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Featured Content

The State of Botanical Drugs

A new route to market may hold promise for botanicals and other complex natural products.

By Freddie Ann Hoffman, MD

With the passage of the Dietary Supplement Health & Education Act (DSHEA) in October 1994, U.S. sales of dietary supplements skyrocketed. Growing at breakneck speed, markets far outstripped expectations. Within a five-year period, however, major downward trends appeared. Since 2000, sales have continued to stumble, particularly for herbals and other naturally derived products.

A key factor cited for the "correction" is flagging consumer confidence, likely due to negative media. Driving concerns are issues with product quality, insufficient federal oversight, absence of manufacturing requirements, adverse events, supplement-drug interactions, and negative clinical trial results. Other factors include "watered-down" claims, high-costs of brand management, lack of scientific research, and "commodity" pricing, all of which may have contributed to poor product differentiation, decreasing sales and diminishing profit margins.

A New Mandate

During the same time period, another "natural products industry" distinct from the supplement industry has been quietly germinating in the U.S. In 1991, the U.S. Congress mandated the establishment of an "Office of Alternative Medicine" at the National Institutes of Health (NIH) in order to explore the role of "complementary" and "alternative" medicine in U.S. healthcare. As a result, dozens of grants received by NIH proposed to study the effects of traditional Chinese herbals and other botanical products in patients with disease. These trials created a conundrum for both scientists and regulators. Federal law defines "drugs" as articles, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease and to affect the structure or function of the body. Any product not already approved as a "drug" must be studied for a drug indication under an Investigational New Drug (IND) application filed with FDA. Although sold as dietary supplements, the products to be tested in the NIH trials were required to have INDs. But most U.S. drugs were well-characterized single chemicals—not multi-component mixtures. How to prepare and review an IND for a botanical drug left both the federal government and the investigators in a quandary.

Precedents—and Predicaments

To clarify the scientific considerations and regulatory requirements for a "new" class of botanical drugs, FDA formed an internal ad hoc working group in June 1994. Plant-based drugs were certainly not new to the U.S. Historically complex drugs played an integral role not only in the practice of medicine, but also in the evolution of U.S. drug regulation. In the late 1800's, proprietary and often toxic mixtures of both chemical and plant-derived ingredients called "patent" medicines were widely marketed to consumers as panaceas. Partly in response to public outcry over increasing numbers of serious and often fatal mishaps from the unbridled use of patent medicines, President Theodore Roosevelt signed into law the first federal Pure Foods and Drugs Act on June 30, 1906. One of the Act's key provisions was the requirement that all drug

ingredients be disclosed on the product label. From 1906 until the passage of the more comprehensive federal Food, Drug and Cosmetic Act in 1938, sales and usage of natural drugs steadily declined. This was likely due to the discovery of the "miracle" drugs—penicillin, quinine, as well as other "active" substances, which were isolated and purified from natural sources.

Following the passage of the Kefauver-Harris "drug amendments" in 1962 that required drugs to be proven not only "safe," but also "effective" for their intended use, most botanicals and other complex drugs were withdrawn from the U.S. market. By the mid-1980's, only a few examples remained: several "pre-1938" ingredients, such as psyllium and cascara; heparins, comprised of repeating molecules of variable chain lengths; and an unpatented preparation of conjugated estrogens derived from pregnant mares' urine (Premarin—Wyeth Pharmaceuticals, Inc.). With the exception of allergenic vaccines regulated under the Public Health Service Act, no botanical "new" drugs—those marketed after 1938 and affirmed as both safe and effective under a "New Drug Application" [NDA] —had been approved in the U.S. Re-entry to the U.S. drug market was attempted in the early 1990's, when a coalition of European and American herbal product manufacturers petitioned the agency to include valerian and ginger as ingredients in the "over-the-counter" (OTC) drug monographs. FDA's subsequent failure to provide a definitive and timely response to the petition may have been a contributing stimulus to the passage of DSHEA a few years later.

Once DSHEA became enacted its explicit mention of "herbs and other botanicals," and "extracts" in the legal definition of a "dietary supplement" misled many into believing that complex natural ingredients could be sold in the U.S. only as dietary supplements. FDA was to dispel this misperception in its public dissemination of a draft policy on botanical drugs in August 2000, followed by the final deliberations of the agency's working group, published as the FDA "Guidance for Industry for Botanical Drug Products" in June 2004. From a regulatory viewpoint, a "botanical" is defined as any product that "contains ingredients of vegetable matter or its constituents as a finished product." The Guidance provides a clear outline of the decision-making process for determining when botanicals can be regulated as foods, cosmetics and drugs. It also discusses what information should be provided in a botanical drug IND. Although nominally limited to botanicals, the general policies and regulatory constructs of the Guidance are also applicable to non-botanical complex products, such as fish oils, as well as traditional combination products.

Advantages of the 'New' Drug Route

For products capable of meeting the requirements, the "new" drug route provides significant advantages over other regulatory categories. Unlike dietary supplements, which must be taken orally and are restricted to specific formulations (e.g., pills, capsules), drugs can be administered by any route and in any formulation. Drug "safety" is assessed in the context of a specific "efficacy" indication based on a "benefit to risk" analysis—a consideration unavailable to foods or dietary supplements. The drug Thalidomide, which caused a public health disaster stimulating the passage of the 1962 drug amendments, represents a striking demonstration of how FDA views drug safety. Banned from the U.S. in the 1960's after the drug was found to produce congenital abnormalities in the infants of women who took it as a sedative during pregnancy, Thalidomide finally received FDA approval in 1998 as a treatment for a serious condition of leprosy. The labeling for the drug specifically excludes pregnancy as a "contra-indication." (One could speculate whether the botanical ephedra, now prohibited from use as a dietary ingredient, would have fared better as a "drug," if its medical benefits could have been shown to outweigh any risks.)

Complex ingredients can receive more protection from direct competition when sold as drugs, than as foods or supplements. Confidentiality, a hallmark of the IND/NDA process required by federal law, protects trade secrets and proprietary information. Scientific data generated with one

drug cannot simply be “borrowed” by a competitor, unless the second drug is a “generic equivalent.” To claim “generic equivalency,” the active(s) from both drugs are administered to human subjects and must demonstrate comparable absorption and distribution patterns, in conformance with standardized “bioequivalence” testing procedures. Complex drugs, with unknown or myriad bioactive constituents, pose an enormous hurdle for bioequivalence testing, making them essentially immune to generic “copies.” Since drug indications and claims are generated from product-specific studies and based on “adequate and well-controlled clinical trials,” for another drug to make the claims of a competitor, it too would need to undergo similar trials. Finally, FDA can award NDA-approved drugs a period of marketing exclusivity (regardless of the existence of a patent), during which FDA is prohibited from accepting another NDA submission for an identical product, as discussed in the applicable law.

State of the New Botanical Drug Industry

Over the past decade, a new U.S. botanical drug industry has been steadily growing. As of May 2006, 229 INDs have been filed with FDA, with 1-3 filings per month, since 2000. In 2004, FDA approved an omega 3 drug [Omacor; Ross Laboratories]. Two major chemical components make up 84% of the product, with the remaining 16% a proprietary ratio of bioactive constituents. The drug is indicated as “an adjunct to diet to reduce very high (>500 mg/dL) triglyceride (TG) levels in adult patients,” and can only be sold through prescription. In December 2005, an NDA application for a topical green tea extract was “accepted for filing” and is currently undergoing agency review. With the “right” products for development, the future for complex drugs in the U.S. is wide open.

About the author:

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References furnished upon request.