Botanical Drugs: A Future for Herbal Medicines

Weishi Li

Follow this and additional works at: http://scholarship.law.edu/jchlp

Recommended Citation
Available at: http://scholarship.law.edu/jchlp/vol19/iss1/6
BOTANICAL DRUGS: A FUTURE FOR HERBAL MEDICINES

Weishi Li*

INTRODUCTION

In recent 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 makes the case that botanical drugs, as a new drug model for herbal medicines, will lend a much-needed arsenal to the perennial fight against human diseases.

The current regulatory state of affairs regarding herbal medicines is sub-optimal as it fails to spur rigorous efforts to research and develop effective drugs from herbal medicines. Due to an unfavorable regulatory climate, few U.S. companies engage in developing drug products from herbal medicines. It is argued here that the Food and Drug Administration (FDA) should promote industrial efforts in exploring herbal medicines by approving botanical drugs using a substantially lower regulatory standard. Such a policy will benefit both consumers and a 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 the lack of standardization and scientific validation for many herbal medicines. The second section examines the crisis facing the American pharmaceutical industry and the limitation of the conventional "silver bullet" approach to 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" facing the pharmaceutical industry, and bring more effective medicines to patients at a faster rate. The fourth section examines the current regulatory climate and points to the disincentive effect of the current regulations. Rationales for adopting a

* J.D. Harvard Law School, 2002; Ph.D. Columbia University, 1996; B.S. Peking University, 1990. I am an associate at the Ropes & Gray law firm in New York, New York. I wish to thank Professor Peter Barton Hutt for helpful discussions and pointers to useful information resources. I am especially indebted to Professor Hutt for taking time to edit this paper in preparation for publication.
lower standard for botanical drug approval are discussed. The last section assesses the Draft Guidance for Botanical Drug Products (Draft Guidance), released by FDA in August 2000 for incentives to industry efforts in developing herbal medicines. Finally, this paper proposes further changes to be adopted in the final Guidance.

I. THE MARKET: THE UNITED STATES AND WORLDWIDE

The projected worldwide market size for herbal medicine is staggering. One study, in 1987, estimated the global market at about eighteen to twenty billion dollars U.S.\(^1\) Asia dominates as the largest market at about forty percent of the share; Europe follows at thirty-five percent, and North America accounts for about seventeen percent.\(^2\)

The U.S. market is equally promising. Partially fueled by the passage of the Dietary Supplement Health and Education Act (DSHEA), the U.S. market saw 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.\(^3\) The rise in the sale of these products can be directly attributed to the increasing number of people using herbs. Within seven years, from 1991 to 1998, the percentage of the American population using herbs increased from a mere four percent to a significant thirty to thirty-five percent in 1998.\(^4\)

Despite the tremendous growth, the U.S. market still has plenty of room to grow. The percentage of American consumers using herbal products remains low compared to many other nations. While Americans were slow to adopt the worldwide trend of consuming herbal products, other nations’ consumption patterns may shed light on the current direction of the U.S. market. For instance, over sixty percent of the population in Germany, and eighty to ninety percent of the population in China, use herbs regularly.\(^5\) By inference, the U.S. market is still capable of expanding to reach another thirty to forty percent of the population,

---

2. Id.
4. See Brevoort, *supra* note 1, at 160.
5. Id.
making the U.S. an enticing market given the consumption power of Americans.

The real picture, however, may be more complicated. Many factors, including cultural, traditional and infra-structural ones, contribute to consumers' purchase choices in medicines. For example, China's use of plant-derived remedies to treat diseases is a part of its national cultural heritage. The practice of traditional Chinese medicine dates back as early as 2800 B.C., as documented in the "Herbal Classic of the Divine Plowman" (Sheng Nung Ben Cao Chien). As an indication of the prevalence of traditional Chinese medicine (TCM), China now boasts more than 2500 TCM hospitals and thirty universities and colleges engaging in the studies of TCM. The 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 is not surprising that eighty to ninety percent of the Chinese population use herbal medicines on a regular basis.

Conversely, the U.S. is a study in stark contrast. The faith in FDA-approved prescription drug and over-the-counter (OTC) drugs is deeply ingrained in American 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 traditional herbal medicine remains largely confined to Chinese enclaves in large coastal cities within the U.S. As a result, while many consumers recognize the merits of herbal medicine, the American medical mainstream remains ambivalent to their efficacy. Such ambivalence makes further expansion of the herbal medicine market in the U.S. a questionable prospect.

The growth trend of the U.S. dietary supplement market to date seems to validate this concern. After witnessing astonishing growth from 1994 to 1997, the American market for dietary supplements leveled off in 1998 and demand may currently be in decline. This stalled growth is fueled partly by a hostile press, hot on the pursuit of fraudulent manufacturers, and partly by the long-held western perception that these herbal medicines are


8. Id.

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 U.S. market.

Botanical drugs, developed from herbal medicines, can potentially overcome the consumer suspicions and fulfill the promise of herbal medicines. A clarification of terminology is necessary. A botanical drug, as defined by the FDA in its Draft Guidance, is a botanical product prepared from a botanical drug substance, and intended for use as a drug. A conventional FDA-approved drug has a single well-characterized active ingredient. By contrast, a botanical drug, by definition, comes in forms of extracts that are composed of multiple chemical constituents. The concept of botanical drugs places herbal medicine into the vigorous FDA drug approval process. As a result, the development of botanical drugs will demand the combination of the merits of advanced western technology and the empirical-based, centuries-old herbal medicine tradition.

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 here and abroad, and allow them to 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 summarize the drug approval process for a new chemical entity (NCE) drug.

A. Conventional FDA Drug Approval Process

Before starting human clinical trials in the U.S., a company must file an investigational new drug (IND) application with FDA. The FDA then has thirty days to intervene. If FDA fails to intervene within that period, the company may proceed with testing. The tests are customarily divided
into three phases. In a Phase I clinical trial, companies test for safety on twenty to eighty healthy volunteers. Before administering the drug to volunteers, companies need to supply preclinical data, including pharmacological and toxicological data, which are subject to review by clinical pharmacologists. If the data are deemed satisfactory, the drug is then administrated to the volunteers. In Phase II, companies test for efficacy of the drug in 100-300 patients under different dosages. 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, the company submits clinical, pharmacological and toxicological data in the form of a new drug application (NDA) to FDA. Currently, it takes FDA on average a year to review an NDA. Only upon the approval of an NDA by FDA can a company proceed to market its drug.

The entire drug development process is long and costly. Bringing a single new chemical entity (NCE) drug to market now takes ten to fifteen years on average and costs over $800 million, a sum exceeding the gross national product of some nations. Moreover, this cost is steadily rising at the rate of eleven percent annually.

A significant portion of the cost comes from candidate attrition during the clinical stage of drug development and the FDA approval process. "[F]or every five to six drug candidates that reach

14. Id.
15. Id.
16. Id.
17. Id.
18. Id.
19. Id.
20. Id.
22. See Joseph Chang, Medicinal Herbs: Drugs or Dietary Supplement? 59 BIOCHEMICAL PHARMACOLOGY 211, 211 (2000).
Investigational New Drug (IND) status, only one becomes a product.\textsuperscript{25} To illustrate, pharmaceutical companies will typically market roughly one out of a hundred of their patented products.\textsuperscript{26} The skyrocketing research and development (R&D) costs have translated directly into soaring prices for prescription drugs. As a \textit{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."\textsuperscript{27}

\textbf{B. Drying Drug Pipelines}

The American pharmaceutical industry is in the midst of a productivity crisis. Jean-Pierre Garnier, the Chief Executive Officer of GlaxoSmithKline, recently lamented that "[w]e don't have enough in our collective pipelines."\textsuperscript{28} This is not a problem for an isolated few, but one that plagues the entire pharmaceutical industry. In 2000, the \textit{Wall Street Journal} reported that since 1996, the production of breakthrough drugs has steadily declined.\textsuperscript{29} In 1996, there were fifty-three new FDA-approved drugs.\textsuperscript{30} This decreased in 1999 to only thirty-five, and to just sixteen in the first half of 2000.\textsuperscript{31} 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."\textsuperscript{32}

Recent news confirms that trouble continues for the largest pharmaceutical companies. Merck, Bristol-Myers Squibb, Schering-Plough and Eli Lilly have all recently issued earnings warnings to Wall Street\textsuperscript{33} due to patent expiration of major drugs and a lack of new drugs.\textsuperscript{34}

\textsuperscript{25} \textit{Id.}
\textsuperscript{29} \textit{Id.} at A12.
\textsuperscript{30} \textit{Id.}
\textsuperscript{31} \textit{Id.}
\textsuperscript{32} \textit{Id.}
\textsuperscript{34} \textit{Id.}
With no new drugs on the horizon, the prospect of a recovery in productivity is slim.

Worse than the decline in productivity is how pharmaceutical companies responded. Rather than increasing research, "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."35 While this strategy is a short-term response to boost a company's bottom line, it is not a long-term solution to the productivity problem. Ultimately, patients will suffer, and society will pay increased medical expenses.

C. Lost faith in "Silver Bullets"

The current crisis in new drug discovery highlights the limitation of the conventional view of drugs as "silver bullets." The traditional belief that a single chemical entity drug, which treats a single disease, rests on a critical premise that human diseases have a uniform, underlying genetic basis across patient populations. Typically, a silver bullet drug is a NCE drug with a single active chemical ingredient. While there have been blockbuster silver bullets like Amgen's EPO and Eli Lilly's Prozac, the hope for new blockbuster drugs has diminished.36 Recent advances in genomics vindicate this pessimism. It appears that diverse genetic changes often underlie a single disease, a phenomenon termed "polymorphism." Thus, different patient populations may require different drugs tailored to their personal needs. The polymorphic nature of diseases suggests an individualized approach in drug design is more likely to succeed, making it even more difficult to develop blockbuster drugs.37

In sum, the American pharmaceutical industry is in a "terrible trough."38 There is a dire need to find a complementary way to supplant the current approach toward drug discovery. Some pin their hopes on the advent of genomics and the complete sequences of the human genome. While genomic knowledge will undoubtedly offer new insight into human

35. Id. at A1.

36. See Harris, supra note 28, at 30 (quoting Fred Hassan, chairman of Pharmacia Corp, as saying "we are well past the low-hanging fruit. It's becoming very difficult to get easy wins.").


38. Harris, supra note 33.
diseases, most genomic experts speculate that significant drug discoveries based on genomics are still years away.\textsuperscript{39} Given the heightened interest in herbal medicines in the United States and worldwide, the development of botanical drugs may be the booster shot that the pharmaceutical industry badly needs.

### III. BOTANICAL DRUGS: A MARRIAGE BETWEEN HERBAL MEDICINES AND WESTERN DRUG DEVELOPMENT

#### A. What Herbal Medicines Offer

Herbal medicines offer hope to alleviate the current crisis in conventional drug development. It is important to stress that herbal medicines will not replace conventional drugs. Rather, they will complement conventional drug discovery. There are at least three reasons why herbal medicines may offer the perfect complement to conventional drug discovery.

First, capitalizing on knowledge of herbal medicines may give rise to cheaper and faster ways of drug discovery. Typically, drug discovery starts with screening millions of chemicals against biological targets using cell-based assays in laboratories.\textsuperscript{40} Promising chemicals (leads) are then tested in animal disease models.\textsuperscript{41} Candidates that survive the animal testing then move on to expensive clinical trials.\textsuperscript{42} As previously mentioned, only a small percentage of these candidates survive the ordeal of clinical trials to become a product. This is often due to unforeseen side effects or lack of efficacy in human subjects.\textsuperscript{43} The lack of a correlation between pharmacological activity against targets and clinical effectiveness is the principal culprit for the high attrition rate at later clinical stages.\textsuperscript{44} The problem lies in the risky practice of using laboratory screening and animal disease models to predict therapeutic efficacy in humans. The lab screening and animal models often carry "inadequate predictive power" as to a product's effectiveness in human patients.\textsuperscript{45}

Capitalizing on knowledge of herbal medicines may lead to a way out of this costly dilemma. Botanical extracts can be directly evaluated for

\begin{itemize}
\item \textsuperscript{39} Id.
\item \textsuperscript{40} See Hutt \& Merrill, supra note 12, at 514.
\item \textsuperscript{41} Id.
\item \textsuperscript{42} Id.
\item \textsuperscript{43} Id.
\item \textsuperscript{44} Id.
\item \textsuperscript{45} See Bindra, supra note 24, at 152.
\end{itemize}
clinical efficacy, rather than subjected to initial chemical isolation. 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.

Naturaceuticals, a new drug development paradigm 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 naturaceuticals 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 then 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.

Indeed, developing drugs from plants is not new to American pharmaceutical companies. Taxol, aspirin, menthol and morphine, are examples of single-ingredient drugs derived from plants. However, taking advantage of the traditional knowledge in herbal medicines to give the drug development process a head start is a new concept for these companies.

Second, herbal medicines offer a holistic approach to complement a pure reductionism approach toward diseases, namely, the silver bullet approach. The drug industry often prides itself on the scientific and reductionist approach toward drug development. History, however, shows that many blockbuster drugs came not necessarily as a result of impeccable R&D, but by way of inadvertent good fortune. For example, the initial discovery of Viagra came from a surprising side effect in clinical trials designed for heart conditions. Thus, merits of the reductionism

46. Id. at 154.
47. Id.
48. Pfizer researchers who gave out Viagra in clinical trials were puzzled by the reluctance of patients to give back the supposedly “ineffective” drug. It took some further digging to uncover the value of the now blockbuster wonder drug. See Paul Witte, Viagra: History in the Making, or Products Liability History Repeating Itself? at http://pegasus.rutgers.edu/~record/drafts/viagra.html (last visited Feb. 8, 2003)
approach may be greatly exaggerated to the exclusion of other useful approaches.

In contrast to the silver bullet approach, herbal medicines often integrate preventive and 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 the immune system works. Modern medicine informs us that, by boosting our immune systems, we can help our bodies to better 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 in some traditional Chinese medicines. Such synergistic action may confer a unique advantage, especially in dealing with complex diseases of polymorphic nature that are unresponsive to the conventional single chemical entity drugs. To this end, many traditional formulas have exhibited activity against asthma, metabolic diseases, pain, depression and infectious diseases including AIDS and cancer. The claims for treating cancer have been supported by findings at the National Institutes of Health (NIH). Researchers at the National Products Branch at NIH reported that camptothecin (CPT), isolated from extracts prepared from the barks of a Chinese medicinal tree, showed broad-spectrum anti-tumor activity. In fact, Pharmacia Upjohn is producing and marketing a CPT analog, CPT-11, under the trade name of camptosar or irinotecan. Additionally, there are over 130 clinical trials involving different versions of CPT analogs, for treating

50. Id. at 112.
51. For example, researchers from the University of Maryland reported that an extract from the roots of a Chinese medicinal herb was found to have antibacterial synergy. Id.
52. See Yang, supra note 6, at 63.
53. Id. at 63.
54. Id. at 71.
diverse cancers, at early and late stages, and in cases where there are multiple cancers.55

B. Validity of Herbal Medicines: Traditional Chinese Medicine as a Case in Study

Advocating for botanical drugs based on knowledge of herbal medicines necessarily raises 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 TCM. However, it is important to stress that the regulatory issues discussed in this paper should be generally applicable to any herbal medicines that are comparably supported by empirical data, as with TCM.

The prevalence of TCM in China and other Asian countries suggests its effectiveness. In China, where western drugs are widely available and relatively affordable in major cities,56 a recent survey reveals that the majority of consumers view TCM as equally or more effective than western drugs.57 This perception is not surprising. The long history of trial-and-error practice and documentation have accumulated a wealth of empirical knowledge and clinical data regarding the effects of herbs on diseases and their associated side effects.

While prevalence builds a circumstantial case for the validity of TCM claims, pharmacological and/or clinical studies performed in the west provide direct evidence. 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, turned out to contain the same active ingredient as Mevacor, Merck's FDA-approved prescription drug.58 Red yeast rice, traditionally prepared by fermenting non-glutinous rice with red yeast, has

55. Id.
56. The availability and affordability of western drugs is in large part due to the prevalence of "me too" drugs, a phenomena likely to end soon as China recently joined WTO. "Me too" drugs are cheap domestically-produced versions of western drugs.
57. See Hui, supra note 7, at 2. (The survey conducted among 1543 households in Beijing, Shanghai and Guangzhou showed that forty-one percent believe that TCM and western medicine are equally effective, thirty-one percent prefer TCM to western drugs and only twenty-three percent prefer western drugs). Id.
58. Pharmanex v. Shalala, 221 F.3d 1151 (10th Cir. 2000).
long been known for its cholesterol-lowering ability.\textsuperscript{59} Indeed, the classical book on TCM, \textit{Ben Cao Gang Mu} (Compendium of Materia Medica, 1578 A.D.) describes the ability of TCM to "invigorate spleen, digestion, and promote blood circulation and resolve blood stasis."\textsuperscript{590} Pharmanex developed a red yeast rice extract and marketed it under the name Cholestin.\textsuperscript{61} Cholestin contains a natural substance, mevinolin, which is chemically identical to the active ingredient, lovastatin, in the prescription drug Mevacor.\textsuperscript{62} Mevacor was developed and marketed by Merck for the treatment of high cholesterol and heart disease.\textsuperscript{63} This illustrates that ancient empirical-based traditional Chinese medicine knowledge and costly state-of-the-art western pharmaceutical research can converge.

The validity of TCM is not limited to this single instance. Laboratory studies validating TCM claims are abundant in scientific literature.\textsuperscript{64} Clinical trials of products based on the knowledge of TCM, in both the United States and Europe, lend further support to its validity.\textsuperscript{65} In the United States, for example, clinical trials funded by NIH – some now in Phase III – suggest that ginkgo extract may be effective for Alzheimer’s disease, that chondroitin sulfate may affect osteoarthritis, and that saw-palmetto extract might ameliorate benign prostrate hypertrophy.\textsuperscript{66}

\textbf{C. The Flip Side: What Western Drug Development Processes Offer Herbal Medicine}

Herbal medicines offer hope for drug development; however, herbal medicines still require rigorous clinical validation and pharmacological studies. On their own, herbal medicines have slim hope of entering the mainstream of American healthcare. This is because herbal medicines, in their traditional forms, suffer a myriad of deficiencies, including heavy reliance on anecdotal data, a lack of randomized controlled clinical data to substantiate the therapeutic claims, overly broad and often vague therapeutic claims, a lack of quality assurance and an unfounded panacea

\textsuperscript{59} See Joseph Chang, \textit{supra} note 22, at 214.
\textsuperscript{60} Id.
\textsuperscript{61} Pharmanex, 221 F.3d at 1153.
\textsuperscript{62} Id.
\textsuperscript{63} Id.
\textsuperscript{64} See generally \textsc{Drug Discovery and Traditional Chinese Medicine} (2001).
\textsuperscript{65} Id.
\textsuperscript{66} See Joseph Chang, \textit{supra} note 22, at 216.
"cure all" belief. If not dealt with properly, these deficiencies will continue to undermine the legitimacy of herbal medicines. Subjecting herbal medicines to standardized manufacturing practice and well-controlled clinical trials will help overcome these deficiencies. Developing a drug model for herbal medicines is essential in establishing the true value and credibility of herbal medicines in the eyes of American consumers. In sum, 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 embody these mutual benefits.

However, it would be simplistic and presumptuous 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 in 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 resolve these technical issues as they go along, presenting a risky business model from the perspective of venture capitalist investors.

Furthermore, while botanical drugs promise to lower the cost of drug R&D, the cost may still remain prohibitive for most industry players, except the big pharmaceutical powerhouses. To make matters worse, the initial stage of botanical drug development necessarily entails experimentation with new protocols and standardization issues, posing a high cost that might prevent new entrants from competing in the field.

Taken together, the idea of botanical drugs promises to capture the best of both tradition-based herbal medicine and western drugs. But bringing this idea from theory to practice will not be automatic or effortless. Thus, there is a need for an adequate regulatory climate to spur industry efforts in this direction. This results in several questions. Is the current regulatory structure adequate to accomplish this goal? Are there any industrial research and development efforts in this direction? What can be done to promote industrial efforts in the United States?

67. See Michael Chang, supra note 9, at 171.

68. See Joseph Chang, supra note 22, at 213.
IV. CURRENT REGULATORY CLIMATE AND ITS RAMIFICATIONS

A. DSHEA and its Impact

In 1994, in response to intense political pressure, Congress enacted the Dietary Supplement Health and Education Act (DSHEA).69 Under DSHEA, medicinal herbs can be marketed as dietary supplements without prior FDA approval.70 The supplements may carry “structure/function” claims, claims that a product affects the structure or functioning of the body, but not claims that they treat, diagnose, cure or prevent disease.71 By offering low market entry cost, DSHEA succeeded in making herbal medicines widely available.72 But the low market entry cost turned out to be a double-edged sword. By setting a lower regulatory standard, DSHEA failed to remedy the fallacies associated with the herbal medicines enumerated in the last section. Four reasons underlie the failures of DSHEA to make safe and high quality herbal medicines available to consumers who need them.

First, the lack of a FDA approval requirement for marketing a dietary supplement provides no incentive for dietary supplement manufacturers to conduct any substantive research and development. In fact, an “anything goes” mentality pervades this new industry. Manufacturers are largely free to experiment with traditional herbs. They 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.”73 Additionally, tremendous price pressure creates a “race to the bottom” phenomenon in terms of the quality of dietary supplements in the market.74

70. Id.
71. Id.
74. See Miller and Longtin, supra note 72 (describing many instances of dietary supplements with poor qualities).
As a result, consumers come to associate questionable effectiveness and harmful side effects with dietary supplements. In turn, this reinforces the old distrust of traditional herbal medicine, and undermines consumer confidence in its proliferation. The recent downturn in the market for dietary supplements seems to obviate this concern.

Second, unsupervised herbal use can potentially pose health and safety concerns. 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 over the counter (OTC) drugs.75

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 the ability to treat diseases, manufacturers are allowed to make unsubstantiated claims on their products, fueling further safety concerns.

Fourth, the FDA has not enforced DSHEA. It has implemented neither the safety requirements, nor the labeling restrictions.76 Some believe the FDA is purposely undermining the Act, while others say that this is the result of inadequate FDA resources.77 The lack of DSHEA enforcement is further amplified by its disincentivizing effect on companies who engage in serious research and development efforts to explore the value of traditional medicines. For example, consider a firm producing herbal medicines. To market in the United States, it is faced with two options. It can market them as dietary supplements. Given the de minimis regulation in this area, this option appears attractive. Alternatively, if the firm wants to get the imprimatur of FDA for its product, its only option is to develop a new single-chemical-entity drug from an herb and complete the costly drug approval process. To date, FDA has never approved a single drug in extract form from a natural resource. Given the two options, it makes more sense for businesses to take the dietary supplement route. The dietary supplement's entry cost is low, and it promises a quick return. The drug route pales in comparison because it requires a large up-front investment, while the chance for return remains highly uncertain.78

The potential return for conventional NCE drugs developed from herbs is directly threatened by dietary supplement free riders. As mentioned

75. See Joseph Chang, supra note 22, at 211.
76. Id., See Also Zuk, supra note 73, at 41-42, 46-47 (references therein).
77. See Miller and Longtin, supra note 72, at 2.
78. See Ward, supra note 26, at 1-2.
above, notwithstanding the potential cost-cutting benefit herbal medicines may provide, a drug company still needs to invest a substantial amount of money to develop an FDA-approved drug made from herbs. After FDA approves an NDA and the drug is marketed, a drug company may find itself directly competing 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, 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 significantly lower price. Compounded with pressures from managed 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 that case, the 10th Circuit recognized the 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. Under DSHEA, the definition of "dietary supplement" excludes both "an article that is approved as a new drug," and "an article authorized for investigation as a new drug...for which substantial investigation has been instituted and for which the existence of such investigations has been made public." The *Pharmanex* opinion construed the word "article" broadly to include active ingredients as well as the final drug product. This construction is likely applicable to the second exclusion, where an investigation has been initiated for a new drug. Thus, under *Pharmanex* and DSHEA, the bar reaches any company that markets the same natural substance as a dietary supplement prior to investigation and approval of the new drug.

To make matters worse, drug products developed from botanical products are often unable to obtain a composition patent due to the fact that these products are naturally occurring. They have to settle for use patents, which are much harder to defend and are less valuable. As a

---

79. *Pharmanex*, 221 F.3d at 1151.
80. *Id.* at 1159.
81. *Id.* at 1158.
83. *Pharmanex*, 221 F.3d at 1154-1156.
result, companies that engage in the risky enterprise of developing drugs from traditional herbs see a serious prospect of getting whipsawed. The chance of recovering the investment is slim and the chance of making a profit is even less probable.

In short, rather than promoting the mainstreaming of traditional medicines, the advent of dietary supplements, in practice, has the opposite effect. The current bifurcation along the line of dietary supplement and drug runs the danger of foreclosing pharmaceutical industry efforts in the United States to develop traditional medicinal herbs into drug products.

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

Given the unfavorable regulatory climate, it is no surprise that there are only a small handful of American companies that develop botanical drugs through the conventional IND/NDA route.

Six American 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 the lack of serious industrial efforts in this area, all six companies are small start-up ventures. For example, Ancile Pharmaceuticals, based in California, employs thirty professionals. Similarly, Phytomedics, Inc., a New Jersey-based company, has a small R&D staff of twenty scientists. Among these companies, only Ancile and Phytomedics have progressed to the clinical trial stage. As of April 2001, Ancile has three effective IND applications filed with the FDA. In December 2000, Ancile successfully completed a double blind, placebo-controlled Phase II trial for ANPH 101, a drug product intended for sleep disorders. Phytoceuticals, based in New Haven, Connecticut, cleared an IND application for one of its

---

85. See infra notes 86-107 and accompanying text.
89. See Ancile Company Profile, supra note 86.
90. Id.
chemotherapy modulating drug products in August 2001. Phase I and II clinical trials are currently under way. Others, like Phytomedics, are still in the early stage of drug development called 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.

Ostensibly missing from the scene are the 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 American botanical drug market. In fact, foreign firms already have a head start. For example, Phytopharm, a British botanical pharmaceutical company, has been in the business of botanical drug development for over eleven years. In September 2000, Phytopharm announced that it had initiated a Phase I clinical evaluation for another botanical product, P58. According to the company news release, “P58 is one of a family of phytochemicals isolated from traditional treatments for the elderly that have previously been shown to offer significant benefit in the treatment of senile dementia.”

Similarly, another British pharmaceutical company, Oxford Natural Products, is dedicated to the “development of novel pharmaceuticals and nutraceuticals from plants.” As of 2001, the company entered three products into clinical evaluations. Among them, ONP-17, which treats hepatitis-C symptoms, is composed of extracts of traditional Chinese and

92. Id.
93. See Phytomedics Company History, supra note 87.
97. Id.
99. Id.
Western herbs. Chronic hepatitis-C inflicts over 300 million patients worldwide. Not shy about its intention to enter the American market, Oxford Natural Products explicitly points out on its website that “in America, [hepatitis-C] is four times more prevalent than AIDS.”

The threat of competition for the American botanical drug market is not limited to European nations. CV Technologies, Inc. (CVT), a Canadian herbal drug developer, has been engaged in the business of developing nutraceuticals for over ten years. In October 1999, CVT obtained its first IND clearance with FDA for its nutraceutical product, CVT-E002. CVT-E002 is a “multicomponent phytopharmaceutical extracted from North American ginseng...intended for use as a preventative against acute respiratory infection.” 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. These trials are double blind and placebo-controlled.

The unusual dominance of foreign entities among the critics of FDA’s new Draft Guidance gives another glimpse of the eagerness of foreign firms to join the American botanical drug market. Of the eighteen firms who filed comments to date, only four are American drug companies, while nine are foreign industrial entities representing either individual companies or associations of companies. According to Dr. Yuan-yuan Chiu, Director of Office of New Chemistry for Drug Evaluation and Research at the FDA, the disparity in responses is possibly indicative of a disparity between the United States and other nations in the level of activities within the botanical drug field.

101. Id.
104. Id.
105. Id.
106. Id.
107. Id.
108. Telephone Interview with Dr. Yuan-yuan Chiu, Director, Office of New Chemistry for Drug Evaluation and Research, Food and Drug Administration (March 11, 2002).
Table 1. Distribution of commentators on the Draft Guidance\textsuperscript{109}

<table>
<thead>
<tr>
<th>Origination</th>
<th>Drug Companies</th>
<th>Others (consulting, governmental agency, trade association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Global</td>
<td>1 (Pfizer)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

If left unchanged, the lack of industrial efforts in the United States 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 beneficial medicines. The massive under-regulation of dietary supplements hardly relieves this deprivation, as the market is now flooded with many dietary supplements of dubious quality.\textsuperscript{110} This unsatisfactory state of affairs calls for changes in regulatory policy.

C. 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, and consequently, a stamp of approval on herbal medicines from FDA will pave the way for their mainstream acceptance by many Americans.

However, a viable alternative is for FDA to alter the current all-or-nothing regulatory state of affairs, which is comprised of stringent armed-to-the-teeth regulation for new drugs approval on one end, and a complete lack of scrutiny for the marketing of dietary supplements on the other. A balance can, and should, be struck. FDA can create a new category for botanical drugs by placing herbal medicines into the FDA approval process, but with the application of substantially lower approval standards.

\textsuperscript{109} Based on a search of the FDA website (http://www.fda.gov) using the term: comment and “botanical products”.

\textsuperscript{110} See Miller and Longtin, supra note 72.
Adopting standards substantially lower than those required for conventional drugs is justified by the fact that many herbal medicines already have extensive prior marketing experience before FDA applications are filed. TCM is an example. Four thousand years of trial-and-error medical practice and documentation have reasonably established their safety and effectiveness. Furthermore, their continued marketing in China and other Asian and European nations provides evidence of their safety.

In fact, many other industrial nations have already adopted a similar practice. For example, France permitted the registration of “vegetable drugs” under “an abridged dossier” in 1990. Moreover, the safety of herbal remedies, including “historical proof of their widespread traditional use and their well established use in self-medication,” was taken into account. 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.

Nevertheless, some might raise the objection that FDA drug approval standards should not be tampered with to accommodate a new category of drugs. This objection is misplaced however, for the conventional drug approval standard for NCE drugs is not set in stone. In fact, the FDA has frequently invoked criticism for its stringent approval standard and several reforms have been proposed. Critics view the approval standard as excessive and unnecessary, and have accused it of “[becoming] more stringent than is socially optimal.” In fact, studies have found that more stringent drug regulations, spurred by the thalidomide tragedy, have

111. Indeed, FDA has acknowledged the value of prior marketing experience in the Botanical Drug Guidance, See BOTANICAL DRUG GUIDANCE, supra note 9, at 4.


113. Id.

114. Id. at 16.

115. See Ward, supra note 26, at 3.

116. Id. at 1.

117. In the early 1960s, many European women who had taken thalidomide, a drug to reduce morning sickness, during pregnancy, gave birth to severely deformed babies. Reports of these incidents prompted the passing of legislation that increased the FDA’s authority over the safety and effectiveness of drugs. See HUTT & MERRILL, supra note 12, at 452.
increased the drug development costs by about six percent per annum in the United States.\textsuperscript{118} Consequently, these regulations have cut the number of new drugs introduced in the United States by half relative to other industrialized nations.\textsuperscript{119} The FDA is blamed for maintaining a higher than optimal drug approval standard out of fear of political pressures.\textsuperscript{120} Approving a non-beneficial and harmful drug leads to more political backlash for FDA than failing to approve, or simply delaying the approval of, a beneficial drug. One critic commented that, "no official wants to be known as the one who approved another thalidomide."\textsuperscript{121} The result is a net social loss due to the failure to approve a truly beneficial drug. Indeed, "the cost in increased mortality and morbidity was valued at $330 million in [a] 1973 [study]."\textsuperscript{122}

While no one anticipates a quick turnaround by FDA in its conventional drug approval standard, adopting a lower standard for a new category of drugs would require less administrative overhaul and would be, perhaps, more likely to succeed.

Nevertheless, some may raise health and safety concerns as a result of reduced FDA scrutiny. While this concern is legitimate, the reality is that the advent of dietary supplements has already become a threat to public health and safety. In fact, having FDA become involved in standard setting will make botanical drugs safer than their dietary supplement cousins. Because physicians will be involved throughout the prescription process, a learned intermediary will be able to inform and educate patients. In contrast to the scarce information provided with the garden-variety dietary supplement, botanical drugs, like other prescription drugs, will come with patient package inserts that will supply extensive information to patients.

A second, and related, concern is that granting FDA approval of botanical drugs under a reduced standard may undermine the credibility of FDA, and consequently all FDA-approved drugs. This paranoia is premised on an unfounded assumption that botanical drugs will cause more health and safety problems than conventional single-entity drugs. As mentioned above, extensive clinical data from a wealth of practice and foreign marketing experience indicates that botanical drugs will at least be as safe as, if not safer than, their synthetic single-chemical-entity

\textsuperscript{118} See Ward, supra note 26, at 2.
\textsuperscript{119} Id.
\textsuperscript{120} Id. at 3.
\textsuperscript{121} Id.
\textsuperscript{122} Id.
counterparts. Therefore, while there are potential pitfalls, they are outweighed by the benefits of permitting new botanical drugs.

By embracing herbal remedies, FDA will not be stepping out of its usual conservative character and taking on a revolutionary role. Rather, it will be keeping pace with a movement that has already been embraced by many different sectors of American society. The following tale of changing names highlights a gradual acceptance of the once deemed unconventional. "In the 1950's: the American Cancer Society had a committee on Quackery." Later, the term quackery was replaced by "questionable methods," followed by "unproven methods of cancer management." Today the same committee is named the "Committee on Complementary and Alternative Medicine (CAM)." This image of keeping up, rather than starting a revolution fits more comfortably with the conservative temperament of FDA. Conversely, inaction will make FDA appear unreasonably stubborn in the face of the sea of change occurring in American society and worldwide, thereby undermining its credibility in the eyes of consumers.

In summary, giving herbal medicines a green light under a new standard that takes into account both clinical and prior market experience is optimal for social and economic benefits. The United States is already behind in the game of herbal medicines. For American pharmaceutical companies to stay competitive in the global drug market, a receptive regulatory environment is urgently needed.

V. FDA DRAFT GUIDANCE

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

The Draft Guidance is significant for two reasons. First, it has the potential, if enforced appropriately, to eliminate non-conforming standards and bring uniformity to the use of herbal medicine, which is now largely dominated by the chaos of dietary supplements. It will promote

124. Id.
125. Id.
126. See BOTANICAL DRAFT GUIDANCE, supra note 10.
the 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 mainstream healthcare in the United States.

In summary, the Draft Guidance explains when a botanical drug may be marketed under an OTC drug monograph and when FDA approval of a new drug application is required for marketing.\(^{127}\) It also provides guidance to sponsors on submitting investigational new drug applications (INDs) for botanical drug products.\(^{128}\) Recognizing the complexity of botanicals, the Draft Guidance deems it appropriate to adopt regulatory policies that differ from those for synthetic, semisynthetic, or otherwise highly purified drugs.\(^{129}\) In certain circumstances, prior domestic marketing data are proposed to substitute, either partially or completely, for the pre-clinical data to support an IND for initial clinical studies.\(^{130}\)

The next 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.

**A. 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 is in line with the basic approach of the Federal Food, Drug, and Cosmetic Act (FDCA), which distinguishes between a food and a drug on the basis of intended use.\(^{131}\) 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."\(^{132}\) From this basic definition, the Draft Guidance explicitly excludes "highly purified or chemically modified substances derived from natural sources" from the reach of

127. *Id.* at 1.
128. *Id.*
129. *Id.*
130. *Id.* at 6.
131. Under FDCA, "food" is defined as including "articles used for food or drink for man", "drugs" are defined as including "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man", and "articles intended to affect the structure or any function of the body of man." *See* 21 U.S.C. § 321(f)(1)(2000) and 21 U.S.C. at § 321(g)(1)(B).
botanical drugs.\textsuperscript{133} As a justification for this exclusion, the Draft Guidance explained that once purified, these substances "can readily be fully characterized."\textsuperscript{134}

At first blush, this narrow definition appears to indicate FDA's reluctance to fully embrace herbal medicines, as it stops short of encouraging full-fledged conventional drug development that builds 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 sum of its parts. Under the idea of synergism, multiple components in many herbal extracts may work together to alleviate disease. Developing a single-chemical-entity drug from herbal medicine appears to be unadvantageous, not to mention the potential side effects resulting from the purified chemicals.

Furthermore, the FDA may need to retain a uniform approval standard for NCE drugs. The FDA should not discriminate among NCE drugs developed with different methodologies; for example, recombinant biotech drugs that are drugs developed using genomic knowledge as opposed to drugs purified from herbal medicines. Given the current complex technology involved in drug development, choosing methodologies is beyond the expertise of a federal bureaucracy like FDA. Thus, it is wise for FDA not to play favoritism among NCE drugs.

It is interesting to note that some industrial nations have adopted broader conceptions of botanical drugs. In France, herbal medicines are simply defined as medicines that have "exclusively plants or plant extracts" as active ingredients.\textsuperscript{135} Similarly, in Greece, a regulation for herbal medicines, published in 1994 by the Ministry of Health, defined herbal medicines as "medicines which contain as active ingredients only plants or preparations of plants."\textsuperscript{136} 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 would not amount to a big compromise in the approval standards in France and Greece. In fact, the narrow conception of botanical

\begin{itemize}
  \item \textsuperscript{133} This is indicated twice in the Draft Guidance, once in the definition of "botanical drug substance," and again in the background section of the text. \textit{Id.} at 2, 36.
  \item \textsuperscript{134} \textit{Id.} at 2.
  \item \textsuperscript{135} See WHO SURVEY, \textit{supra} note 112, at 14.
  \item \textsuperscript{136} \textit{Id.} at 16.
\end{itemize}
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 NCE drugs that are developed from botanicals into the botanical drug category may be too drastic a measure for the FDA.

Makers of new NCE drugs purified 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". As noted by the comment from Tibotec Pharmaceuticals Ltd., a Belgium-based pharmaceutical company, the preparation of many herbal extracts entails multiple steps of purification. Would the herbal extracts prepared this way satisfy the "highly purified" standard in the Draft Guidance and thus not be a botanical drug for the purpose of the Draft 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.

B. Regulatory Carrots: Games of Gives and Takes

The Draft Guidance grants 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 an NCE drug.

The foremost benefit is the recognition of prior human use as supporting data in the initial stages of clinical trials. In the case of botanical products legally marketed in the United States with no known safety issues, the chemistry, manufacturing and controls (CMC) and animal toxicology data may be "markedly reduced" for initial clinical studies. Indeed, the Draft Guidance points out that "in most cases, additional toxicology and CMC data will not be required." But, not all prior human use data are treated equally. Positive foreign marketing experience is deemed less valuable than marketing experience in the

137. BOTANICAL DRUG GUIDANCE, supra note 10, at 36-38.
139. BOTANICAL DRUG GUIDANCE, supra note 10, at 4.
140. Id.
United States. Botanical products previously marketed exclusively in foreign markets must supply more information to initiate clinical Phase I and II trials. Decisions as to the nature of information needed for these products will be determined on a case-by-case basis. At the other end 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 are 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 trials. Manufacturers will have to supply 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. 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.

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". 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. 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 less stringent standard.

The problem with this regulatory carrot, however, is that it is tethered to an ambiguous "infeasible" standard. Several comments raised this objection. The Consumer Healthcare Products Association suggested that FDA not "leave open-ended statements" that can lead to inconsistent

141. See id. at 6-7 and 12-16.
142. See id. at 15.
143. See Draft Guidance, supra note 10, Section IX, at 24-35.
144. Id.
146. BOTANICAL DRUG GUIDANCE, supra note 10, at 4.
147. Id.
interpretations. Phytopharm, an UK-based pharmaceutical company requested that the final Guidance clarify the issue by including examples of botanical drugs that satisfy the burden of demonstrating infeasibility.

Finally, a less articulated but nonetheless valuable benefit is the exemption from the combination drug regulations. By definition, botanical drugs are combinations of multiple components, and sometimes, multiple active ingredients. Under the FDA combination drug regulation, 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, such as leaves, stems, roots or seeds, or from an alga or macroscopic fungus. Botanical drug products 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”.

The exemption from the 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


149. Letter from Andrew Whiles, Director of Regulatory Affairs, Phytopharm, to the Food and Drug Administration, Dockets Management Branch (December 21, 2000), available at http://www.fda.gov/ohrms/dockets/dailys/00/Dec00/122600/c000026.pdf.

150. See BOTANICAL DRUG GUIDANCE, supra note 10, at 5.

151. Id. at 4.


153. BOTANICAL DRUG GUIDANCE, supra note 10, at 5.

154. Id.
multiple components, as mentioned above, underscores the need for crafting rules different from conventional NCE drugs.

C. Potential Ramification for Makers of Botanical Drugs

1. On the Cost Side

Despite the best intentions, the Draft Guidance delivers limited incentives for the development of botanical drugs. Lowering the entry 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 trials remains formidable. As Phase III entails the most extensive clinical trials and thus the most expense, preserving the stringent standard for Phase III clinical trials means that the bulk of the cost in bringing a drug to market of marketing a drug 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, the FDA offers the reason that “these substances can readily be fully characterized.” A negative corollary of this statement is that botanical drug products are much harder to “fully characterize” according to the FDA’s standard. Yet, the FDA presses on, and demands essentially the same stringent requirement for botanical drugs as for NCE drugs in Phase III trials. For prospective botanical drug developers, a requirement to comply with the arcane standards of Phase III, which was originally designed for NCE drugs, may translate into additional costs. Thus, by essentially forcing square pegs into round holes, the FDA places additional burdens 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 them back with another (reservation at Phase III). The net result is a de minimis benefit for botanical drug makers.

To further complicate the picture, the Draft Guidance provides no simple “cook book for new botanical drug applications.” While the document signals a clear willingness by the FDA to work with drug

155. Id. at 4.
156. Id. at 2.
157. Leaders, supra note 145.
makers to foster the growth of botanical drug development, the guidance itself is perforated with ambiguities. The use of “may” and “might”, instead of “shall” and “must” is profuse throughout the document.\(^\text{158}\) Similarly, as mentioned above, the use of phrases such as “shown to be infeasible”,\(^\text{159}\) “when possible”\(^\text{160}\) and “under certain circumstances”\(^\text{161}\) leaves many approval standards undesirably open-ended.

To an industry where certainty equals gold, uncertainty undercuts incentives. As expected, comments from the pharmaceutical industry vigorously objected to the ambiguities in the document. These comments uniformly requested the FDA to provide clarification in the final Guidance.\(^\text{162}\) Conceivably, the industry will need to rely on the framework provided by the final Guidance to shape itself.

This said, it should be recognized that the profuse use of ambiguous language could simply be an indicia of a new field. At the beginning stages of any new field, flexible standards, rather than rigid rules are more workable and conducive to future, as well as, gradual improvement. Given this consideration, the final Guidance is perhaps unlikely to incorporate a much clearer standard.

\(^{158}\) See, e.g., BOTANICAL DRUG DRAFT GUIDANCE, supra note 10, at 4, (“active constituents in a botanical drug might not need to be identified”; and “preclinical pharmacology and toxicology information that should be provided for legally available botanical products with no known safety issues during initial clinical trials may be markedly reduced.”).

\(^{159}\) Id. at 4.

\(^{160}\) Id. at 10.

\(^{161}\) Id. at 5.

In this context, it is worth noting that historically, IND and NDA reviews have been conducted on a case-by-case basis for NCE drugs. By the same token, IND and NDA reviews for botanical drugs will likely be subjected to the same case-by-case review. Thus, the implication for the industry will become increasingly clear as FDA begins to review and make decisions whether to approve or disapprove botanical drugs. Currently there are more than one hundred botanicals either individually or in formulas currently going through FDA's clinical trials. To date, no single NDA has been approved or even reviewed by an advisory committee, for a botanical drug product. The methods with which the FDA carries out the Guidance in the IND/NDA approval process for these botanical drugs in the next few years will be instrumental in shaping the direction of the industry.

2. The Return Side

The incentive structure for botanical drugs, provided by the Draft Guidance, also tracks the structure for other kinds of drugs. In other words, the Draft Guidance provides that a botanical drug enjoys five-year marketing exclusivity if it is a new chemical entity, or otherwise a three-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 to be anything but simple with botanical drugs. As acknowledged in the Draft Guidance, in most cases the active constituent of a botanical drug will be unknown. Therefore the length of the marketing exclusivity for these botanical drugs depends on how one interprets the term “active constituent” in the Draft Guidance. A narrow construction of “active constituent” means that most applicants for botanical drugs will not be able to claim the benefit of new chemical entity and the five-year exclusivity associated with it. As a result, most botanical drugs with unknown active constituents will enjoy only three-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.

163. See Leaders, supra note 145.
164. See Brevoort, supra note 1, at 161.
165. Id.
166. See BOTANICAL DRUG DRAFT GUIDANCE, supra note 10, at 4.
167. Id.
168. See id. at 4.
constituent, and thus the "new chemical entity." Under this broad construction, these botanical drugs will enjoy five-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 initiation of clinical trials of a 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.

**D. 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 a faster rate to patients, the final guidance should consider making the following changes.

The foremost change should be in the requirement for 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, the 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, the FDA may capitalize on the resources and expertise

---

170. See *Pharmanex*, 221 F.3d at 1158-1159.
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 to be used for a life-threatening disease, all the provisions for expedited review, treatment INDs and 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 seven-year marketing exclusivity).171

CONCLUSION

While herbal medicines are attractive alternatives for new drug development, it is important to recognize both the advantages and problems of herbal medicines from both technical and regulatory perspectives. To this end, special rules for governing the development of herbal medicines into FDA approved drugs are needed. With such rules in place, herbal medicines will become a crucial component of our arsenal against diseases. The FDA Draft Guidance for Botanical Drug Products represents a positive step toward this direction. However, the Draft Guidance is still largely based on regulations and policies developed for traditional new chemical entity drugs. As such, it fails to provide clarity and adequate incentives clarity for the drug industry to develop botanical drugs from herbal medicines. These concerns should be addressed in the FDA Final Guidance for botanical drug products.

171. Id.