New therapies from old medicines

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Although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met.

On October 31, 2006, the US Food and Drug Administration (FDA) approved the new drug application (NDA) for marketing of Veregen (sinecatechins), a topical treatment for perianal and genital condyloma. Unlike most small-molecule drugs that comprise a single chemical compound, Veregen, an extract of green tea leaves, contains a mixture of known and possibly active compounds. It is the first new botanical prescription drug approved since the publication of the FDA's industry guidelines for botanical drug products[1] in June 2004. The approval shows that new therapies from natural complex mixtures can be developed to meet current FDA standards of quality control and clinical testing. In recent years, interest in further development of herbal or botanical drug products derived from traditional preparations has been increasing steadily. Between 1982 and 2007, more than 350 botanical investigational new drug (IND) applications and pre-IND consultation requests were submitted to the agency. Nevertheless, doubts about the feasibility of subjecting such complex products to current investigation standards remain, and overall progress in the development of botanical new drugs has been slow. In this article, we describe the current regulatory environment in the United States for botanical new drug development, summarize our regulatory experiences and delineate the scientific and regulatory issues involved. We hope the introduction of the first botanical new drug in the modern era of FDA regulation will stimulate more clinical testing of potentially useful botanical products and eventually lead to new therapies derived from complex natural mixtures that will satisfy unmet medical needs.

Green tea leaves are the source for sinecatechins, the active ingredients of Veregen—the first botanical product to be approved as a prescription drug by the FDA.

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From dietary supplements to new drugs

In the United States, botanical products with health-related claims may be marketed as conventional foods, dietary supplements or drugs, depending on the specific claim, as described in the Dietary Supplement Health and Education Act (DSHEA)[2] of 1994. Conventional food and dietary supplements without disease claims are regulated by the Center for Food Safety and Applied Nutrition of the FDA. Under the Food, Drug and Cosmetic Act, a drug is defined as an article intended to mitigate, treat, cure, diagnose or prevent a disease or its related symptoms (disease claim), or as an article intended to affect the structure or function of the body (structure-function claim). Under DSHEA, a dietary supplement is considered a drug only if it bears a disease claim. In this case, dietary supplements are regulated by the FDA's Center for Drug Evaluation and Research (CDER). Botanical drugs are, in general, no different from nonbotanical drug products in terms of the applicable FDA regulations. Specifically, to be marketed, botanical drugs must be shown to meet the legal requirements for demonstration of the safety and effectiveness of a new drug in accordance with the relevant sections

of the Food, Drug & Cosmetic Act and to comply with the manufacturing requirements to ensure product quality.

Although dietary supplement manufacturers cannot legally make disease claims without approval of a new drug application, unsubstantiated medical uses for many botanical dietary supplements are well known and promoted in literature and news media or on the Internet. For products marketed without disease claims under DSHEA, reporting of clinical testing to FDA is not required. The distinction between disease claims and structure-function claims (sometimes called 'health claims') is defined in the FDA Final Rules of January 5, 2000 (and subsequent amendments)[3], but the distinctions are often subtle and can be confusing. Thus, a dietary supplement can claim a beneficial effect on 'bone health' but not on osteoporosis or fractures. People other than manufacturers, however, can place overt disease claims into the community. It is thus inevitable that many botanical dietary supplements are used by self-medicating consumers as drugs without regulatory assurance of efficacy and safety. To date, aside from a few nonprescription drugs marketed under over-the-counter monographs for botanical ingredients (e.g., psyllium and senna) and digitalis leaf (historically available in preparations controlled for glycoside content), only one botanical product, Veregen, has been approved by the FDA as a new prescription drug (see **Box 1** and **Table 1**).

Current US regulatory environment

In principle, the standards for product quality and the evidence of effectiveness and safety that are required for all new drugs approved by FDA also apply to new botanical products intended to be marketed as drugs in the United States. This is relatively straightforward for the clinical data, but product quality assurance needs to accommodate the fact that botanicals are mixtures in which the active compounds may not be known. Nevertheless, the regulatory intent is not to create a separate category of therapeutic agents for botanicals, but to ensure the same degree of confidence in their quality and clinical usefulness as exists for nonbotanical drugs.

To encourage and facilitate botanical drug development, CDER published its industry guidelines for botanical drug products in June 2004 (ref. 1). The new requirements for initial botanical investigations accommodate the unique features of botanicals and the practical difficulties in their development (e.g., complex mixtures, unknown or incompletely identified active ingredient and substantial prior human use). To support initial human trials, the early requirements for nonclinical pharmacology and toxicology studies and chemistry, manufacturing and controls (CMC) may be significantly reduced compared to those for a synthetic drug with no prior human exposure. For example, sponsors are not required to further purify or identify the active ingredients of botanical products. Unlike pure nonbotanical drugs, however, typical CMCs for the botanical drug substance and drug product may not be sufficient. Additional controls for the raw materials may be required to ensure batch-to-batch consistency.

The extent of the CMC requirements and nonclinical evaluation to support the IND submission depends on previous human experience with the preparation, deviation from traditional formulation and usage, and scale of the proposed clinical studies. In general, CDER encourages sponsors to submit all types of documentation of prior human experience for its preliminary safety assessment and will determine the relevance of that experience to the proposed studies. Although it is possible to initiate expanded clinical trials on some well-characterized and widely used botanical preparations without the support of nonclinical toxicity data, additional animal studies may be needed for final marketing approval[4,5]. It must be emphasized that the overall standards of evidence for safety and efficacy to support approval for botanical drugs are not more or less stringent than those of nonbotanical drug products.

It is worth noting that in the FDA's guidance[1], botanical drugs are considered by regulators to be in the same category as nonbotanical drugs[4,5]. They are subject to the same rigorous quality standards and requirement of clinical data. This is different from the approaches adopted by European (European Medicines Evaluation Agency (EMEA); London) and Canadian (Health Canada; Toronto) regulatory authorities. In addition to having categories of conventional (nonbotanical) drugs and food and dietary supplements, EMEA and Health Canada have established additional product categories, such as "herbal medicine products—well established use and traditional use"[6] and "natural health products" (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php). These regulatory agencies may rely on prior human use (including marketed traditional or herbal medicine use) and expert or literature reviews of available data on safety and efficacy, but may not have to include clinical trials conducted under the sanctions of the regulatory agencies, to authorize marketing approvals of botanical products with drug claims.

Review of botanical applications at CDER

To ensure consistent implementation of the guidance, CDER established the Botanical Review Team (BRT) in February 2003. The BRT provides scientific expertise on botanical issues to the reviewing staff, ensures consistent interpretation and implementation of the Botanical Guidance and related policies, consolidates experiences in regulatory review of botanical applications and compiles information on the status of botanical drug submissions for agency management. In addition, the BRT shares its pharmacognosy expertise (defined by the scope of BRT review outlined below) and regulatory experiences with other offices and centers in the FDA and various government public health agencies with responsibilities and interests in the medicinal use of botanical products. The BRT also provides assistance to sponsors of botanical applications in the interpretation of the regulation and their interaction with the Agency (contact information available at http://www.fda.gov/cder/Offices/ODE%5FV%5FBRT).

Applications for botanical drugs are reviewed by the same FDA scientific staff in chemistry, pharmacology, toxicology, clinical pharmacology, clinical medicine and statistics that reviews nonbotanical drugs. Botanical products are also reviewed by the BRT, which covers the areas of biology of the medicinal plants (identification and potential misuse of related species), pharmacology of the botanical product (activity and toxicity in old literature and new studies) and prior human experience with the botanical product (past clinical use and relevance to the current setting).

The purpose of BRT review is to provide historical background of the botanical, to help the clinical review division better understand the product and to search for information that may be relevant to the new use but not submitted in the application. Similar to the guidelines[1], the botanical manual of policies and procedures[7] was also designed mainly for the initial IND review. As the development of some botanical INDs progressed, other concerns more pertinent to NDA approval emerged. One such issue unique to botanical new drugs is a concern about the therapeutic consistency of marketed batches.

As products of natural complex mixtures, batch-to-batch variations in botanical products may be unavoidable. Therapeutic consistency of marketed batches cannot rely solely on CMC, as is the case for nonbotanical drugs, and may require additional support from non-CMC data. New thinking is needed to address this challenging botanical review issue (see below).

Box 1 Veregen: experience from the first botanical NDA

The subject of the first botanical NDA, Veregen, indicated for the topical treatment of external genital and perianal warts, is an extract of a single part (leaf) of a single plant (tea). The established name of the drug substance, sinecatechins, was derived from the Latin name for the Chinese green tea (*Camellia sinensis*) and the major chemical constituents (catechins). Compared to many preparations being used in alternative medicine and some under development, it is a relatively simple botanical product. As a naturally occurring mixture from a single part of a single plant, Veregen was not considered a combination product and was not subject to the FDA's combination rules (for more complex botanicals that are combinations, the current policy is under review at the FDA). Nevertheless, this NDA posed many challenging issues, and its approval is a significant milestone for botanical new drug development, providing valuable experience for both the FDA and industry. Reviews of this NDA are available on the FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

Plant biology of tea. FDA required that all cultivars used in clinical studies of Veregen be identified and that raw materials for future batches be limited to the same cultivars. In addition, the cultivars for future manufacturing had to come from the same farms that provided the clinical trial material. Any future request for change, either in cultivars or tea farms, would have to be submitted to FDA and approved by the agency before implementation. These control measures were designed to help reduce the variability in the chemical composition at the plant and raw material level.

Chemistry, manufacturing and controls. Compared to nonbotanical drugs, quality control for botanicals is more complicated, and the impact of changes in process and specification on clinical effects may be difficult to delineate. The quality specifications should be as stringent as technology permits, but, as noted above, they can rarely be as precise as those of pure drugs. Without data to correlate chemical quality with clinical response, the range of specifications can be based only on those of the clinical trial material. Even so, the necessity of controlling each individual major and minor catechin (rather than controlling only the total catechins) and the tightness of the control for the high-performance liquid chromatography peaks with unknown identities were important and unique NDA review issues that were considered carefully in setting the quality specifications for Veregen. As these measures will help ensure therapeutic consistency of marketing batches, any future changes in specifications must be preapproved by the agency.

Prior experience with green tea. There is an extensive body of research on green tea, but its clinical benefits are unsubstantiated, and little of it was relevant to Veregen's NDA because of the differences in dosage forms and clinical settings.

Judged by the vast human exposure to tea as a beverage, doses of catechins up to those ingested by heavy tea drinking (10 g of tea leaf, or approximately 1 g of catechins) per day seem to be safe[16,17]. But drinks containing concentrated tea are known to cause gastrointestinal symptoms, and serious adverse events have been associated with green tea extracts sold as dietary supplements for weight loss on the market[18–20]. These reports, however, had little bearing on the safety of Veregen's NDA because the product is administered as a low-concentration topical formulation (0.1 g of catechins per day) with low systemic absorption; this is approximately one-thirtieth of the same dose given orally. The clinical setting and treatment duration are also different from that of dietary supplement use. The sponsor conducted a full battery of nonclinical toxicity studies on this product, with no observed safety problems.

Overall, the BRT concluded that, other than the assurance provided by the history of tea drinking, prior experience with green tea was only marginally relevant to the safe and effective use of Veregen.

Clinical studies. For clinical data to support marketing approval, there is no difference between the regulatory requirements for botanical and those for nonbotanical drugs. Aside from the concern of therapeutic consistency for marketing batches (see below), the clinical development of Veregen presented no issue specific for botanicals. The efficacy of the drug in clearing external genital and perianal warts was studied using complete clearance of lesions as the endpoint and was shown adequately in two studies of conventional design (randomized, placebo controlled and multicenter) conducted in the United States and foreign countries (see http://www.accessdata.fda.gov/scripts/cder/drugsatfda). The overall response rates are shown in **Table 1**.

Therapeutic consistency of marketing batches. In approving this NDA, the FDA determined that therapeutic consistency of the commercial batches could be assured on the basis of the following considerations: first, Veregen is a relatively simple (single part of a single plant) botanical extract composed of a class of well-studied compounds (catechins); second, variations in raw material quality were minimized by restricting the cultivars and farms for the marketing batches to those used in the original application; third, robust CMC measures were required and put in place to assure that the composition of the extract was equivalent to that used in the clinical trial batches; and fourth, there was no significant difference in clinical response between the two doses (10% and 15%; see **Table 1** for efficacy results of clinical studies), indicating that the dose response curve is effectively flat and that the subtle variations within the uncharacterized fraction may not be crucial to therapeutic effect.

The FDA thus had adequate assurance of the therapeutic consistency of future marketing batches. Additional evidence (as suggested in the main text; see "Botanicals as variable, complex mixtures"), such as a clinically relevant bioassay, would be considered were the sponsor to request changes in cultivars and/or farm facilities. These were not needed, however, for approval of the application.

As the 10% preparation of Veregen could not be differentiated clinically from the 15% preparation, one question that arose was whether the lower ends of specifications could be extended. The BRT did not think this was needed, as the flat dose response of Veregen provides assurance that the variations and uncertainties that often cannot be measured with botanicals (other than the controlled chromatographic peaks) are not crucial to clinical response. At the same time, however, this should not be used to justify changes in major CMC specifications of the product, which provide the greatest confidence in consistency.

Choosing an appropriate established or generic name for a botanical drug can also be challenging, especially if more than one plant is included. Ideally, the generic name of the botanical should not only identify the plant species and variety, but also indicate any special agricultural and manufacturing processes. It is often not an easy task to incorporate all this within a name of practically useful length.

Table 1 Primary endpoint efficacy results of intent-to-treat trial

	Study CT 1017			Study CT 1018		
	Placebo	10% Veregen ointment	15% Veregen ointment	Placebo	10% Veregen ointment	15% Veregen ointment
n	103	199	201	104	202	196
Success (%)	38 (36.0)	99 (49.7)	102 (50.7)	35 (33.7)	111 (55.0)	111 (56.6)
Fail (%)	65 (63.1)	100 (50.3)	99 (49.3)	69 (66.3)	91 (45.0)	85 (43.3)
P value	—	0.0384	0.0284	—	<0.001	<0.001

Data were analyzed by Fisher's exact test. Source: US Food and Drug Administration

Analysis of botanical drug IND submissions

Before the early 1990s, fewer than ten botanical INDs had been submitted to the FDA. As the FDA initiated its plan to draft botanical guidelines in the mid-1990s, interest in developing botanical drugs escalated. The number of submissions increased rapidly from 5–10 per year in 1990–1998 to an average of 22 per year in 1999–2002 and nearly 40 per year in 2003–2007 (**Table 2**).

The distribution of botanical submissions from 1999 to 2007 among therapeutic categories is shown in **Figure 1**. Among the therapeutic areas, cancer and related conditions received more attention than others, followed by inflammatory and pain disorders, endocrine and metabolic diseases, viral infections, and dermatological and dental indications. These data indicate a growing interest over several therapeutic areas in rigorous clinical evaluation of botanical drugs, with a focus on indications where there is a clear medical need for new treatments (e.g., cancer, inflammatory disorders and viral infections).

Of the 282 pre-INDs and INDs submitted during this period, only 36% were multiple-plant combinations, reflecting the difficulties in working with more complex preparations. Of the 282, 113 (40%) were submitted by commercial sponsors; the remaining 169 (60%) were proposed by academic investigators, mostly to conduct small-scale proof-of-concept studies and without intention to commercialize the products. Although most investigators had manufacturers' support for the submission, however, many manufacturers were reluctant to be directly involved in sponsoring the products. And without detailed CMC information from a manufacturer, it is often difficult for the FDA to assess product quality and safety.

Nonclinical toxicity studies to support the initial human trials were waived for most botanical applications. Instead, as contemplated in the guidelines[1], the assessment of safety for preliminary clinical studies has relied on past human experiences documented in literature and reference compendia, including previous clinical studies, historical use of the botanical ingredients in alternative medicine or recent marketing as dietary supplements.

Although pre-IND consultation is not required by regulations, many sponsors benefited from preliminary discussion with the review divisions. In most cases, the botanical INDs were well prepared, and for 87% of them the proposed initial clinical studies were allowed to proceed, either after initial review or after correction of deficiencies by the sponsor.

For the 225 INDs submitted during the last 9 years, 37 (13%) had their proposed studies placed on clinical hold (clinical studies cannot proceed) for one or more serious deficiencies that could not be resolved. These were either withdrawn by the sponsors or remain on clinical hold. Common serious deficiencies that resulted in clinical hold include previous human experiences and/or existing animal toxicity data that were inadequate to support the safety of the proposed clinical trial; insufficient characterization of the botanical materials, substances or products; ingredients in the botanical drug product with potentially serious toxicity that had not been tested adequately in animal studies; quality issues such as contamination or adulteration that compromised the safety and integrity of the study; and problems with the clinical trial design, such as inadequate controls, protracted study duration not supported by prior clinical experience or animal data, and inappropriately defined trial subjects.

Unique regulatory issues

Botanical products have unique characteristics that distinguish them from highly purified or synthetic drugs. These include variable complex mixtures, multiple-plant combinations, extensive previous human use and availability as dietary supplements before approval as drugs.

Botanicals as variable, complex mixtures. Botanical products derived from multiple or even single plants are complex mixtures of numerous chemical entities. Even for extensively studied plants, only a small fraction of the constituents have been isolated and identified. Complete characterization of each individual constituent in botanical drugs, even those derived from a single plant, remains a formidable task. Thus, even in the best case, the chemical composition of a botanical preparation is not completely defined, nor are all active ingredients identified. Strength and potency of these vaguely defined products are not easy to determine, adding to the difficulties in CMC controls and clinical pharmacology studies.

As botanical drugs are often not highly purified from raw materials, contamination with trace heavy metals, residual pesticides and infectious microorganisms is a major quality concern, and control of these impurities is more complicated than it is for pure chemical drugs. In addition, maintaining stability of botanical drugs can be difficult because of their biological nature.

Because plant growth and composition can be affected by soil, weather, seasonal variations, geographic location and other agricultural practices, batch-to-batch inconsistency is a common problem. Manufacturers can achieve adequate quality control of botanical

Table 2 Number of botanical pre-INDs and INDs submitted to CDER from 1999 to 2007

Submissions	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total for all years
Pre-IND	0	4	3	5	9	12	6	11	7	57
IND	21	16	21	16	31	21	38	22	39	225
Total	21	20	24	21	40	33	44	33	46	282

Source: US Food and Drug Administration

starting materials by applying the principles outlined in the FDA's botanical guidance and by following good agricultural and good collection practices for starting materials of botanical origin (e.g., ref. 8). After cultivation, the variation in processing methods and their potential influence on the therapeutic effects further complicate the quality issue of botanical materials. For example, processing of certain Chinese herbs according to ancient methods may reduce their toxicity[9]. For these reasons, a detailed description of the raw materials and processes, not just of the drug substances and the final drug products, is required for all botanical products.

Even though the quality control of botanicals is more complicated than that of highly purified drugs, reasonable quality assurance is still possible and must be implemented. Useful measures include controlling the raw material in the field, 'fingerprinting', conducting chromatographic analyses of marker compounds and developing clinically relevant bioassays to quantify their activity (for more detailed recommendations, see ref. 1). Although the degree of batch-to-batch consistency at the molecular level required for highly purified compounds may not be attainable for many botanical drugs, an integrated assessment with several different analytical technologies may provide the needed level of quality control for botanical drug products. The crucial question for approval of botanical drugs is whether the future marketed batches will have the same therapeutic effect as that observed in clinical trials, an especially difficult question for botanical drugs with unknown numbers and identities of active ingredients. Recent recommendations delineated in the EMEA's guidelines on quality of combination herbal and traditional medicinal products[10] are in agreement with the FDA's current thinking. We have proposed several approaches to address this concern.

First, manufacturers should attempt to control CMC robustly. A set of tight CMC specifications comparable to those for small-molecule drugs, achievable if all or most active ingredients are recognized, would be adequate to ensure therapeutic consistency of future batches, even in the absence of a clinically relevant bioassay (see below). For many botanicals, however, active ingredients are uncertain, and it may not be possible to narrow the ranges of specification parameters as much as would be needed to assure therapeutic consistency.

Second, clinically relevant bioassays should be adopted. For botanicals with numerous potentially active ingredients, such assays provide a measure of overall potency that would ease many aspects of new drug development and greatly facilitate quality control in post-approval manufacturing.

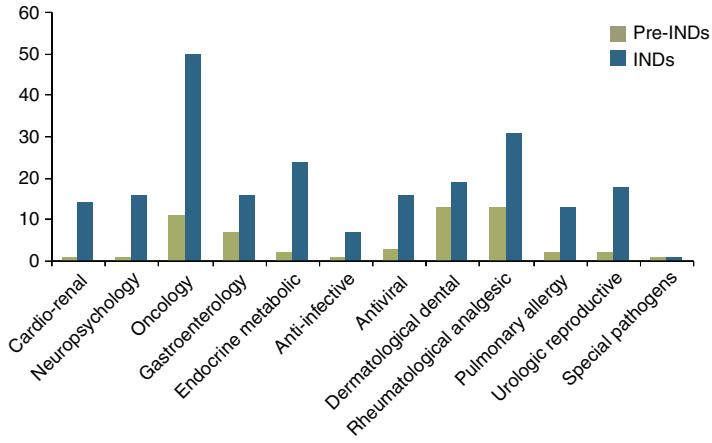

Figure 1 Botanical pre-INDs and INDs submitted to CDER from 1999 to 2007, categorized by therapeutic area.

Third, clinical dose response data are a must. If clinical effects are not sensitive to dose (flat dose response), then the batch variations in CMC specifications (still within the acceptable range) and other uncontrollable uncertainties may be of less concern.

Fourth, sponsors should test multiple batches of their botanical drug in phase 3 trials. Differences in the clinical efficacy and safety of various batches (representative of those within the acceptable ranges of specifications) can be tested in such clinical studies, similar in concept to that of a multicenter clinical trial. It is not necessary to show significant effects for each individual batch; a negative 'treatment by batch' interaction will provide some assurance that therapeutic effects will not be affected by batch-to-batch variations. This approach can help in setting the appropriate CMC specifications for the product for future batches, especially when a clinically relevant bioassay is not available.

Finally, postmarketing confirmation trials should be considered. When none of the above measures can provide the needed assurance on therapeutic consistency of future marketing batches, especially when the source of raw material and/or manufacturing processes are significantly changed after approval, repeating clinical trials to reconfirm the efficacy may be necessary. Whether this can be done will depend on the indication, the kind of study needed (placebo control or comparison of batches) and a variety of other factors.

Not all of the above approaches will be necessary for every case, but a combination of some of these approaches will usually be needed. Available evidence from each of the above should be considered together with other information in the overall context. For example, in cases with strong assurance from non-CMC data, the CMC requirements could be adjusted accordingly. Again, the ultimate objective is consistency in clinical efficacy and safety, for which chemical quality control is an important measure but may not be sufficient by itself.

The variability and complexity of natural compounds will make it extremely difficult in most cases to establish a definition of 'equivalence' for botanical drugs and to prove that two 'similar' products are pharmacologically identical or therapeutically interchangeable. Unlike highly purified drugs, the active compounds in botanical drugs are often not identified, and many unknown compounds in the natural mixture could be potentially active. It will therefore be technically challenging to define acceptable generic copies of botanical new drugs.

Botanicals as multiple-plant combinations. The fact that many botanical products are combinations of materials from multiple plants also makes clinical assessment difficult. Regulations require that the contribution of each component of the fixed combination be shown. Although each of the individual plants in the combination may have been used widely, either alone or in combination with other plants, the reasons for combining many plants in the specific product are often not clear, and there is rarely good evidence of a contribution to effectiveness. Although factorial trials to show such a contribution can be designed, for combinations of more than three or four components, the clinical study

can become quite large, and demonstration of a significant effect of each component very challenging.

Botanical drugs may contain a single part of one plant, multiple parts of the same plant, or different parts from many (often more than three) plants. In general, the agency has not treated naturally occurring mixtures of components in a single plant part as combinations, but does consider parts of plants and different plants elements of a fixed-combination product. How the FDA should consider combinations of more than one plant part or of different plants is currently under discussion. In the IND stages, early clinical studies of botanical products need not establish the contribution of each component but would focus on the entire combination. For final NDA approval for marketing, at this time, the sponsors should consult with the review divisions in CDER.

Previous human use of botanicals. For many botanical preparations, extensive human experience can provide some degree of comfort in their safety, but these past human experiences have rarely been documented rigorously. They are often of large quantity but mostly anecdotal and of poor quality, and may be without clear relevance because of changes in the botanical products and differences in the clinical settings. How these types of human data can substitute for conventional animal toxicity studies in the safety evaluation is a significant challenge. As a result, safety assessment for studies of certain botanical preparations without nonclinical toxicity data can be difficult, and judgments are necessary.

As the traditional uses of many botanical products are largely based on theory and practice of alternative medicine, interpretation of these experiences has been a problem in designing clinical trials. In standard references, the pharmacology of botanical products is typically complicated because of complexity of the natural mixtures. The products are often indicated to treat a great variety of seemingly unrelated symptoms, without reference to the mechanism of action or the effect on the underlying diseases. Furthermore, in alternative medicine, the definitions of diagnoses, symptoms and treatment-related adverse events are often vague and difficult to understand or correlate with Western medical terminology. In contrast, development of new drugs usually starts with a clear understanding of its pharmacology and potentially drug-related adverse effects. Thus, the previous human experience documented in the language of alternative medicine is usually not very helpful to people trained in Western medicine in designing studies and is often difficult to use in assessing the safety of the proposed clinical protocol.

Prior human experience and strong beliefs arising from it may, however, make it difficult to recruit subjects for placebo-controlled trials, which would generally be needed for most conditions treated by botanicals. The beliefs also make it especially crucial to ensure that blinding is maintained, even if it requires double and triple dummy approaches. This may seem a small difficulty to those familiar with the randomized, controlled clinical trials of pure chemical drugs, but for many sponsors engaged in the development of botanical drugs, the importance of these issues needs to be stressed.

Botanicals marketed as dietary supplements. For botanical products legally marketed as dietary supplements, an IND submission to the FDA may confer a favorable distinction that translates into a marketing advantage over other competing products. Many promotions for botanical dietary supplements have explicit descriptions of the ongoing FDA-sanctioned clinical trials with implications that extend well beyond the structure-function claims allowed dietary supplements. Because the average consumer cannot differentiate an IND from an NDA, the sponsor's announcement of an IND allowing clinical trials to proceed may be perceived as the government's approval for a drug claim. Furthermore, if the sponsor actually proceeds with clinical investigations under the IND, there is always the risk that an unfavorable result of the studies might jeopardize the current sale of a botanical dietary supplement. Thus, the IND submission has become the end of the commercial development for some sponsors, rather than the means to continue further investigations leading to NDA approval. Unfortunately, there is no legal mechanism to discourage this opportunistic practice or to distinguish it from a genuine development effort, other than assuring that studies are of adequate design.

Pre-existing market access of botanicals as dietary supplements may complicate and diminish the regulatory distinction between an approved botanical new drug and competing dietary supplements of the same botanical ingredient(s). The continued availability of previously marketed botanical dietary supplements will not be affected by a new drug approval for the same ingredient(s), and labeling differences between the products may or may not be appreciated by the general public. If patients and medical practitioners are not convinced that the approved new botanical drug is distinct from the dietary supplements, any advantage of an NDA approval and market exclusivity may not be realized. Because no botanical dietary supplements have pursued investigations leading to approval as new drugs in the United States, this concern remains hypothetical. But the potential lack of marketing advantage seems to be a disincentive for the development of botanical new drugs beyond the initial IND stages. Probably for this reason, few clinical trials have been proposed by industry sponsors to study many old, widely used botanical formulations.

Conclusions

To encourage and facilitate botanical drug development in the United States, the FDA has published guidelines[1] and established a new review process that includes a dedicated BRT in CDER. More than 350 botanical pre-INDs and INDs have been submitted to the FDA since 1982, most of which were filed after DSHEA was enacted in 1994. Interest in the development of botanical products through the IND process from 1990 to 1998 (ref. 5) has continued to grow.

Despite the increasing IND activity, progress in developing new drugs from botanicals has been slow, with only one botanical NDA submission and approval to date. Although recent clinical studies, including a few sponsored by the US National Institutes of Health (Bethesda, MD, USA), were not able to confirm the effectiveness of even the well-known botanicals (e.g., echinacea and St. John's wort)[11–15], it is probably premature to draw any conclusion about the prospects of botanical drugs in general, as few commercial botanical INDs have reached late-stage development.

Possible reasons for the disappointing pace of development include the difficulties in characterizing ill-defined mixtures to provide assurance of quality before entering large phase 3 studies, and the problematic translation of anecdotal experiences in traditional alternative medicine into testable hypotheses that can be applied in modern clinical research. Botanicals providers have also noted during public meetings that the existing marketing of botanical dietary supplements, and thus the absence of meaningful exclusivity, is a significant disincentive to rigorous drug development.

In general, most botanical IND applications were allowed to proceed with their proposed initial clinical studies; few were placed on clinical hold because of safety concerns. Although many technical challenges remain unresolved, both CDER and botanical product companies have started to address the regulatory issues that are specific for the sector and are rapidly

gaining experience in applying the current pharmaceutical standards to botanical drug products. The agency's regulatory policies are intended to encourage botanical drug development, and clinical investigations of botanicals are in fact expanding. Although Veregen was a relatively simple botanical product, its approval attests to the success of this approach and gives both the FDA and industry a framework for bringing other botanicals to market as new drugs that are held to the same standards as conventional nonbotanical drugs.

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