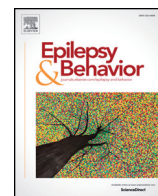




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Botanicals as “new” drugs: US development

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ABSTRACT

Botanicals are ingredients that can be marketed as foods, drugs, cosmetics, and medical devices in the United States. When a botanical is intended to diagnose, treat, prevent, mitigate, or cure a disease, it is considered to be a “drug”. This article reviews the US regulatory requirements for botanicals as “new” drugs. An overview of the regulatory principles used to determine product category and the basic elements of an Investigational New Drug application and New Drug Application with the US Food and Drug Administration are presented.

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1. Introduction

Current treatment options for people with epilepsy include a variety of options: drugs, surgery, and procedures, such as neurostimulation. For some forms of epilepsy, special diets may also be of benefit. Seizures in approximately 70% of those diagnosed with epilepsy respond to treatment “at least some of the time”. The remaining 30% may develop intractable seizures, with inadequate relief from available treatments [1]. Current interventions are obviously not working for all patients.

Individuals who experience suboptimal efficacy from mainstream interventions often turn to “complementary or alternative medicine” (CAM). Such use is quite prevalent in patients with refractory epilepsy [2]. The US government has considered botanicals (herbal or traditional medicines) a category of CAM [3].

Historically, botanicals were an intrinsic part of the US drug armamentarium. However, since the 1940s, the majority of US drugs have been single “active” molecular ingredients, or “New Chemical Entities” (NCEs). When a natural product is the source material for a new drug, the process most favored for pharmaceutical development has been identification, isolation, purification, and whenever feasible, synthesis of the active drug substance [4]. As a result of many factors, complex drugs disappeared from the US market by the early 1980s. Drug sponsors were struggling with the lack of clarity regarding botanicals in the United States, particularly for those products that represented complex mixtures where the components acted in concert to produce biological effects [6].

The passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 brought some hope. This was the first time that US food and drug law specifically called out “an herb or other botanical” as ingredients that can be used to constitute dietary supplements [7]. This caused many in the industry to conclude that botanicals must be sold as either conventional foods or dietary supplements. In particular, it reinforced the notion that nonpurified botanicals could not be considered as “drugs” in the United States.

Around the same time period, the FDA started an internal working group on botanicals to improve transparency regarding the agency's regulation of botanicals. These efforts resulted in a policy guidance: the *FDA Guidance for Industry – Botanical Drug Products* [Chemistry – Final June 2004]. From a regulatory stand point, “botanicals” are defined as *products that contain ingredients of vegetable matter or its constituents as a finished product*. These ingredients can be *whole plants or plant parts, including plant materials – either juices, gums, fatty oils, scent oils, etc., also algae or macroscopic fungi and similar products*. Products of fermentation (yeast, bacteria), highly purified or chemically modified substances derived from botanical sources (such as digoxin or paclitaxel), and homeopathic drugs or elixirs are excluded from the regulatory definition, as these are handled in other parts of FDA regulation and policy [8].

The FDA has been advising sponsors on how to develop botanicals as drugs. By the time the guidance was made public, the agency had received hundreds of inquiries and filings on botanicals. Within the past decade, two botanical new drugs have been approved by the FDA. Veregen® (sinicatechins; ointment, 15%; Medigene, Planegg/Martinsried, Germany) is a proprietary extract of green tea (*Camellia sinensis* Kuntze) for the topical treatment of genital and

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perianal warts [9,10]. Fulyzaq™ (crofelemer; 125-mg tablet; Salix Pharmaceuticals, Raleigh, North Carolina, USA), is a proprietary oral extract of the blood-red latex of the South American croton tree (*Croton lechlerii* Müll. Arg) [11,12]. Both drugs were shown to meet the same legal criteria for safety and efficacy and are manufactured to the same quality standards as other prescription drugs in the United States.

2. Principles of US regulation

The 2004 FDA botanical policy guidance provides an algorithm regarding decision points for sponsors to determine which regulatory pathways could be available to their products, based on product attributes. The four basic principles are: route, form (formulation), safety, and “intended use”.

Route refers to how a product is administered. A product that is administered by the oral or enteral (digested by the gastrointestinal tract) route has the broadest range of potential market categories, including foods (including dietary supplements), cosmetics, and drugs; whereas sublingual administration is restricted to drugs.

Form or formulation can also help to define the regulatory category/ies. For example, by law, a dietary supplement must be in the form of a capsule, powder, softgel, gelcap, tablet, liquid, and other specific forms [7]. Dietary supplements cannot be beverages, meals, or other forms of “conventional” foods. A drug, however, can assume any formulation.

Safety is also dependent upon the regulatory category chosen. Foods, including dietary supplements, must be “generally recognized as safe” or contain ingredients with “a history of use or other evidence of safety” which “will reasonably be expected to be safe...” Foods and categories of foods, including dietary supplements, must be safe for the general population.

In distinct contrast, a “new drug” is defined as a drug (marketed after 1938) that is *not generally recognized as safe and effective* under the conditions prescribed, recommended, or suggested in the labeling [FD&C Act Section 201p.; 13]. In the context of drug approval, the meaning of “safety” is not explicitly defined in statute or regulations. It is a relative term derived from the recognition that all drugs with biological activity have some capacity to cause adverse effects. Thus, the safety of a drug is assessed by determining whether a drug’s benefits outweigh the risks for the intended purpose and population [14].

3. “Intended use”

The overarching principle by which the regulatory category of a product is determined is its *intended use*, as defined by its labeling. *Labeling* encompasses not only the required elements that make up the printed packaging (including the Drug label), but also any direct or implied claims from the manufacturer or distributor in the product packaging, advertising, and promotional materials displayed in any format, including oral, written, and electronic.

The federal Food, Drug and Cosmetic Act (FD&C Act) defines “drugs” as “articles intended for use in the **diagnosis, cure, mitigation, treatment, or prevention** of disease...” and “articles (other than food) **intended to affect the structure or any function of the body** of man or other animals” [Sec. 201(g)(1) of the FD&C Act; 13]. For example, the approved drug, Dilantin Infatabs (Phenytoin Chewable Tablets, USP), is “indicated for the *control* of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and *prevention and treatment* of seizures occurring during or following neurosurgery” [Drug label – FDA website; *emphasis added*].

In contrast, a dietary supplement is legally defined as “a product (other than tobacco) that is **intended to supplement the diet**...” [7]. While a dietary supplement is permitted to make “structure” or “function” claims, this category is explicitly prohibited from making “disease” (drug claims). Dietary supplements bearing “structure-

function” claims must also carry the following disclaimer on the product label: “The FDA has not evaluated this claim. This product is not intended to diagnose, mitigate, treat, cure or prevent disease.” [7].

The United States, unlike other regulatory systems, has no separate category for “herbal” or “traditional” medicine or botanicals. Botanicals are considered ingredients, which can be marketed in many different ways. They can be conventional foods, dietary supplements, drugs, cosmetics, or medical devices, depending on the attributes of the finished product. Regardless of how a product is currently marketed, if it is intended to “treat”, “prevent”, or “mitigate” seizures, it becomes a “drug” under the statute.

4. “New” drug regulations (the IND–NDA process)

The development of a “new” drug invokes the Investigational New Drug (IND) and New Drug Application (NDA) regulations [13].

It is legal for consumers and patients to purchase and use foods, dietary supplements, and other nonapproved interventions to treat their medical conditions. Practicing physicians can also recommend such products to their own patients, considered as the “practice of medicine”. However, to conduct clinical assessment or research of a nondrug product that is intended to diagnose, treat, prevent, mitigate, or cure a disease and to affect the structure or function of the body, will require the filing of an IND application.

An IND is a “Notice of Claimed Investigational Exemption for a New Drug”. By allowing an IND to proceed, the FDA is exempting the unapproved new drug from the legal requirements of an approved drug, thereby allowing the unapproved drug to cross state lines (interstate commerce) for the purposes of testing and development.

5. INDs (“three-legged” stool)

The IND application can be best envisioned as a “three-legged” stool (see Fig. 1), with the “legs” representing key sections of the filing: 1) Chemistry–Manufacturing–Controls (“CMC”) – defines the product and how it is made; 2) Nonclinical – in vitro and in vivo animal testing for toxicity, as predictors of human toxicity; and 3) Clinical – studies in humans to determine safety and efficacy of the drug for a specific clinical use, and to define the dose, route and schedule.

6. Clinical testing

In most cases, an IND must be considered at the point when a product is to be tested in humans [19]. Under the drug regulations, an IND is required to be filed for research that involves:

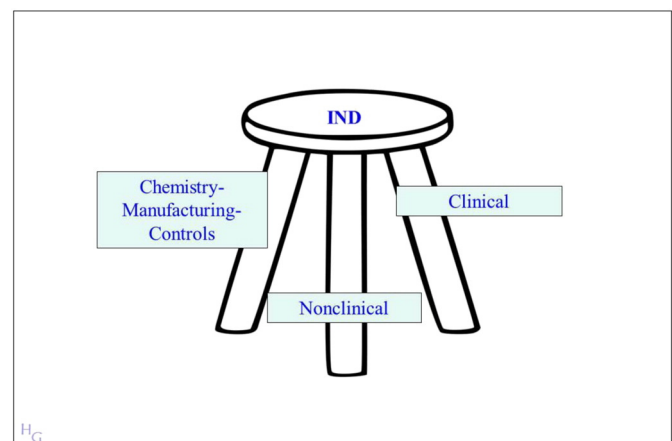


Fig. 1. The IND: “3-Legged” stool of drug development.

- A *drug*, as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1)).
- A *clinical investigation* as defined in the IND regulations (21 CFR 312.3).
- A *drug* that is not otherwise *exempt* from the IND requirements in part 312 [see 15].

A development program of a botanical drug would not generally differ in design and execution of clinical studies from that of any other drug for the same or similar intended use. Each clinical protocol must fully describe the study population(s), include standard outcome measures assessed through validated instruments, and be designed to have reasonable controls and planned analyses. Subjects must be appropriately monitored for safety, including “early stopping rules” as needed, depending on both the nature of the botanical product and the study population(s). Thus, clinical research under an IND must adhere to Good Clinical Practices (GCPs), which govern most research in human subjects. This includes human subject protections and privacy, review of the research by a qualified ethical review board, proper informed consent, and adequate safety monitoring and reporting of adverse events [FDA-ICH Guidance E6]. The protocol and other documentation must be submitted as part of the IND, which the FDA will review and discuss, and must “allow” to proceed.

Because botanicals are products of nature, they may be marketed and used as foods, nutritional or dietary supplements, or even as foreign drugs. Thus, they may be available for human use, prior to and concomitant with the filing of a US IND. As such, the sponsor may be aware of a substantial history of prior human use for the botanical. Knowledge of prior human use can expedite the US development process, if properly documented. Ideally, prior use should represent the same formulation, dose, route, and schedule for the intended use to be developed under the IND.

Foreign clinical studies can also be used to support safety and efficacy in US regulatory applications, if they conform to GCPs. However, it is rare that foreign data would represent the only clinical data submitted to the FDA in support of a marketing application. In most cases, a non-FDA vetted study was not designed to meet US regulatory needs, or the product may not have been compliant with drug standards (see below).

7. Nonclinical testing

Regardless of the amount of prior human use, additional safety data will likely be required by the FDA to support a drug approval application. Nonclinical testing may be required to address specific safety questions that cannot be easily assessed in humans [29]. Routine nonclinical toxicity studies generally required for all drugs are shown in Fig. 2 [16, 17].

Although the FDA may be willing to negotiate the amount of nonclinical toxicity data necessary to initiate clinical studies under an IND based on the sponsor's ability to document prior human use and safety, nonclinical testing becomes particularly important when a botanical drug is being developed for a new route, new dose, new formulation, or new target population (indication) not supported by prior human use.

In addition to the standard testing, the FDA may request additional nonclinical studies, depending on the product, its biological effects, and route of administration. Such studies may include: nonclinical pharmacologic, toxicokinetic, or nonclinical pharmacokinetic studies; reproductive–development toxicity studies for drugs that are intended to be used by pediatric populations or those of child-bearing capacity; and skin sensitivity studies for topical applications. For certain products, assessment of carcinogenic potential may be prudent, as well as

Test	<i>In Vitro</i>	<i>In Vivo</i>	Comments
Mutagenicity (Ames Test)	X		Standard testing for new food, dietary and drug ingredients.
Genotoxicity	X	X	[as above]
Clastogenicity (chromosomal aberration test)	X		[as above]
Acute Toxicity (single/repeat dose)		X	If no prior human safety information; or depending on intended use (<7 days)
Subacute Acute Toxicity (e.g., 28 day)		X	For intended use from days to 28 days
Subchronic Toxicity (3 months)		X	For intended use up to 3 months
Chronic Toxicity (6 -12 months)		X	For intended use exceeding 3 months
Reproductive-Developmental		X	For pediatric and child-bearing populations
Carcinogenicity		X	Depends on ingredient safety
Specialty testing	X	X	For special routes (e.g., topical, transdermal, ophthalmologic, etc.); special purpose (e.g., immunogenicity, sensitivity, etc.); special target organs (e.g., cardiac, neurologic toxicity, etc.)
Pharmacology/Pharmacokinetics	(X)	(X)	May not always be feasible [See text.]

Fig. 2. “Standard” nonclinical testing for drug ingredient (scheduling of nonclinical testing can be negotiated with the FDA, particularly for botanicals).

phototoxicity, immunotoxicity, juvenile animal toxicity, and abuse liability studies. It may be necessary to assess potential interactions of the botanical with other drugs and with foods [18].

Such studies should be conducted under internationally harmonized testing protocols. Testing in animals should be conducted in laboratories that have been certified to meet requirements called 21 CFR Part 58 Good Laboratory Practices.

Sponsors of botanical drugs will, therefore, need to negotiate the types of studies that are required for their products on a case-by-case basis, but which depend on many factors (route, product properties, intended use, safety profile).

8. Chemistry–Manufacturing–Controls (CMC)

To be approved, an investigational new drug must demonstrate quality. This includes documentation of identity, purity, potency, and stability, which translates into lot-to-lot consistency and clinical reproducibility.

Compared to a standard small molecule (NCE), the CMC section for a botanical drug can be particularly onerous. Documentation of each of the source materials and chemicals used during the product manufacturing processes is required. It starts with detailed information on how the drug is manufactured, starting with the botanical raw material (BRM). The identity of the BRM will include proper classification (genus, species, cultivar), collection of voucher specimens, and documentation of handling (e.g., vendors qualification, growing conditions, harvesting, processing). Potential drug sponsors and researchers interested in a particular botanical to study or develop for a drug indication should consider its availability and supply of the botanical raw material (BRM). Consideration regarding BRM sustainability and environmental impact and local laws and treaties where the BRM is grown, regarding “rights” to the product, should be addressed up front. All of the above fall under Good Agricultural and Cultivation Practices (GACPs).

Determining what is ‘active’ in a botanical is rarely straightforward. By regulatory definition, a botanical drug substance must contain more than one molecular constituent. Most botanical processes yield drug substances with legions of constituents with diverse biochemical profiles and pharmacologic effects. A constituent identified as “active” for one particular effect may be “inactive” for others. The so-called “inactive” ingredients have also been found to contribute to the biological effects of a product indirectly, through modulation of the actives. For these reasons, the FDA often considers the entire botanical drug substance to be the “active” [8].

Characterization of the botanical drug substance can also be difficult to achieve. Rather than standard chemical testing, a botanical drug may be characterized using biomarkers and chemical “fingerprinting”.

Prior to conducting pivotal clinical studies for an NDA application, the drug manufacturing processes must meet the requirements for a drug (drug Good Manufacturing Practices — “GMPs”). Detailed descriptions of each process step, including reference standards, are needed. Analytical steps and assays, batch records, lot-release specifications, and stability testing are all important parts of the CMC section. They help to ensure reproducible dosing in the clinic and consistent clinical safety and efficacy from lot-to-lot.

9. Marketing application (NDA)

Drugs, as a category, are subject to the FDA’s greatest level of oversight. US law requires that new drugs undergo premarket approval. The FD&C Act requires: “...evidence consisting of *adequate and well controlled investigations*, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling...” [13; 505(D), as amended].

A New Drug Application (NDA) must be submitted to the FDA for review and approval in order to market the new drug in the United States. It represents the compilation of data gathered under the IND and from

other sources to support the legal requirements for drug approval. The NDA includes detailed information and validation on the steps, processes, and systems used throughout the manufacturing process. It includes the raw data as well as integrated summaries of both safety and efficacy. The agency reviews the drug sponsor’s documentation of conformance to the regulations. Thus, raw data sets are reviewed by the agency’s experts. In addition, the FDA staff conducts audits of the drug’s manufacturing facilities, as well as selective audits of the nonclinical and clinical testing sites, both on a “for cause” basis, and as a prerequisite of drug approval [20].

To approve a new drug for marketing, sufficient documentation must be presented to the FDA in the NDA to support the drug’s safety and efficacy for its intended use. “*FDA grants approval to drugs after a sponsor demonstrates that their benefits outweigh their risks for a specific population and a specific use, and that the drug meets the statutory standard for safety and efficacy*” [21].

10. Unique characteristics of botanicals

A botanical new drug must meet the same legal standards for FDA approval as other new drugs; however, it may do so by providing somewhat different information than a NCE drug. Botanicals may also have some distinct advantages over NCEs. Some of these characteristics and differences are shown in Fig. 3.

Unlike NCEs developed in a laboratory, botanicals are products of nature. For most drugs, the IND is the initial step in the federal regulatory process, which allows the investigational drug to be tested in humans (“first in Man”). In contrast, botanicals often begin the US regulatory process with a significant history of prior human use. This is because many botanicals are already marketed as foods, dietary ingredients, or are foreign drugs.

Most botanicals have a multitude of components, not all of them chemically defined. Due to their complex nature, many botanicals cannot be easily assessed using standard testing for NCEs. This makes the provenance of the BRM, knowledge of the process steps in the manufacturing, standardization, and formulation essential to product identity and consistency [29,30].

The mechanisms by which a botanical exerts its biological effects may be unknown or too complex to define. When pharmacologic and pharmacokinetics testing is infeasible, such testing can be waived as a requirement. In the absence of such testing, it may be more difficult to determine a “wash out” period for a botanical, or to predict and study “drug–drug” interactions.

In many ways, botanicals may more closely resemble complex biologics regarding how they are handled in the clinical setting. The FDA applies approaches that are more commonly used for biologics. Because complete characterization may not be possible to achieve, botanicals from different manufacturers or different processes cannot be considered as interchangeable. Thus, botanicals are most often defined by process control and validation, for which “the process is the product, and the product is the process” [FDA]. Such complexity can, however, provide intellectual property protections, even in the absence of patents.

In reviewing botanical drug applications, these factors are taken into account by the FDA, and the agency advises sponsors and makes adjustments on a “case-by-case” basis.

Botanicals hold limitless possibilities for drug development. Based on their complex, polymolecular nature, they may be uniquely positioned to address refractory states in patients who experienced efficacy from single molecular drugs.

Although most botanicals are currently being sold as “dietary supplements” in the US, there is no ability to promote or to test such products for their effects on disease states. As drugs, botanicals may be able to offer a wealth of possibilities regarding treatments for previously drug-resistant clinical conditions, such as refractory seizure disorders [5, 22–28].

Characteristics	Botanical* Drug	Standard** Drug
Chemical composition	complex heterogeneous polymolecular	“simple” single molecular
Active(s)	multiple active constituents; true active constituents may be unknown; (entire drug substance is the “active”)	single active ingredient
Characterization	high or low	high
Control	process controlled	“final vial” controlled
Source materials	“dedicated” sourcing Good Agricultural & Cultivation Practices (GACPs) may apply	may or may not require dedicated sourcing
Dose/Route/Schedule	may already be known (prior human use)	discovered through nonclinical and clinical testing
Predictors of efficacy	clinical (prior human use)	generally based on nonclinical testing
Mechanism of action known	rarely	often
Nonclinical toxicity testing	scheduling may be negotiable (depends on prior human use)	prior to starting clinical studies
Pharmacokinetics	depends on product (may be infeasible)	required
Clinical targets	polymorphic	single receptor
“Patent protected”	sometimes, but not always	generally
Expedited programs apply	Yes	Yes
Generic equivalents	May be avoidable	Generally unavoidable

Fig. 3. Characteristics of botanical and standard drugs. *Polymolecular drug substance, as defined by the FDA Guidance for Industry on Botanical Drug Products. **Single molecular drug substance.

Botanicals that can demonstrate consistent, clinically relevant, biological activity in scientifically sound nonclinical and clinical studies may be prime opportunities for new drug development in the United States. Sponsors considering to pursue the rigorous US drug approval process may find that the development (“time to market”) can be expedited as a result of the unique characteristics of botanicals as a novel drug “class”.

Conflict of interest statement

Dr. Hoffman has no conflicts of interest.

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