Botanical Drug Development – How Natural Health Products Can Become Drugs

Jay Udani

Chief Executive Officer and Medical Director, Medicus Research, and Medical Director, Northridge Hospital Integrative Medicine Program, and Assistant Clinical Professor, UCLA School of Medicine

Abstract

Botanical drugs (BDs) represent an untapped global opportunity in which natural health products (NHPs) are developed and marketed as drugs. These products are a potentially disruptive technology that could help fill drying pharmaceutical developmental pipelines while simultaneously addressing the demographic shift of the rapidly ageing population that is seeking products perceived as effective, naturally derived and safe. This article provides an overview of the BD-development process, highlighting the differences between BDs and single chemical entities. Lastly, the business process by which these products can be simultaneously developed across multiple regulatory environments is described, along with suggestions of how the pharmaceutical industry can work with the companies currently developing NHPs. Ultimately, successful US Food and Drug Administration (FDA) approvals and successful marketing of BDs will benefit the pharmaceutical industry, the NHP industry and patients alike.

Keywords

Botanical drug, natural health product, clinical trial management

Disclosure: The author has no conflicts of interest to declare.
Received: 7 September 2010 **Accepted:** 29 October 2010 **Citation:** *Drug Development*, 2010;5:34–6
Correspondence: Jay Udani, 18250 Roscoe Blvd, Suite 240, Northridge, CA 91325, US. E: Jay.Udani@MedicusResearch.com

The confluence of several global trends has driven botanical drug (BD) development to a level that warrants close attention. On the one hand, the outlook looks bleak; the single chemical entity (SCE) pipeline is drying up, blockbuster drugs appear to be a thing of the past, reimbursements are shrinking and public scepticism over the safety of pharmaceutical products is growing with each new class action lawsuit. Taking a more optimistic perspective, one can see that although the 20th century model of the world is unlikely to return, the opportunities ahead are even greater. The democratisation of information through the Internet has given physicians and consumers access to almost incomprehensible levels of medical information and they are using these tools to educate themselves on safety and efficacy, among other things. Compared with their parents' generation, the ageing baby boomers in the US have a radically different expectation of what it means to grow old, and they fully expect to live long, maintain their health and appearance and continue an active lifestyle well into their 70s and beyond. The global economy, travel and immigration have brought traditional medicinal practices from around the globe to the developed world, including the use of indigenous herbal products. Finally, the desire for natural and sustainable alternatives is driving purchasing decisions, even in this time of lingering economic difficulty.

Natural health products (NHPs) are a disruptive technology that can meet these changing needs. One of the most unique aspects is that the demand curve is driven by consumers and not exclusively by physicians, as was the case up until the last decade. While disruptive, this technology does not have to be destructive, and opportunities for the integration of these products into the strategic plans of pharmaceutical companies are underway across the globe.

NHPs are derived from natural sources, contain multiple ingredients and are not purified to homogeneity. The vast majority of these products are derived from vegetable material (i.e. plants, algae and fungi), although there are other NHPs, such as fish oil, which have animal origins. What makes an NHP a drug is primarily its intended use, rather than the characteristics of the product. The route of administration, formulation, safety profile and/or method of preparation also play a role, but to a lesser extent. In practical terms, the way in which the product is studied, sold and marketed governs the category under which it is regulated. The same NHP can therefore be a dietary supplement, functional food, medical food, biological, cosmetic or drug, and not infrequently these products are sold under multiple categories. This article will concentrate on the products that are regulated as drugs owing to their intended use in the diagnosis, mitigation, treatment, prevention and/or cure of disease.

Botanical Drugs

BDs are NHPs derived from plant sources. Between 1999 and 2007 there were 225 BD investigational new drug (IND) applications filed with the US Food and Drug Administration (FDA)[1] and in 2004 the FDA published its Guidance for Industry on Botanical Drug Products.[2] What makes these products unique is that they are often complex mixtures of active components, either from a single plant, or from multiple plants. The true active component is not generally

known, and often the marker compound for the plant is not the only potentially active constituent, meaning that standardisation is much more difficult than with SCEs. Incoming raw materials for BDs must undergo 100% testing across several domains including the plant part, extraction methodology, identity, characterisation or standardisation, stability, purity and variability. It is critical that companies producing BDs have sufficient reliable sources of their raw ingredients. Some companies have gone so far as to purchase all the farms required for their source material to ensure supply and quality. The rest of the regulatory Chemistry, Manufacturing and Controls (CMC) requirements for BDs are similar to those for SCEs regarding process validation (i.e. installation, operational and performance qualification). Often, the NHPs from which the BDs are derived have been manufactured under other regulatory categories, and upgrades may be required to meet these CMC requirements.[2]

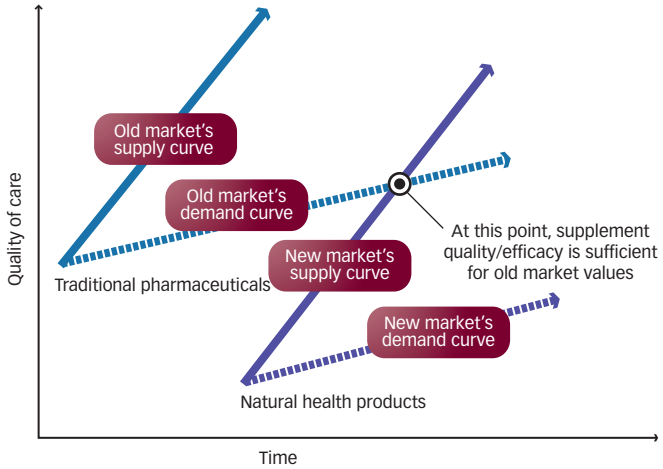
The other distinctive feature of these products is that human usage data exist before the product undergoes phase I testing. In some cases, human usage may have been thousands of years of traditional use, or the sales of millions of dosages under a different regulatory category, for example, as food or as a dietary supplement. These data do not substitute for adequate and well-controlled clinical trials, but it does provide a glimpse into the efficacy and safety profile of the product that cannot be obtained with SCEs. The first BD was approved by the FDA in 2006. The product was Veregen® – a green tea extract for the topical treatment of genital warts. This first approval has validated the theory that such botanical drugs are possible and that complex botanical preparations can be standardised to meet the FDA's requirements.[1]

Clinical Development Process for Botanical Drugs

From the perspective of a clinical trial development plan, the pathway may not be as linear as traditional development plans because certain steps may be skipped or re-ordered by the FDA. Also, there are many companies simultaneously running clinical studies under multiple regulatory categories. In the US, a less purified version of the product may be sold and studied as a dietary supplement and later the BD IND application may be filed. The opposite is not true; if the BD IND application is filed first, the product cannot later be sold as a dietary supplement. If the NHP has an application in the dietary supplement marketplace, it may therefore be advantageous to run clinical studies in that regulatory category in order to obtain human dose justification and safety data that can be used to support the IND application. This type of human data does not exist in the usual SCE development route and, on occasion, the FDA has allowed companies to reduce certain pre-clinical requirements and to skip all or part of some phase I requirements. The other advantage to the parallel track approach (i.e. developing the product under both the dietary supplement and the BD category) is that sales of the dietary supplement version of the product can be used to support the BD clinical trials.

Most aspects of the BD clinical trial plan are identical to SCE studies, including the need for adequate and well-controlled studies, the following of International Conference on Harmonisation (ICH)/World Health Organization (WHO) Good Clinical Practice (GCP) standards, and the statistical requirements. End-point selection will be based on the therapeutic area, but may also take into account prior human use data for the product. The other area in the design of clinical trials different from that of SCEs is the careful consideration of the way in which diet may interact with the investigational product. As NHPs usually have a history of traditional use as medicine or even food, they may be present in the background diet of certain cultures and in various geographic locations. This must be accounted for in the selection of the target population by choosing subjects who will not be exposed to the test ingredients through their diet and who will not be exposed to other non-pharmaceutical (i.e. dietary supplement) products that may contain the same ingredients. All subjects should be monitored for potential drug–drug and herb–drug interactions.

Figure 1: Natural Health Products as a Disruptive Technology



Source: Christensen CM, 2000.[4]

Who is Involved in Botanical Drugs Today?

There are two groups of companies advancing the field of BD development. The first is the NHP (non-pharmaceutical) companies who have often developed the NHP under the dietary supplement or food category, and are investing in developing their product into a BD. These are generally smaller companies, usually Asian, European or Australia/New Zealand, and have invested in clinical trials for the food or dietary supplement version of their product. They have raised enough financing internally or externally to file the IND application and begin phase I and/or phase II studies, but cannot finish the job alone. The second group of companies advancing this field comprises the forward-thinking pharmaceutical companies who see the opportunity and consumer demand. These companies need new products, have the resources to finance the later-stage studies and have the marketing and distribution relationships as well as the sales forces necessary to commercialise these products. It is only when these two groups of companies work together in synergy that a BD product would have a chance of success.

The Opportunity

Opportunity knocks today. NHPs can be developed into BDs, the proof of concept of this model being Veregen. The development of NHPs into BDs will require co-operation between those companies developing these products, and those companies with the experience and resources to successfully navigate both the

FDA-approval process and the drug-commercialisation process. In order to fully benefit from this investment, the marketing of these products should focus on the natural derivative of the drug. Physicians are looking for such treatments, both for their patients and for themselves, and are genuinely interested in finding and prescribing products in which they are confident of the purity, content and efficacy. The omega-3-acid ethyl esters fish oil product, Lovaza®, provides an example of the rapid change in prescribing habits that can occur when an NHP that was previously only available as a dietary supplement becomes available as a prescription drug.

Those pharmaceutical companies that now begin the process of identifying and developing NHPs into BDs will be at the forefront of the convergence of the consumer and physician demographic and psychographic shifts that are driving the demand for these high-quality naturally derived products. ■

Jay Udani is the Founder and chief executive officer of Medicus Research, the premier clinical research organisation for the natural health product industries, including botanical drugs, dietary supplements and functional foods. He is a board-certified internist who served as Chief Resident at Cedars-Sinai Medical Center in Beverly Hills, before completing two fellowships in Health Services Research and Integrative Medicine at Cedars-Sinai/UCLA. Dr Udani is the Medical Director of the Northridge Hospital Integrative Medicine Program, where he successfully incorporated evidence-based alternative medicine treatments into his private practice and into hospital service lines including oncology, cardiology and gastroenterology. He is also on the clinical faculty of the UCLA School of Medicine and was one of the first physicians to become a Certified Principal Investigator (CPI) through the Academy of Pharmaceutical Physicians and Investigators/Association of Clinical Research Professionals (APPI/ACRP). He is the recipient of many prestigious awards, including the 2008 Natural Products Association Clinician of the Year, the AMA National Achievement Award and the Harvard Medical School Pinkney Fellowship in Orthopaedic Research. He was also voted Best Physician Specialist and Best Medical Speaker in Los Angeles by the *Daily News*.

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