of expanding to reach another 30 or 40% of the population, making US an enticing market given the consumption power of the US consumers.

The simple logical inference, however, may not stand. Many factors, including cultural, traditional and infrastructural ones, contribute to consumers' purchase choices in medicines. Take China as example, using plant-derived remedies to treat diseases is part of its national cultural heritage. The practice of traditional Chinese medicine dates back to as early as 2800 B.C., as documented in the "Herbal Classic of the Divine Plowman" (Sheng Nung Ben Cao Chien).[7] As an indication of the prevalence of traditional Chinese medicine (TCM), China now boasts more than 2500 TCM hospitals, 30 universities and colleges engaging in the studies of TCM.[8] Chinese government, consumers and medical professionals hold TCM and western medical science at equal status. Given the tradition and the supportive infrastructures in place, it comes as no surprise that 80-90% of the Chines population use herbs on a regular basis.

US, on the other hand, is a study in stark contrast. The faith in FDA-approved prescription drug and OTC drugs is deeply ingrained in US consumers. On the one hand, the medical profession, conservative by training, is understandably reluctant to embrace herbal medicine. On the other hand, the practice of herbal medicine such as traditional Chinese medicine, remains largely confined to China towns in large coastal cities in the US. As a result, while many consumers recognize the merits of herbal medicine, the American mainstream remains ambivalent about the efficacy of herbal medicines. Such ambivalence makes further expansion of the herbal medicine market in US a questionable prospect.

The growth trend of the US dietary supplement market to date seems to vindicate this concern. After the astonishing growth from 1994 to 1997, the US market for dietary supplements has leveled off in 1998, and there may even be a lessening in demand.[9] The shift in trend is fueled partly by a hostile press hot on the pursuit of fraudulent manufacturers, partly by the long-held western perception that these herbal medicines are in the league of quackery. This plateau in sales growth highlights the concern about the sustainability of herbal medicines in their traditional form in the US market.

While the flattening growth leaves the future of the dietary supplement industry uncertain, it presents an unique opportunity for American pharmaceutical companies, who so far have largely stayed off the market of herbal medicine supplies. The opportunity lies in developing botanical drugs, an approach that combines the merits of advanced western technology with the empirical-based century-old herbal medicine knowledge.

A clarification of terminology is due here. A botanical drug, as defined by FDA in its Draft Guidance, is a botanical product that is prepared from a botanical drug substance, and is intended for use as a drug. A conventional FDA-approved drug has a single well-characterized active ingredient. In contrast, a botanical drug, by definition, comes in forms of extracts that are composed of multiple chemical constituents.

The development of botanical drugs, given the right regulatory climate, will allow American pharmaceutical companies to capitalize on the existing market for herbal medicines, both US and worldwide, and to expand and reach those consumers traditionally suspicious of herbal medicines.

II.

Crisis in Conventional Drug Discovery

The American pharmaceutical industry is currently in the midst of a productivity crisis. To better understand the plight of pharmaceutical companies, it is necessary to briefly recap the drug approval process for a new chemical entity (NCE) drug.

Conventional FDA Drug Approval Process

Before starting human clinical trials in the United States, a company must file an investigational new drug (IND) application with the FDA. FDA has 30 days to intervene. If FDA fails to intervene within the 30 days, the company may proceed with testing. The tests are divided into three phases. In the Phase I clinical trial, companies test for safety on twenty to eighty healthy volunteers. Before administrating the drug to volunteers, companies need to supply preclinical data, including pharmacological and toxicological data, which are subject to the review by clinical pharmacologists. If the data are deemed satisfactory, the drug is then administrated to the volunteers. In the Phase II, companies test for efficacy of the drug in 100-300 patients under different dosages. The Phase III calls for extensive trials on hundreds or even thousands of patients. Usually at least two adequate and well-controlled Phase III studies are required. The objective is to establish proof of efficacy and acceptable side effects. If the drug remains promising after all three phases, then the company submits to FDA clinical, pharmacological and toxicological data in the form of a new drug application (NDA). Currently, it takes FDA on average 2 to 3 years to evaluate and approve a NDA.[10]

Drying Drug Pipelines

The American pharmaceutical industry is in the midst of a productivity crisis. Jean-Pierre Garnier, the chief executive of GlaxoSmithKline recently lamented that "We don't have enough in our collective pipelines".[11] Apparently, this is not a problem limited to the isolated few, but one that plagued the pharmaceutical industry across the board. In 2000, the Wall Street Journal reported that since 1996, the production of breakthrough drugs has steadily declined.[12] In 1996, there were 53 new FDA-approved drugs. The number went down to 35 in 1999, and 16 through the first half of 2000.[13] Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development, summed it up: "...these [pharmaceutical] firms will need to put out at least three or four new chemical entities per year [to sustain growth rates] and there's no firm right now doing anything more than one per year. It is a very tenuous time for the pharmaceutical industry."[14]

More recent news confirmed that the trouble continues for large pharmaceutical companies. Merck, Bristol-Myers Squibb, Schering-Plough and Eli Lily have all recently issued warnings on their prospective earnings.[15] Patent expiration of their major drugs, combined with the lack of new drugs led to the earning woes.[16] As patents continue to expire and no new drugs on the horizon, the prospect of a recovery in productivity is slim.

Worse than the decline in productivity is how these pharmaceutical companies responded. Rather than beefing up research, a Wall Street Journal article reported, "the pharmaceutical industry is gradually shifting the core of its businesses away from the unpredictable and increasingly expensive task of creating drugs and toward the steadier business of marketing them."[17] While this strategy is working in the short term to boost the bottom line, it will not solve the productivity problem in the long run. Ultimately, patients will suffer, and the society at large will pay through increased medical expenses for patient care.

The costly FDA approval process adds further salt to the injury. Bringing a single new chemical entity (NCE) drug to market now takes 10-15 years on average, and costs over 800 million dollars, exceeding the gross national product of some nations.[18] Moreover, this cost is steadily rising at the rate of 6% annually.

A significant portion of the cost comes from candidate attrition during the clinical stage of the FDA approval process.[19] For every five to six drug candidates that reach Investigational New Drug (IND) status, only one lucky star survives to become a product.[20] To illustrate the point from a different angle, pharmaceutical companies will typically market only roughly one out of a hundred of their patented products.[21] The skyrocketing costs of the R&D costs have translated directly into soaring price tags for prescription drugs. As a Wall Street Journal article observed, drugs "commonly [cost] no more than $2 a pill a few years ago. The new-generation drugs cost $4, $11, even $15 per pill". [22]

Lost faith in "Silver Bullets"

The current crisis in new drug discovery highlights the limitation of conventional "silver bullet" view of drugs. The traditional belief in "silver bullets", a single drug that takes care of a single disease, rests on a critical premise that human diseases have a uniform underlying genetic basis across patients populations. Typically, a "silver bullet" drug is a new chemical entity (NCE) drug with a single active chemical ingredient. While there have been blockbuster "silver bullets" like Amgen's EPO and Eli Lily's Prozac, the hope in new blockbuster drugs has been waning. Recent advances in genomics vindicate this pessimism. It now appears that diverse genetic changes often underline a single disease, a phenomenon termed "polymorphism". Thus different patient populations may require different drugs tailored to their needs. The polymorphic nature of diseases suggests an individualized approach in drug design is more likely to succeed.[23]

In sum, the American pharmaceutical industry is in a "terrible trough".[24] There is a dire need to find a complementary way to supplant their current approach toward drug discovery. Some pin their hopes on the advent of genomics and the complete sequences of human genome. While genomic knowledge will undoubtedly offer new insights into the human diseases, most experts in genomics think that significant drug discoveries based on genomics are still years away.[25] Given the heightened interest in herbal medicines in the United States and worldwide, developing botanical drugs based on herbal medicines may be the booster shot that the industry badly needs.

III.

Botanical Drugs: A Marriage Between Herbal Medicines and Western Drug Development

What Herbal Medicines Offer

Herbal medicines offer hope to alleviate the current crisis in the conventional drug development. It is important to stress here that herbal medicines will not be "alternative", in the sense that it will replace conventional drugs. But rather, they will be "complementary" to the conventional drug discovery. At least three reasons explain why herbal medicines may offer the perfect complement to the ailing conventional drug discovery.

First, capitalizing on herbal medicine knowledge may give rise to a cheaper and faster way to drug discovery. Typically, drug discovery starts with screening millions of chemicals against biological targets using cell-based assays in laboratories. Promising chemicals ("leads") are then tested in animal disease models. Candidates that survive the animal testing then move on to expensive clinical trials. As already mentioned, only a small percentage of these candidates survive the ordeal of clinical trials to become a product, often due to unforeseen side effects, or lack of efficacy in human subjects. Lack of link between pharmacological activity against targets and clinical effectiveness is the principal culprit for the later high attrition rate at later clinical stage. The problem lies in the risky practice of using laboratory screening and animal disease models to predict therapeutic efficacy in human. As it turns out, the lab screening and animal models often have "inadequate predictive power".[26]

Capitalizing on herbal medicine knowledge may lead a way out of this costly dilemma. Briefly, botanical extracts can be directly evaluated for clinical efficacy first rather than subjected to initial chemical isolation first. This releases drug discovery from absolute reliance on laboratory screens and enables the development of drugs for poorly understood diseases that lack laboratory screening methods and animal models. These products can then be developed either as botanical drugs - standardized, heterogeneous mixtures - or as purified single-chemical entity drugs.

A new drug development paradigm, neutraceuticals, championed by Pfizer, seeks to accomplish this end. At an international conference on traditional Chinese medicine, Pfizer's representative described this new paradigm:

> "The development paradigm for naturalceuticals differs from the established pharmaceutical strategy in that it seeks up front to rapidly address clinical efficacy with candidates having anecdotal or folklore histories of use in humans, before investing in costly, time-consuming R&D work.... Opportunities with proven clinical efficacy may become fully invested for the costly process..... While this approach appears to turn conventional R&D on its head, it only acknowledges the way drugs were discovered once upon a time."[27]

Indeed, developing drugs from plants are not new to American pharmaceutical companies. Taxol, Aspirin, Menthol, Morphine, just to name a few, are examples of single-ingredient drugs derived from plants. What is new is taking advantage of the traditional knowledge in herbal medicines to give the drug development process a head start.

Second, herbal medicines offers a holistic approach to complement a pure reductionism approach toward diseases, namely, the "silver bullet" approach. The drug industry often prizes itself for its scientific and reductionism approach toward drug development. But the history shows that many blockbuster drugs came not necessarily as a result of impeccable R&D, but as a result of lucky breaks. For example, the initial discovery of Viagra came from a surprising "side effect" in clinical trials designed for heart conditions.[28] The upshot is that merits of the reductionism approach may be greatly exaggerated to the exclusion of other useful approaches.

In contrast to the "silver bullet" approach, herbal medicines often integrate preventative measures with curative measures. For example, traditional Chinese medicine recipes typically contain multiple herbs. While one herb alleviates disease directly, the others may work by promoting general well being of the body to boost its defense abilities. Such a strategy indeed makes sense in view of the modern knowledge of how our immune system works. Modern medicine informs us that by boosting our immune systems, we can help our bodies to fight diseases.

Tied to the holistic approach is the third advantage of herbal medicines, namely, synergism among different components. While the mechanism of most herbal medicines remains elusive, it appears that synergy among different elements can be an important part of their overall medicinal effects. Indeed, laboratory studies have demonstrated the existence of such synergy at the molecular level for some traditional Chinese medicine. For example, researchers from University of Maryland reported that an extract from the roots of a Chinese medicinal herb was found to have antibacterial synergy.[29] Such synergistic action may confer a unique advantage, especially in dealing with complex diseases with polymorphic nature that are recalcitrant to the conventional single chemical entity drugs. To this end, many traditional formulas have been reported to exhibit activity against asthma, metabolic diseases, pain, depression, infectious diseases including AIDS and cancer.[30] The claims for treating cancer has been supported by findings at National Institute of Health (NIH). Researchers at National Products Branch at the National Institute of Health (NIH) reported that Camptothecin (CPT) isolated from extracts prepared from the barks of a Chinese medicinal tree, showed broad-spectrum anti-tumor activity.[31] In fact, Pharmacia Upjohn is producing and marketing a CPT analog, CPT-11, under the trade name of camptosar or irnnotecan.[32] There are additionally over 130 clinical trials involving

Advocating for botanical drugs based on herbal medicine knowledge necessarily begs the question: are the underlying herbal medicine claims valid? As herbal medicines encompass a formidable range of medicines from vastly different sources, this section examines only the validity of traditional Chinese medicine. It is important to stress, however, that the regulatory issues discussed in this paper should be generally applicable to any herbal medicines that are comparably supported by empirical data as traditional Chinese medicine.

The prevalence of traditional Chinese medicine in China in this day of age at least suggests its effectiveness. In China, where western drugs are widely available and relatively affordable in major cities,[34] a recent survey reveals that a majority of consumers view traditional Chinese medicine as equally or more effective than western drugs.[35] The perception is not surprising. Long history of trial-and-error practice and documentation have accumulated a wealth of empirical knowledge and clinical data about the effects of herbs on diseases and their associated side effects.

While prevalence at best builds a circumstantial case for the validity of TCM claims, pharmacological and/or clinical studies performed in the west supply direct evidence.

To this end, a weighty piece of evidence came from a recent controversy involving Merck, a pharmaceutical powerhouse, and Pharmanex, a California-based dietary supplement manufacturer. In this case, Cholestin, a dietary supplement based on traditional Chinese medicine knowledge turns out to contain the same active ingredient as Mevacor, Merck's FDA-approved prescription drug.[36] Red yeast rice, traditionally prepared by fermenting non-glutinous rice with red yeast, has long been known for its cholesterol-lowering ability. Indeed, the classical book on TCM, Ben Cao Gang Mu (Compendium of Materia Medica, 1578 A.D.) describes it as "invigorate spleen, digestion, and promote blood circulation and resolve blood stasis."[37] Pharmanex developed a red yeast rice extract and marketed under the name "Cholestin". It turned out, that Cholestin contains a natural substance, mevinolin, which is chemically identical to the active ingredient, lovastatin, in the prescription drug, Mevacor. Coincidentally, Mevacor, was developed and marketed by Merck for the treatment of high cholesterol and heart disease.[38] The story illustrates that ancient empirical-based traditional Chinese medicine knowledge and costly state-of-the-art western pharmaceutical research can converge.

The validity of traditional Chinese medicine is not limited to this single drama. In fact, laboratory

The flip Side: What Western Drug Development Process Offers Herbal Medicine

While herbal medicines offer hope for drug development, the argument is equally compelling that herbal medicines need the injection of rigorous clinical validation and pharmacological studies. On its own, herbal medicines have slim hope of entering the mainstream of healthcare in the United States. This is because herbal medicines in their traditional forms suffer a myriad of deficits. Just to name a few: the heavy reliance on anecdotal data, the lack of randomized controlled clinical data to substantiate the claims, overly broad and often vague claims, the lack of quality assurance, and an unfounded panacea "cure all" belief.[42] These deficits, if not dealt with properly, will continue to undermine the legitimacy of herbal medicine. Subjecting herbal medicines to standardized manufacturing practice and well-controlled clinical trials will help overcome these deficits. Developing a drug model for herbal medicines is thus essential in establishing the true value of herbal medicines and their credibility in the eyes of American consumers.

In sum, it appears that the tradition-based herbal medicines and the science-based western drug development regime have something to offer each other. The concept of botanical drugs has the potential to culminate these mutual benefits.

It would be simplistic and presumptuous, however, to view botanical drugs as the answer to all problems. In fact, there are many challenges for developing botanical drugs. For example, technical issues are abundant for developing herbal extracts with batch-to-batch quality consistency. As the endeavor is largely unprecedented, there is no ready protocol to follow. Consequently, companies will need to invent the wheels as they go along, presenting a risky business model from the perspective of venture capital investors.

Furthermore, while botanical drugs promise to lower the cost of drug R&D, the cost may still be prohibitive for most players except the big powerhouses in the field. Considering that the current price tag for a new FDA-approved drug is $800 million, an arbitrary $\frac{3}{4}$ reduction still leaves the price tag at a whopping $200 million. To make the matter worse, the initial stage of botanical drug development necessarily entails experimentation with new protocols and standardization issues, posing a higher entry cost that might prevent new entrants into the field.

Taken together, the idea of botanical drugs promises to capture the best of both worlds. But putting this idea to practice will not be automatic and effortless. There is thus a need for adequate regulatory climate to spur industry efforts in this direction. The question then becomes, is the current regulatory structure adequate to accomplish this goal? Are there any industrial efforts in this direction? What can be done to promote industrial efforts in the United States?

IV.

Current Regulatory Climate and Its Ramifications

DSHEA and its Impact

In 1994, in response to immense political pressure, the Congress enacted the Dietary Supplement Health and Education Act (DSHEA). Under DSHEA, medicinal herbs can be marketed as dietary supplements without prior FDA approval. The supplements may carry "structure/function" claims – claims that a product may affect the structure or functioning of the body – but not claims that they can treat, diagnose, cure or prevent a disease.

By offering low market entry cost, DSHEA succeeded in making herbal medicines widely available by offering low market entry cost. But low market entry cost turned out to be a double-edged sword. By setting a bare minimum regulatory standard, DSHEA failed to remediate the fallacies associated with herbal medicines enumerated in the last Section. Three reasons underlie the failures of DSHEA to make safe and high quality herbal medicines available to consumers who need them.

First, the lack of FDA approval requirement for marketing dietary supplement means no incentive to conduct any substantive research and development on products. In fact, an "anything goes" mentality pervades this new cottage industry. Manufacturers are largely free to experiment with traditional herbs. As one commentator noted: Manufacturers often combine traditional herbs "with other herbs to make new, non-traditional products, use non-traditional but more cost-effective preparation techniques, promote traditional herbs for non-traditional purposes, and put them in a more consumer-friendly yet non-traditional form. This experimentation eliminates whatever safeguards and level of effectiveness traditional use offers."[43] On top of it, tremendous price pressure leads to a "race to the bottom" in terms of qualities of dietary supplements in the market.

As a result, consumers come to associate questionable effectiveness and harmful side effects with dietary supplements. In turn, this serves to reinforce the old distrust for traditional herbal medicines, and undermines consumer confidence in herbal medicines. The downturn in the market for dietary supplement seems to vindicate this concern.

Second, unsupervised herbal use poses health and safety threats. Many people now use traditional medicine without informing their physicians, falsely believing that herbal medicines, unlike western synthetic medicines, have no side effects and no harmful interaction with prescription or OTC drugs.

Third, the requirement that dietary supplements are not permitted to make disease claims prevents the dissemination of potentially useful information. Ironically, as long as they do not claim treating diseases, manufacturers are allowed to make unsubstantiated claims on their products, fueling further safety concerns.

The deleterious effect of DSHEA is further amplified by its disincentivizing effect on companies who engage in serious research and development efforts to explore the value of traditional medicines. To illustrate, consider a firm making herbal medicines. To market in the United States, it is faced with two options. First, it can market them as dietary supplements. Given the de minimis regulation in this area, this option appears attractive. Second, if the firm wants to get the imprimatur of FDA on its product, its only option, at least for the time being, is to develop a new single-chemical-entity drug from herbs and complete the costly drug approval process. To date, FDA has never approved a single drug in extract form. Given the two options, it makes every business sense to go with the dietary supplement route. Its entry cost is low, and it promises quick bucks. The drug route pales in comparison. It requires large up front investment, and the chance for return remains highly uncertain. The potential return for drugs developed from herbs is directly threatened by dietary supplement free riders. As mentioned above, notwithstanding the potential cost-cutting benefit herbal medicines may provide, a drug company still needs to invest substantial amount of money to develop a FDA-approved drug from herbs. As the drug gets the nod from FDA and gets on the market, it may find itself competing head on with a dietary supplement containing the same active ingredient. Given the low entry cost of the dietary supplement industry, and the abundance of dietary supplement companies already in the United States (numbered between 2000 and 3000), this scenario will not be an infrequent event. Spared of R&D expenses, these free riders will be able to sell their products at a significant lower price. Compounded with pressures from managed health care providers to cut drug costs, patients are more likely to purchase the cheap substitutes, especially given the added lure of a "natural product". This nightmarish scenario for pharmaceutical companies has recently been mitigated by the Pharmanex decision. In this case, the 10^{th} Circuit Court recognized that disincentive effect of the DSHEA for drug development. The Pharmanex decision stands for the proposition that a company will be barred from marketing a dietary supplement containing a natural substance that is the active ingredient in a *previously* approved drug product.[49] The bar does not reach, however, those companies that marketed the same natural substance as a dietary supplement *prior to* approval of the new drug. Given the long and drawn out FDA drug approval process, "enterprising" businesses have ample opportunities to jump on the bandwagon and hitch a free ride anytime prior to a drug's final approval.

The Danger: American Companies Losing Competitive Advantages in Developing Botanical Drugs?

Given the unfavorable regulatory climate, it is no surprise that there are only a handful of US companies in the field of developing botanical drugs through the conventional IND/NDA route.[46] Six US companies claim to be in the business of developing botanical drugs, including Ancile Pharmaceuticals, Pharmanex, Phytomedics, Pharmaprint Botanical Pharmaceuticals, Andes Pharmaceuticals and Phytoceutica. As an indication of lack of serious industrial efforts in this area, all six companies are small start-up companies. For example, Ancile Pharmaceuticals, based in California, employs 30 professionals.[47] Similarly, Phytomedics, Inc., a New Jersey-based company, has a small R&D staff of 20 scientists.[48] Among these companies, only Ancile and Phytomedics have progressed into clinical trial stage. As of April 2001, Ancile has three allowed IND applications filed with the FDA. In December 2000, Ancile successfully completed a double blind, placebo-controlled Phase 2 trial for ANPH 101, a drug product intended for sleep disorders.[49] Phytoceuticals, a New Haven based company, cleared its IND application for one of its drug products for modulating chemotherapy in August 2001. Phase 1 and 2 clinical trials are currently under way.[50] Others, like Phytomedics, are still in the early stage of drug development of lead identification. For Pharmanex and Pharmaprint Botanical Pharmaceuticals, botanical drug development through the IND/NDA route remains no more than a grand vision. Instead, the primary business of these two companies is currently dedicated to marketing dietary supplements.[51]

Ostensibly missing from the scene are major pharmaceutical powerhouses, with Pfizer as the only exception. In the absence of major pharmaceutical players, large-scale investment in this area seems unlikely.

On the other hand, foreign firms are eager for a slice of the US botanical drug market. In fact, foreign firms have already got a head start in the game. For example, Phytopharm, a British botanical pharmaceutical company, has been in the business of botanical drug development for over 11 years.[52] Back in December 1997, Phytopharm cleared its first IND application with the US FDA for its botanical product, Zemaphyte.[53] Subsequently, Phytopharm initiated clinical studies in 20 centers in the US on using Zemaphyte to treat severe ectopic eczema.[54] In addition, in September 2000, Phytopharm announced that it has initiated Phase I clinical evaluation for another botanical product, P58.[55] According to the company news release, "P58 is one of a family of phytochemicals isolated

Similarly, another British pharmaceutical company, Oxford Natural Products, is dedicated to the "development of novel pharmaceuticals and nutraceuticals from plants".[57] As of 2001, the company has three products entering clinical evaluations.[58] Among them, ONP-17, which treats hepatitis-C symptoms, is composed of extracts of traditional Chinese and Western herbs. Chronic hepatitis-C inflicts over 300 million patients worldwide. Not shy about its intention to enter the US market, Oxford Natural Products explicitly points out on its website that in America, hepatitis-C is four times more prevalent than AIDS.[59]

The threat of competition for the US botanical drug market comes not only from European nations. CV Technologies, Inc. (CVT), a Canadian herbal drug developer, has already been engaged in the business of developing nutraceuticals for over 10 years.[60] In October 1999, CVT obtained its first IND clearance with the US FDA for its nutraceutical product, CVT-E002.[61] CVT-E002 is a multicomponent extracts from North American ginseng intended for use as a preventative against acute respiratory infection.[62] In September 2000, CVT announced the successful completion of its first Phase II clinical trial of CVT-E002, and is ready to proceed with a second, much larger Phase II clinical trial.[63] All these trials are open-labeled, double blind and placebo-controlled.

An unusual dominance of foreign entities among commentators on the US FDA's new Draft Guidance gives another glimpse of the eagerness of foreign firms for the American botanical drug market. Among 18 who filed comments to date, only four are American drug companies, nine are foreign industrial entities, representing either individual companies or association of companies (see Table 1). According to Dr.Yuan-yuan Chiu, Director of Office of New Chemistry for Drug Evaluation and Research at FDA, the disparity in responses possibly indicates a disparity between the United States and other nations in the level of activities in the field.[64]

Table 1. Distribution of commentators on the Draft Guidance

Origination	Drug Companies	Others (consulting, governmental agency, trade association)
United States	4	3
Europe	4	0
Asia	2	1
Canada	3	0
Global	1 (Pfizer)	0
Total	14	4

The lack of industrial efforts in the United States, if left unchanged, can potentially cost America its competitive advantage in the global market. The American drug industry is not the only one suffering from the current regulatory regime. As pharmaceutical companies shy away from making effective drugs from herbal medicines, consumers will be deprived of these potentially effective medicines. The massive under regulation of dietary supplements hardly relieves this deprivation, as the market is now flooded with dietary supplements with dubious qualities. This unsatisfactory state of affair calls for changes in regulatory policy.

The Case for Lowering Approval Standards for Botanical Drugs

It is time for FDA to get involved. Americans have grown to trust FDA as the gatekeeper of new drugs. A stamp of approval of herbal medicines from FDA will pave the way for herbal medicines to be accepted by the American mainstream.

A viable alternative is for FDA to alter the current all-or-nothing state of affair: on the one hand the stringent armed-to-the-teeth regulation for new drugs approval, and on the other, no FDA scrutiny for marketing dietary supplements. A balance can be struck somewhere in the middle. FDA could create a new category for botanical drugs, by placing herbal medicines into the FDA approval process but with substantially lower approval standards.

Adopting standards substantially lower than that required for conventional drugs is justified by the fact that many herbal medicines already have extensive prior marketing experience before filing applications with FDA. Take traditional Chinese medicine as an example, four thousand years of trial-and-error medical practice and documentation have reasonably established their safety and effectiveness. Their continuing marketing in China and in other Asian, European nations provide further evidence for their safety.

In fact, many other industrial nations have already adopted similar practice. For example, France permitted the registration of "vegetable drugs" under "an abridged dossier" in 1990. The safety of herbal remedies, "historical proof of their widespread traditional use and their well established use in self-medication" were taken into account.[65] Likewise, in Germany, "bibliographic data on the well established use of herbal medicines are accepted" by the Federal Institute for Drugs and Medical Devices (the German equivalent of the FDA) for determining safety and efficacy of drug products.[66]

Some might think that the FDA drug approval standard should not be tempered with to accommodate a new category of drugs. To the contrary, the conventional drug approval standard for NCE drugs is not set in stone. In fact, FDA has frequently invoked criticism for its stringent approval standard and several reforms have been proposed.[67] Critic called the approval standard overly stringent and unnecessary, that it has "become more stringent than is socially optimal".[68] Studies have found that more stringent drug regulations, spurred by the thalidomide tragedy, have increased the drug development costs by about 6 percent per year in the United States. Consequently, it has cut by half the number of new drugs introduced in the United States relative to other industrialized nations.[69] The FDA is blamed for maintaining a higher than optimal drug approval standard out of fear of political pressures. Approving a nonbeneficial and harmful drug leads to more political backlash for FDA than failing or simply delaying to approve a beneficial drug. As put by one critic, "no official wants to be

V.

FDA Draft Guidance

The FDA Draft Guidance for Industry on Botanical Drug Products, released in August 2000 for public comments, signals a meaningful first step toward a favorable regulatory climate for companies to engage in substantial R&D efforts with herbal medicines.[73] In this document, FDA, for the first time in its history, proposes to approve botanical drugs in extract forms as a new class of drugs.

The Draft Guidance is significant for two reasons. First, it has the potential, if enforced appropriately, to eliminate non-conforming standards and bring about more uniformity in the use of herbal medicine, which is now largely dominated by the chaos of dietary supplements. It will promote safety, quality and efficacy of herbal medicine usage. Second, with the blessing of FDA, herbal medicines, in their reincarnation as botanical drugs, will finally have a real hope of entering the mainstream of healthcare in the United States.

To briefly summarize, the Draft Guidance explains when a botanical drug may be marketed under an over-the-counter (OTC) drug monograph, and when FDA approval of a new drug application is required for marketing. It also provides guidance to sponsors on submitting investigational new drug applications (INDs) for botanical drug products. Recognizing the complexity of botanicals and prior marketing experience with many herbal medicines, the Draft Guidance deems appropriate to enact regulatory policies that differ from those for synthetic, semisynthetic, or otherwise highly purified drugs. In particular, in certain circumstances, prior domestic marketing data is proposed to substitute, either partially or completely, the preclinical data to support an IND for initial clinical studies.

This section will focus on the coverage of the Draft Guidance and new approval standard for botanical drugs. The analysis will take into account relevant public comments submitted to FDA to date.

Scope of Botanical Drugs

The Draft Guidance delineates the scope of botanical drugs quite narrowly. The basic definition of botanical drugs in the Draft Guidance keeps in line with the basic approach of the Food Drug & Cosmetics Act (FDCA), which is to distinguish between food and drug on the basis of intended use. Thus the Draft Guidance defines botanical drugs as "a botanical product that is intended for use as a drug; a drug product that is prepared from a botanical drug substance".[74] From this basic definition, the Draft Guidance explicitly excludes "highly purified or chemically modified substances derived from botanical sources" from the reach of botanical drugs.[75] As a justification for this exclusion, the Draft Guidance explained that once purified, these substances "can readily be fully characterized".[76]

On a first blush, the narrow definition appears to indicate FDA's reluctance to fully embrace herbal medicines, as it stops short of encouraging full-fledged conventional drug development building on herbal medicine knowledge. But there may be other justifications for this approach. For example, the narrow definition may well indicate that FDA has accepted the conventional wisdom of herbal medicine practitioners, that "the whole is greater than the parts". Under the idea of synergism, that multiple components in many herbal extracts work together to alleviate diseases, developing a single-chemical-entity drug from herbal medicine appears not to be advantageous, not to mention the potential side effects resulting from the purified chemicals.

Furthermore, FDA may need to retain a uniform approval standard for new-chemical-entity (NCE) drugs. FDA would not want to discriminate among NCE drugs developed with different methodologies, for example, recombinant biotech drugs, drugs developed using genomic knowledge, versus drugs developed from herbal medicines. Given the current technology complexity in drug development, choosing methodologies is beyond the expertise of a federal bureaucracy like FDA. Thus, it is perhaps wise for FDA not to play favoritism for NCE drugs.

It is interesting to note that some industrial nations have adopted broader conceptions of botanical drugs. For example, in France, herbal medicines are simply defined as medicines that have exclusively plants or plant extracts as active ingredients.[77] Similarly, in Greece, a regulation for herbal medicines, published in 1994 by the Ministry of Health, defined herbal medicines as medicines that contain as active ingredients only plants or preparations of plants.[78] These broader definitions would cover NCE drugs developed from plants. It should be noted, however, that regulations for NCE drugs in these nations are much less stringent than those in the United States. Thus, granting herbal medicine status to NCE drugs derived from botanicals does not amount to a big compromise in the approval standards in France and Greece. To put it another way, the narrow conception of botanical drugs in the Draft Guidance could simply be a function of the highly stringent regulation for conventional drugs imposed by the FDA in the United States. Absent a drastic reform to lower the NCE drug approval standard, bringing in NCE drugs developed from botanicals under the botanical drugs may be too drastic a measure for the FDA.

Makers of new NCE drugs derived from medicinal herbs are thus directly barred from benefiting under the relaxed approval standard. It is unclear, however, what comes within the ambit of "highly purified" and therefore gets excluded from the scope of botanical drugs. The definition section gives no definition to the term "highly purified".[79] As pointed out by the comment from Tibotec Pharmaceuticals Ltd., a Belgium-based pharmaceutical company, the preparation of many herbal extracts entails multiple steps of purification.[80] Would the herbal extracts prepared this way satisfy the "highly purified" standard in the Draft Guidance and thus not a botanical drug for the purpose of the Guidance? Such a construction is unlikely as it directly conflicts with the basic premise of the Draft Guidance, which is to grant new drug status to botanical extracts. The final Guidance should clarify that the term "highly purified" is limited to drugs with single active chemical ingredient purified from botanicals.

Regulatory Carrots: Games of Gives and Takes

The Draft Guidance highlights three main benefits for botanical drug developers. In general, the NDA route for botanical drugs espoused by the Draft Guidance parallels closely the route for a NCE drug.

The foremost benefit is the recognition of prior human use as supporting data in the initial stages of clinical trials. For botanical products legally marketed in the United States with no known safety issues, the Chemistry, Manufacturing and Control (CMC) and animal toxicology data may be "markedly reduced" for initial clinical studies.[81] Indeed, the Draft Guidance points out that "in most cases, additional toxicology and CMC data will not be required".[82] But not all prior human use data are treated equally. Botanical products that have been previously marketed only in foreign markets need to supply more information to initiate clinical phase I and II. Decisions as to the nature of information needed for these products will be determined on a case-by-case basis.[83] At the other extreme of the spectrum, those botanical products that have not been legally marketed anywhere or have known safety issues are subject to the same standard as their NCE counterparts.

This benefit, however, stops at Phase III. Here the Draft Guidance turns a sudden blind eye to the fact that high quality human safety data is available for many botanical products. Botanical drugs are held to the same high standard as a NCE drug for the purpose of Phase III clinical. Manufacturers will have to supply the whole gamut of full non-clinical toxicology program, full clinical program and equivalent CMC data. As one commentator pointed out, the reservation here highlights the general difficulty to alter "institutional thinking" at FDA.[84] The reservation here gives the Draft Guidance a schizophrenic character and seriously undermines the benefits granted to botanical drugs. The next section will discuss more about its effect on incentives for botanical drug makers.

Second, the Draft Guidance indicates that applicants for a botanical drug may not need to identify its active constituents during the IND stage or in an NDA submission if identification "is shown to be infeasible".[85] More importantly, the Draft Guidance acknowledges broadly that in many cases of botanical drugs, neither the active ingredient nor its biological activity is well characterized.[86] This acknowledgement is likely to figure into the case-by-case approval review process and tip the scale further to favor approving botanical drugs under a reduced standard.

The problem with this regulatory carrot, however, is that it is tethered to an ambiguous "infeasible" standard. Several comments raised this objection. Consumer Healthcare products Association suggested that FDA not to "leave open-ended statements" that can lead to inconsistent interpretations.[87] Phytopharm, a UK-based pharmaceutical company requested that the final guidance clarify the issue by including examples of botanical drugs that satisfy the burden of demonstrating infeasiblity.[88]

Thirdly, a less articulated but nonetheless valuable benefit is the exemption from the combination drug regulations.[89] By definition, botanical drugs are combinations of multiple components, and sometimes, multiple active ingredients. Under the combination drug regulations, the maker of a fixed-combination drug would have to demonstrate that each component or active ingredient contributes to the claimed therapeutic effects. Imposing such a requirement on botanical drugs would mean practical death for these drugs. Thus, an exemption from the requirement is valuable.

The exemption is limited, however, to botanical drug products that are derived from a single part of a plant, say leaves, stems, roots or seeds, or from an alga or macroscopic fungus.[90] Botanical drug products that are composed of multiple parts of a single plant, or of parts from different plants, are not within the exemption. Thus, these drugs will still have to comply with the combination drug requirement. FDA, however, does not completely shut the door. A ray of hope remains as FDA indicated its intention to exempt this group of botanical drugs from the combination drug requirement "under certain circumstances".[91]

The exemption from combination drug requirement is consistent with the general recognition of the difficulty of identifying active ingredients in the herbs. In addition, the exemption is also in line with a more fundamental recognition that herbal medicines work in ways different from that of conventional NCE drugs. Synergism among multiple components, as mentioned above, underscores the need for crafting rules different from conventional NCE drugs.

Potential Ramification for Makers of Botanical DrugsOn the Cost Side

Despite its best of intention, the Draft Guidance delivers, at best, limited incentives for the development of botanical drugs. Lowering the barrier to initial phases of clinical trials for botanical drugs conceivably reduces the cost of preparing botanical drug candidates for clinical trials. But the hurdle of the Phase III clinical remains formidable. As Phase III entails the most extensive clinical trials and thus most expenses, preserving the stringent standard for Phase III clinical means that the bulk of the cost in bringing a drug to market will not go away for botanical drugs.

Furthermore, retaining the same requirement for Phase III may impose more costs on botanical drug makers than on NCE drug makers. As FDA itself concedes in the Draft Guidance, the nature of botanical products makes them non-conducive to conventional methods of purification and characterization. In fact, to justify its exclusion of "highly purified" substances from the scope of botanical drugs, FDA offers the reason that "because these substances can readily be fully characterized".[92] A negative corollary of that statement is that botanical drug products are much harder to be "fully characterized" according to FDA's standard. Yet FDA presses on and demands essentially the same stringent requirement for botanical drugs as for NCE drugs. For prospective botanical drug developers, a requirement to comply with the arcane standards of Phase III, originally designed for NCE drugs, may translate into more costs. Thus, by essentially forcing square pegs into round holes, FDA places additional burden on botanical drug developers. In a sense, FDA is giving benefits to botanical drug makers with one hand (concession at Phase I and II), and taking back with another (reservation at Phase III). The net result is de minimis benefit for botanical drug makers.

To further complicate the picture, the Draft Guidance provides no simple "cook book" for botanical drug applications.[93] While the document signals a clear willingness by FDA to work with drug makers to foster the growth of botanical drug development, the guidance itself is unfortunately perforated with ambiguities. The use of "may" and "might", instead of "shall" and "must" is profuse throughout the document. Similarly, as mentioned above, the use of phrases such as "shown to be infeasible" and "under certain circumstances" leaves many approval standards undesirably open-ended.

To an industry that certainty equals gold, uncertainty undercuts incentives. As expected, comments from pharmaceutical industry vigorously objected the ambiguities in the document. They uniformly requested FDA to provide clarification in the final guidance. Conceivably, industry will need to rely

On the Return Side

The incentive structure for botanical drugs, provided by the Draft Guidance, tracks the structure for other kinds of drugs. In other words, the Draft Guidance provides that botanical drugs enjoy 5-year marketing exclusivity if it is a new chemical entity, or otherwise a 3-year exclusivity from the time of approval. The differential treatment depends on whether a drug's active constituent is a new chemical entity.

This simple scheme turns out not to be so simple with botanical drugs. As acknowledged in the Draft Guidance, in most cases, the active constituent of a botanical drug will be unknown.[96] Therefore the length of the marketing exclusivity for these botanical drugs depends on how one interprets the term "active constitute" in the Draft Guidance. A narrow construction leads to the conclusion that most botanical drugs with unknown active constituents will enjoy only 3-year marketing exclusivity. On the other hand, a broader construction, as espoused by the Consumer Healthcare Products Association, suggests that the entire botanical drug product should be considered the active constituent, and thus the "new chemical entity".[97] Under this broad construction, these botanical drugs will enjoy 5-year marketing exclusivity.

Moreover, the Draft Guidance does nothing to prevent the free rider problem mentioned in Section IV. The marketing exclusivity only works against other drug makers, not against dietary supplements manufacturers. Therefore this arrangement does not solve the remaining free rider problem after the limit prescribed by the Pharmanex decision, as described in Section IV. More specifically, dietary supplement manufacturers are free to market a dietary supplement with the same or substantially similar herbal extracts as that in a botanical drug, as long as they can prove that they marketed their product prior to the FDA approval of the botanical drug. The advent of final guidance means that botanical drugs will have the blessing of FDA approval and come with better quality and safety assurance. But they will also come at a substantially higher price compared to their dietary supplement counterparts, making botanical drug makers vulnerable to price undercutting by dietary supplement manufacturers. This free rider problem threatens the chance for pharmaceutical companies to recoup their R&D costs, which will be substantial under the Draft Guidance.

Taken together, the Draft Guidance fails to deliver real and substantial cost-cutting benefit for botanical drug developers. At the same time, it leaves the return for botanical drugs uncertain.

A Viable Solution for the Industry?

To counter the free rider problem, pharmaceutical companies could take on the offense. The idea is simple. Pharmaceutical companies can disarm potential free riders by taking over their weapon: the market for dietary supplements. Before initiating clinical trials on any botanical drug candidates, or during clinical trials, pharmaceutical companies could market herbal extracts containing the same ingredients as dietary supplements themselves at the same time they pursue R&D for botanical drug. Considering the low entry cost for the dietary supplement market, big pharmaceutical companies can easily establish itself in this market. Bayer is a successful example in this regard.[98] In addition, big pharmaceutical companies may capitalize on their name powers and effectively drive out small dietary supplement manufacturers and block any future competitors marketing the same herbal extracts. Although no big pharmaceutical companies have taken this route to date, small pharmaceutical companies have seen this strategy as a viable business model and have put it to practice. For example, CV Technologies (CVT), a small Canadian pharmaceutical company, has marketed COLD-FX as a dietary supplement for cold prevention for some time. At the same time, it is actively conducting Phase I and II clinical trials for the same product under the name CVT-E002.[99] Upon its successful completion of Phase II clinical trials, CVT will seek a major pharmaceutical partner to license CVT-E002 for Phase III testing, drug approval by FDA and marketing of the new drug. The fact that CVT already has the dietary supplement market for the drug product is certainly a favorable consideration in the negotiation process. This strategy is also what Pharmanex, a California-based pharmaceutical company, proposes to do.[100]

Proposals for Further Rule Changes

While the Draft Guidance is a meaningful step forward, it still imposes daunting hurdles for botanical drug makers to overcome. To effectively promote the growth of botanical drug development and to bring beneficial drugs at faster rate to patients, the final guidance should consider making the following changes.

The foremost change is due in the requirement for the Phase III clinical trials. Prior human use data should be taken into account as valid data in this phase, consistent with the approach taken in the Draft Guidance for the first two phases. In addition, FDA should consider the nature of the botanical products when crafting standards for Phase III. Blind adherence to the existing standards designed for NCE drugs makes no analytical sense. To aid its efforts to craft standards that are applicable to botanical products, FDA may capitalize on the resource and expertise of another federal agency, namely the newly created National Center for Complementary and Alternative Medicine (NCCAM). The final guidance should also state clearly that all the special benefits available to small Molecular Weight or Recombinant drug products are offered to botanical drug products. For example, if a botanical drug is intended for use for a life-threatening disease, all the provisions for expedited review, treatment INDs, emergency INDs, should apply to the botanical drug. Similarly, if a botanical drug is intended for use for a rare disease, it should also be considered under the Orphan Product Amendments (including Orphan Product Designation, tax advantages, and 7-year marketing exclusivity).[101]