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From Pre-Market Approval to Post-Market Removal

The Implications of Lifestyle Drugs for the Regulation of Herbal Remedies

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Abstract

Both a popular lifestyle drug and an herbal remedy have recently been recalled due to concerns of safety.

In the wake of these recalls, reforms were proposed to strengthen the FDA's post-marketing enforcement powers and resources. The emphasis on post-marketing enforcement is not surprising as the effectiveness of pre-market approval is reaching its limitations for the markets of both lifestyle drugs and herbal remedies. Moreover, consumer conceptions of both markets are conceptually converging, requiring the need for more consistent regulations. The FDCA provides sufficient post-marketing enforcement power over lifestyle drugs, but not for herbal remedies. An enhanced regulatory regime for herbal remedies would have the additional benefit of addressing the intellectual property issues that have plagued the full development of herbal remedies.

Introduction

The front cover of the May 11, 1998 issue of BusinessWeek heralded “The New Era of Lifestyle Drugs” and predicted that drugs such as Viagra would transform the pharmaceutical industry.¹ BusinessWeek observed that the pharmaceutical industry was shifting; where once the industry on focused on life-threatening conditions, it has now turned its attention to conditions that are merely uncomfortable, and where treatment could be considered optional. The shift was being driven in part by the changing demographics of the United States: “baby boomers would gladly pay to pop a pill rather than diet, exercise, watch their cholesterol – or do without sex.”²

While term “lifestyle drug” is used frequently in scientific literature and the popular media, there is no consensus on an exact definition.³ A reasonable working definition, suggested in an article in the British Medical Journal, is that a lifestyle drug is a drug “used for ‘nonhealth’ problems or for problems that lie at the margins of health and wellbeing” or one “used for health problems that might be better treated by a change in lifestyle[.]”⁴ This definition would include not only drugs for conditions such as erectile dysfunction, such as Viagra, but also drugs that reduce high cholesterol, or heart burn, as these conditions could arguably also be treated by adjustments to lifestyle by altering diet and increasing exercise. Even with this working definition, line between “lifestyle” and “traditional” drug is by no means clear-cut and has been the subject of debate over the boundaries between therapy and enhancement; disease and the realities of aging.⁵

However, lifestyle drugs may be perhaps be characterized by their shared characteristics: prolonged use for

¹Joseph Weber et. al., *The New Era of Lifestyle Drugs*, BUSINESSWEEK, Apr. 28, 2003, available at <http://www.businessweek.com/1998/19/b3577001.htm>

²See id.

³Claus Møldrup, *The Use of the Terms ‘Lifestyle Medicines’ or ‘Lifestyle Drugs,’* 26 PHARM WORLD SCI 193, 195 (2004).

⁴David Gilbert et. al., *Lifestyle Medicines*, 325 BRIT. MED. J. 321, 321 (2000)

⁵See e.g., Joel Lexchin, *Lifestyle Drugs, Issues for Debate*, 164 CANADIAN MED. ASSN. J. 1449, 1449-51 (2001)

common conditions that lie at the boundary of enhancement and treatment.

BusinessWeek has largely proven clairvoyant. The era of lifestyles drugs has arrived, at least based on sales of pharmaceuticals. In 2005, the top five of the best selling prescription drugs in the United States could be classified as lifestyle drugs. Lipitor, which treats high cholesterol, and had the highest sales, at \$8.4 billion, followed by, Zocor, which also treats cholesterol, at \$4.4 billion. The third and fourth top selling, Nexium and Prevacid, both treat heartburn, and the fifth, Advair Diskus, treats asthma; sales were \$4.4 billion, \$3.8 billion, and \$3.6 billion respectively.⁶ While the epitome lifestyle drug, Viagra, was not in a top twenty, it still accounted for \$1.6 billion of revenue for Pfizer in 2005.⁷

While not receiving top billing on the front cover, herbal remedies have also received attention from BusinessWeek. The April 28, 2003 issue contained an article with the headline “Herbal Remedies: A \$4 Billion Enigma.”⁸ Declaring the next decade as the era of herbal remedies would be somewhat ethnocentric, as herbal and botanical products have been used by humans throughout history, having a central role in the traditional medicines of the cultures of China,⁹ South Asia,¹⁰ and the Middle-East,¹¹ well as indigenous peoples.¹² While herbal remedies may have been widely used in other cultures and countries, it has only recently found popularity in the United States. A telephone survey conducted in 1991 found that only 2.5% of the U.S. adult population used herbal products in the past 12 months¹³ A follow-up survey conducted in

⁶See Matthew Herper, The Best-Selling Drugs In America (Feb. 27, 2006), http://www.forbes.com/sciencesandmedicine/2006/02/27/pfizer-merck-genentech-cx_mh_0224topsellingdrugs.html

⁷Pfizer Inc., Annual Report 2005, 10-K 13 (filed Mar. 1, 2006) available at <http://www.pfizer.com/pfizer/annualreport/2005/financial/financial2005.pdf>

⁸See John Carey, *Herbal Remedies: A \$4 Billion Enigma?*, BUSINESSWEEK, April 28, 2003, http://www.businessweek.com/magazine/content/03_17/b3830095_mz025.htm

⁹See e.g., Weishi Li, *Botanical Drugs: A Future for Herbal Medicines*, 19 J. CONTEMP. HEALTH L. & POL'Y 117, 118-27 (2002) (describing the use of botanical products in traditional Chinese medicines)

¹⁰See e.g., Sita Reddy, *Asian Medicine in America: The Ayurvedic Case*, 583 THE ANNALS AM. ACAD. POL. AND SOCIAL SCI. 97, 100-106 (providing a brief overview of Ayurvedic medicine)

¹¹See Bashir Saad et. al., *Tradition and Perspectives of Arab Herbal Medicine: A Review*, 2 EVID BASED COMPLEMENT ALTERNAT MED, 475, 475-479 (2005)

¹²See e.g., Michael J. Huft, *Indigenous Peoples and Drug Discovery Research, A Question of Property Rights*, 89 N.W.U. L. Rev. 1678, 1695-1704 (2005) (describing the use of herbal medicines in indigenous cultures)

¹³See David M. Eisenburg et. al., *Unconventional mMedicine in the United States. Prevalence, Costs, and Patterns of Use*, 328 NEW ENG. J. MED. 246, 246-251 (1993)

1997 found that the use of herbal products within the past 12 months had increased to 12.1%.¹⁴ And a subsequent questionnaire based study in 2002 found that the prevalence of use of herbal medical had increased to 18.1%.¹⁵ These consumers spent an estimated \$4.2 billion on herbal and botanical medicines in 2001.¹⁶ Both lifestyle drugs and herbal remedies are regulated by the Food and Drug Administration (FDA). The regulations, however, are vastly different. Lifestyle drugs are regulated as “new drugs” and as such, subject to extensive FDA oversight, including pre-market approval. Herbal remedies are typically regulated as “dietary supplements,” and as a result subject to substantially far less regulatory oversight, with no pre-market approval. These regulatory regimes persist despite the converging uses for lifestyle drugs and herbal remedies, and despite potentially similar if not identical active compounds. Ironically, part of the convergence is driven by the bi-polar regulatory schemes. Equally ironic, the bi-polar regulatory schemes have resulted in safety concerns after the withdrawal of both a popular and widely used lifestyle drug and herbal remedy. These withdrawals led to Congressional hearings on the role of the FDA and the adequacy of its regulations. And as a final bit of irony, the recommendations for regulatory reform in both cases was the same: more aggressive post-marketing regulation through increased monitoring for adverse health effects and withdrawals of unsafe products from the market.

For lifestyle drugs, increased post-marketing surveillance and withdrawal represents a regulatory adaptation to the specific characteristics of lifestyle drugs. For herbal remedies, however, the provisions under current regulations for increased postmarketing surveillance and withdrawals are insufficient. A new regulatory

¹⁴See David M. Eisenburg, *Trends in alternative Medicine Use in the United States, 1990-1997: Results of a Follow-up National Survey*. 280 JAMA 1569, 1572 (1998)

¹⁵See Hilary A. Tindle et. al, *Trends in the Use of Complementary and Alternative Medicine by U.S. Adults: 1997-2002*, ALTERNATIVE THERAPIES 42, 47 (2005)

¹⁶See Donald M. Marcus & Arthur P. Grollman, *Botanical Medicines – the Need for New Regulations*, NEW ENG. J. OF MED. 2073, 2073 (2002); see also Weber *supra* note 1 (noting that herbal remedies are a \$4 billion per year industry).

regime is needed to enable the FDA to balance the demands of protecting the safety of consumers, and providing consumers with access to beneficial medicines. One such system could be the use of a licensing system, similar to the current drug approval system for lifestyle drugs. Such a system not only provides the FDA the flexibility necessary to effectively regulate herbal remedies, but also provides has the potential to unlock the full potential of herbal remedies by providing a solution to one of its most perplexing dilemmas – the protection of intellectual property rights of natural plant medicines.

Regulation of Lifestyle Drugs

Brief History of Drug Regulation

The first major and comprehensive regulation of drugs began with the Food and Drug Act of 1906. (the “1906 Act”)¹⁷ The 1906 Act adopted a reactive, policing model for regulating drugs. Moreover, after the Supreme Court’s decision in *United States v. Johnson*,¹⁸ the FDA had to not only demonstrate that the product failed to work as claimed, but that manufacturer or distributor had knowledge that the claims were false.¹⁹ The deficiencies in the 1906 Act became apparent in 1937 with the “Elixir Sulfanilamide” where the solvent diethylene glycol, a poison, had been used to dissolve sulfanilamide, a drug used to treat streptococcal infections.²⁰ As the elixir had not been pre-tested, the use of the poisonous solvent was undetected until it had killed over 100 people in fifteen states.²¹ The tragedy prompted Congress to pass the Food Drug and Cosmetic Act. (the “FDCA”) of 1938,²² which required that manufacturers of new drugs notify the FDA prior to marketing, and give the FDA up to 180 days to review the drug for safety.²³ In 1962, Congress amended the FDCA in the wake of the thalidomide tragedy. Thalidomide had been widely used in Europe as a sedative by pregnant women, but such use was later found to cause birth defects, including the development flipper-like limbs in the fetus.²⁴ The 1962 amendments to the FDCA converted the pre-notification system of the 1938 Act to a pre-approval system, requiring the FDA to affirmatively approve

¹⁷ch. 3915, 34 Stat. 768 (1907)

¹⁸*United States v. Johnson*, 221 U.S. 488 (1911)

¹⁹Richard A. Merrill, Symposium on Regulating Medical Innovation: The Architecture of Government Regulation of Medical Products, 82 VA L. Rev. 1753, 1757-61 (1996)

²⁰See Caroline Bellentine, Taste of Raspberries, Taste of Death, The 1937 Elixir Sulfanilamide Incident, <http://www.fda.gov/oc/history/elixir.html>

²¹See *id.*

²²ch. 675, 52 Stat. 1040 (1938)

²³505(b)-(c), 52 Stat. at 1052

²⁴See Merrill, *supra* note 19 at n35

each new drug. In addition, manufacturers were now required to show not only safety, but effectiveness and safety and effectiveness needed to be demonstrated through “adequate and well-controlled studies.”²⁵

Overview of the Current Drug Regulations

All drugs, including “traditional” and “lifestyle” drugs, are regulated by the under the same provisions of the FDCA. A drug is defined as a “new drug” and requires the submission of a new drug application (NDA) and pre-market approval from the FDA,²⁶ unless it “generally recognized as safe and effective” (GRAS/E) and has been used for a material extent and material time.²⁷ The hurdle for a drug to be considered GRAS/E is substantial and generally requires the types of scientific, well-controlled studies necessary to obtain pre-market approval for a new drug.²⁸ Moreover, the FDA has the jurisdiction to determine whether a drug is a “new drug” subject to only minimal judicial review under²⁹

Regulation as a New Drug

To receive pre-market approval for the marketing of a new drug, the manufacturer, or other sponsor, must submit a NDA to the FDA,³⁰ which must include data from clinical investigations detailing the safety and effectiveness of the drug.³¹ In order to conduct the necessary clinical trials to provide the data for the NDA, the sponsor must also obtain FDA approval,³² by submitting an investigation new drug (IND)

²⁵See *id.* at 176-79

²⁶21 U.S.C. § 355

²⁷21 U.S.C. § 321(p)

²⁸See Margaret Gilhooley, *Drug Regulation and the Constitution After Western States*, 37 U. Rich. L. Rev. 901, 929 (2003)

²⁹*Weingerer v. Bentex Pharmaceuticals, Inc.* 412, U.S. 645 (1973). Judicial review of the FDA determination is available under the Administrative Procedures Act. 5 U. S. C. §§ 701-704. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 627 (1973)

³⁰21 U.S.C. § 355(a)

³¹21 U.S.C. § 314.50(d)(5)

³²FDA approval is required even for the clinical trials since a new drug cannot be distributed without a NDA. See 21 C.F.R.

application.³³ The IND application must include information on the safety of using the drug in the clinical investigations, through pre-clinical pharmacological and toxicity studies in animals or in vitro,³⁴ and a description of the chemical and manufacturing processes.³⁵ Clinical investigations are generally conducted in three phases. Phase I studies typically consist of twenty (20) to eighty (80) people and are used to determine the metabolism and pharmacology of the drug in humans so that the design of Phase II can be optimized.³⁶ Phase II studies are designed to evaluate the effectiveness of the drug and determine short-term side-effects and risks; Phase 2 typically consist of several hundred people.³⁷ Phase III studies are designed to assess safety and effectiveness, evaluate the overall risk and benefit of the drug, and determine the drug's labeling; Phase III usually require several hundred to several thousand people.³⁸ Furthermore, the FDA can also conditionally approve a new drug, by requiring that the sponsor conduct post-marketing studies, and provide the FDA with annual reports on these studies.³⁹

Regulation as OTC

Through the Over-The-Counter (OTC) Drug Review process, the FDA provided a process through which a drug can be marketed with undergoing the extensive pre-market approval requirements of new drugs. The FDA established the OTC Drug Review in 1972, in response to inadequacy and impracticality of case-by-case determinations of the GRAS/E status of drugs.⁴⁰ The review process is structured around monographs,

314.1.

³³21 C.F.R. 314.20

³⁴21 C.F.R. 312.23(a)(8)

³⁵21 C.F.R. 312.23(a)(7)

³⁶21 C.F.R. 312.21(a)

³⁷21 C.F.R. 312.21(b)

³⁸21 C.F.R. 312.21(c)

³⁹21 U.S.C. § 356b(a); see also Other post-marketing reports, 21 C.F.R. 314.81

⁴⁰See 37 *Fed. Reg.* 85; see also PETER B. HUTT & RICHARD A. MERILL FOOD AND DRUG LAW, CASES AND MATERIAL 588-89 (1991); Robert G. Pinco, *Implications of FDA's Proposal to Include Foreign Marketing Experience in the Over-the-Counter Drug Review Process*, 54 *Food Drug L.J.* 105, 106-07 (1998)

each corresponding to a specific therapeutic effect (e.g. antacids, stimulants, cold remedies).⁴¹ Drugs falling within a given monograph are reviewed by the monograph's scientific advisory panel, which recommends the conditions of use, if any, under which a particular drug is considered GRAS/E and not misbranded.⁴² Inclusion of a drug in a monograph is a determination that the drug is GRAS/E and not misbranded under the conditions of use specified under the monograph.⁴³ Moreover, only drugs that have been marketed for a material extent and for a material time are eligible for inclusion in a monograph.⁴⁴ Therefore, since the inclusion of a drug that is in a monograph requires that the drug is both GRASE/E and has been marketed for a material extent and time, the drug no longer meets the definition of "new drug" and can be marketed without the submission and approval of a NDA.

While lifestyle drugs, given the prevalence and frequency of use, are arguably good candidates as OTC drugs, they are typically not marketed under a directly under an OTC monograph without going through a NDA process. A manufacturer, or any other interested person, may petition to amend an OTC monograph to incorporate a drug,⁴⁵ Under the OTC review process, a drug is evaluated for safety and effectiveness,⁴⁶ which generally must be established by published studies.⁴⁷ There is little advantage of going directly to the OTC monograph as proof of effectiveness also requires the same type of adequate and well-controlled studies necessary to demonstrate effectiveness for approval for marketing approval under a NDA.⁴⁸ If anything,

⁴¹21 C.F.R. 330.5

⁴²21 C.F.R. 330.10

⁴³21 C.F.R. 330.1

⁴⁴The material extent / time eligibility criterion was established 21 C.F.R 330.14. *See* Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded, 67 *Fed. Reg.* 3060. Prior to 21 C.F.R. 330.14, the FDA has treated drugs which were marketed prior to December 4, 1975 as presumptively meeting the material / time requirements of avoiding classification as a "new drug." *See* Pinco, *supra* note 40 at 108. Under 21 C.F.R. 330.14, a drug must be marketed continuously for at least five (5) years to meet the material extent / time criterion. 21 C.F.R. 330.14(c).

⁴⁵21 C.F.R. 330.10(12)

⁴⁶*Id.*

⁴⁷21 C.F.R. 330.10(a)(4)

⁴⁸21 C.F.R. 330.10(a)(4)(ii) (requiring that effectiveness be determined 21 C.F.R. § 314.126(b), which defines adequate and well-controlled studies for approval under a NDA)

marketing as an OTC drug entails additional, more stringent requirements as the drug must have been marketed for a material extent and for a material time, and be safe for use without the supervision of a physician.⁴⁹ The novelty of a lifestyle drug means that it typically cannot establish the necessary history for inclusion in an OTC monograph. Moreover, because evaluation for OTC status requires that a drug have a low incidence of adverse effects under conditions of widespread use,⁵⁰ more studies are usually required to gather the necessary data. Recently, drugs that have become OTC have predominately the result of a switch from previously approved prescription status.⁵¹

Regulatory Blindspots of Lifestyle Drugs

Lifestyle drugs raise concerns over the adequacy of the current regulatory system for drugs. The pre-market approval regulatory system that governs lifestyle drugs was designed in 1962, and thus did not envision the coverage of lifestyle drugs. Instead, the regulations are best suited tailored for traditional drugs where both the clinical endpoint and the length of use is well-defined. In lifestyle drugs, however, the clinical end-point, such as “lower cholesterol” may not always be universally defined for everyone, but is instead a relative measure. Moreover, the usage of lifestyle drugs is both more widespread and more frequent, and thus statistically rare events could affect a large number of people, in absolute terms. Given the practical constraints on the size and length of clinical tests, many adverse events from lifestyle drugs could be lost in the statistically noise.⁵²

Regulation of Herbal Remedies

There are no specific provisions regulating traditional herbal medicines in the Food Drug and Cosmetic Act

⁴⁹See 21 C.F.R. 330.14(b)(1); 21 U.S.C. § 353(b)(1)(B) (defining criteria for requiring prescription)

⁵⁰21 C.F.R. 330.10(a)(i)

⁵¹See David E. Collins, *Report of the Task Force on the Future of OTC Drugs*, 55 FOOD DRUG L.J. 27, 27 (2000)

⁵²See Michelle D. Roth-Cline, *Clinical Trials in the Wake of Vioxx*, 113 CIRCULATION 2253, 2257-58 (2006)

(FDCA). Herbal remedies can theoretically be regulated under the same drug provisions as drugs. Indeed, the FDA has attempted address the application of drug regulations to herbal remedies.⁵³ However, herbal remedies typically also qualify for regulation as dietary supplements under the Dietary Supplement Health and Education Act of 1994 (DSHEA).⁵⁴ The regulatory regime applied to a given product is determined by the manufacturer or distributor’s intended use.⁵⁵ Intended use can be determined from any relevant source, including claims in the product’s advertising and labeling.⁵⁶ If the claims of the product include the cure, treatment, mitigation, or prevention of disease, the herbal remedy will be regulated as a drug.⁵⁷ However, under DSHEA, dietary supplements can make “structure/function” claims,⁵⁸ and still be excluded from regulation as a drug.⁵⁹ In exchange for the prohibition on disease claims, a dietary supplements are not subject to pre-market approval. Despite the FDA’s efforts to adapt drug regulations to herbal remedies, the availability of substantially less stringent regulatory regime of “dietary supplements” under DSHEA has effectively resulted in herbal remedies being regulated as dietary supplements.

Brief History of DSHEA

Congress passed DSHEA in 1994, concluding a series of battles between the FDA, Congress, and the courts over the regulation dietary supplements.⁶⁰ In 1973, the FDA promulgated regulations which would have classified as drugs, any multivitamins with a dosage exceeding 150% of the recommended daily allowance.⁶¹ Enforcement of the regulations were suspended pending a challenge to the regulations in administrative

⁵³See *infra* notes 252-

⁵⁴Pub. L. No. 103-417, 108 Stat. 4325, codified in 21 U.S.C. § 301 et seq.

⁵⁵*United States v. Articles of Drug for Veterinary Use*, 50 F.3d 497, 500 (8th Cir. 1995)

⁵⁶*Id.*

⁵⁷321 U.S.C. § 321(g)

⁵⁸See *infra* --

⁵⁹See 21 U.S.C. § 321(g) (excluding dietary supplements from inclusion as a “drug” solely due to structure/function, but not disease claims if made in accordance with 21 U.S.C. § 343(r)(6)), which, *inter alia*, bars dietary supplements from “claim[ing] to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases.”)

⁶⁰See generally Michael A. McCann, *Dietary Supplement Labeling: Cognitive Biases, Market Manipulation & Consumer Choice*, 31 AM. J. L. MED 215, 234-39 (2005) (describing the history of the FDA’s efforts to regulate dietary supplements)

⁶¹Statements of General Policy or Interpretation, 38 *Fed. Reg.* 20713, 20717-18 (July 25, 1973)

hearings.⁶² While the hearings were ongoing, Congress passed the Vitamin-Mineral Amendment of 1976,⁶³ which prohibited the FDA from setting limits of the potency of vitamins or minerals, from regulating vitamins and minerals as drugs solely on the basis of potency, and from limiting the combinations of vitamins.⁶⁴

Despite being stymied in regulation, the FDA proceeded to take regulatory action against dietary supplements through litigation. It attempted to seize a dietary supplement consisting of capsules containing black current oil on the basis that the encapsulated oil was a food additive under 21 U.S.C. § 321(s) and therefore required the manufacturer to demonstrate safety prior to marketing.⁶⁵ The FDA asserted that a capsule's gelatin and glycerin, when combined with the black currant oil, resulted in the oil becoming a food additive, even though the oil was not a food additive if un-encapsulated, and even though neither gelatin nor glycerin were food additives.⁶⁶ The Seventh Circuit disagreed, and found that FDA's interpretation to be inconsistent with the FDCA. The court found that the FDA's interpretation would "arbitrarily classify a substance as either food or food additive by how it is marketed rather than by the nature and use of the substance itself."⁶⁷

In response to the FDA's aggressive regulation of dietary supplements, and to lobbying by the dietary supplements industry, Congress passed DSHEA in 1994.⁶⁸ In passing DSHEA, Congress including findings that "although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers"⁶⁹ and that "legislative action

⁶²Regulation of Dietary Supplements, Advanced Notice of Rulemaking, 58 *Fed. Reg.* 33690, 33693 (June 18, 1993)

⁶³Pub. L. No. 94-278, 90 Stat. 410 (1976) (codifying 21 U.S.C. § 350)

⁶⁴21 U.S.C. § 350(a) (2006); vitamins and minerals for children, and pregnant lactating women are exempt from the limitations. See 21 U.S.C. § 350(b) (2006)

⁶⁵See *United States v. Two Plastic Drums*, 984 F.2d 814, 816 (7th Cir. 1993)

⁶⁶See *id.*

⁶⁷See *id.* at 816-18

⁶⁸McCann *supra* note 60 at 243-44

⁶⁹108 Stat. 4325, s 2(13)

that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness” and that “a rational Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements.”⁷⁰ Thus, with DSHEA, Congress hoped to reign in the FDA’s regulation of dietary supplements. In essence, as a result of DSHEA, dietary supplements are regulated only somewhat more stringently than convention foods.⁷¹

Regulation of Herbal Remedies as Dietary Supplements

Herbal remedies usually fall under the definition of “dietary supplement.” DSHEA defines “dietary supplement” broadly, to include “an herb or other botanical”⁷² as well as “a concentrate, metabolite, constituent, extract, or combination” of the botanical or other dietary supplement.⁷³ An article that has been marketed as a dietary supplement does not lose its status as a dietary supplement even if it is later approved to as a new drug.⁷⁴ However, an article that has been approved as a new drug prior to any marketing as a dietary supplement is excluded from the definition of dietary supplement.⁷⁵ Thus, an herbal remedy could lose its status as an dietary supplement due simply to the timing of an NDA.

Dietary supplements are excluded from the definition of food additives, thereby precluding the possibility of stricter regulation through classification of dietary supplements as food additives.⁷⁶ Unlike drugs and food additives, dietary supplements are not subject to pre-market approval. Unless the dietary supplement also meets the definition of a drug, a dietary supplement is considered a food.⁷⁷ However, unlike for conventional

⁷⁰108 Stat. 4325, s 2(15) (1994)

⁷¹See Peter B. Hutt, FDA Statutory Authority to Regulate the Safety of Dietary Supplements, 31 Am. J. L. and Med 155, 156-57 (2005)

⁷²21 U.S.C. § 321(ff)(1)(C)

⁷³21 U.S.C. § 321(ff)(1)(F)

⁷⁴21 U.S.C. § 321(ff)(3)(A)

⁷⁵21 U.S.C. § 321(ff)(3)(B)

⁷⁶21 U.S.C. § 321(s)(6)

⁷⁷21 U.S.C. § 321(ff). In addition, dietary supplements are excluded from the definition of “food additive,” see 21. U.S.C. § 321(s)(6) and therefore not subject to pre-market approval requirements of food additives under 21 U.S.C. § 348.

foods, the manufacturer of a dietary supplement containing a “new dietary ingredient” is required to notify the FDA 75 days prior to marketing, and to include support for the safety of ingredient, unless the ingredient is chemically unaltered and is used in the food supply as food.⁷⁸ A “new dietary ingredient” is one that is marketed prior to the passage of DSHEA (October 15, 1994).⁷⁹

A dietary supplement, regardless of whether it contains old or new dietary ingredients, is prohibited if it presents “a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling, or (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.”⁸⁰ The burden of proof for demonstrating the lack of safety of a dietary supplement is placed on the FDA.⁸¹ However, the Secretary of Health and Human Services has the power to ban a dietary supplement by declaring it be an imminent health hazard.⁸² The declaration cannot be delegated, and therefore cannot be made by the FDA Commissioner alone. Moreover, the declaration must be followed by an administrative proceeding to affirm or withdraw the ban.⁸³ However, the FDA has the authority to promulgate regulations for good manufacturing processes.⁸⁴

Dietary supplements may make “structure or function” claims without being classified and regulated as a drug.⁸⁵ To make structure/function claims, the manufacturer must have substantiation that claims are truthful and not misleading, notify the FDA within 30 days of making the claim, and include with the claim the boilerplate disclaimer: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”⁸⁶

In addition to permitting structure / function claims on labels for dietary supplements, DSHEA narrowed

⁷⁸21 U.S.C. § 350b(a)(2)

⁷⁹See Hutt, *supra* note 71 at 160

⁸⁰21 U.S.C. § 342(f)

⁸¹21 U.S.C. § 342(f); The FDA generally also bears the burden of proof on demonstrating the safety of foods. See Hutt, *supra* note 71 at 161

⁸²21 U.S.C. § 342(f)

⁸³*Id.*

⁸⁴21 U.S.C. § 342(g)

⁸⁵21 U.S.C. § 321(g)

⁸⁶21 U.S.C. § 343(s).

the definition of “labeling.” Labeling is a critical component of the FDA’s regulatory powers, as labeling is used to determine the intended use of an article, and thus the regulatory scheme that applies to the article. Furthermore, the labeling is a key factor in determining whether an article is misbranded.⁸⁷ Through a determination that an article is misbranded the FDA has the power to seize the article⁸⁸ and criminally prosecute the manufacturers or distributors.⁸⁹

Under the FDCA, “labeling” is defined as “written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”⁹⁰ Supreme Court adopted a broad interpretation of “labeling” in *Kordel v. United States*⁹¹ and *United States v. Ubuteit*,⁹² finding that leaflets, pamphlets, and circulars could be part of the an article’s labeling even if shipped separately from the article,⁹³ and even if pamphlet is offered for sale separately.⁹⁴

DSHEA excludes accompanying publications from the definition of labeling, if certain conditions are met. The publication cannot promote a specific manufacturer and must present a balanced view of available scientific information.⁹⁵ However, the FDA has the burden of proving that the accompanying publications are not exempt from the definition of labeling.⁹⁶ In summary, DSHEA eliminates the possibility of expansive

⁸⁷21 U.S.C. § 321(n); see also 21 U.S.C. § 343 (misbranding of food, including dietary supplements), 21 U.S.C. § 352 (misbranding of drugs and medical devices)

⁸⁸21 U.S.C. § 334

⁸⁹21 U.S.C. § 333

⁹⁰21 U.S.C. § 321(m)

⁹¹335 U.S. 345, 346-47 (1948)

⁹²335 U.S. 355 (1948)

⁹³In *Kordel* the Supreme Court considered whether circulars and pamphlets shipped separately from drugs were considered to be part of the drug’s labeling, 335 U.S. at 346-47 and found “that the phrase ‘accompanying such article’ is not restricted to labels that are on or in the article or package that is transported.” *Id.* at 349. In *Ubuteit*, the Court determined that leaflets that explained the usefulness of a medical device for curing and treating various diseases, but that were shipped separately were nevertheless part of the device’s labeling. 335 U.S. at 357. The Court held that the definition of labeling could be interpreted by functional standards and found that leaflets were labeling as the purpose of the leaflet was integrated with the use of the device. *Id.* at 358.

⁹⁴*See id.*

⁹⁵21 U.S.C. § 343-2. Specifically 1) is not false or misleading; (2) does not promote a particular manufacturer or brand of a dietary supplement; (3) is displayed or presented, or is displayed or presented with other such items on the same subject matter, so as to present a balanced view of the available scientific information on a dietary supplement; (4) if displayed in an establishment, is physically separate from the dietary supplements; and (5) does not have appended to it any information by sticker or any other method. *Id.*

⁹⁶*Id.*

FDA regulation of dietary supplements through the definition of labeling.⁹⁷

Regulatory Blindspots for Herbal Remedies under DSHEA

DSHEA has been the target for criticism over its loosening of safety for herbal remedies. DSHEA defined dietary supplements broadly to not only include vitamins and minerals, but also the “concentrate, metabolite, constituent, extract” of herbs and other botanicals.⁹⁸ While DSHEA was passed in 1994, the FDA did not propose regulations for good manufacturing processes until 2003; the proposed rules have yet to be finalized.⁹⁹ As a result, the potency and purity of herbal remedies has been suspect. Large variations in the parts the plants used, dosages, and chemical consistency were found between brands of many brands of the ten most popular herbal remedies.¹⁰⁰ Moreover, dangerously high concentrations of lead were found in traditional South Indian Asian herbal remedies sold in Boston.¹⁰¹ Thus, consumers are exposed to both the risk of overdosing due to an inability to accurately determine their intake of herbal compounds, and the risk of consuming toxic substances that contaminate herbal remedies.

While issues of quality can perhaps be improved through the passage of regulations of good manufacturing practices, other concerns of safety can only be addressed by amending DSHEA. Medical journals have reported serious side effects, from the use of herbal remedies, side effects including liver damage, kidney failure, and death.¹⁰² Kava, an herb used for psychotherapy for anxiety, was removed from the market

⁹⁷See *United States v. 250 Jars...* “*Cal’s Tupelo Blossom U.S. Fancy Pure Honey*,” 344 F.2d 288 (6th Cir. 1965) (booklet shown to FDA inspector posing as prospective customer was labeling); *United States v. 8 Cartons, “Plantation The Original’... Molasses*,” 103 F. Supp. 626 (W.D.N.Y. 1951) (books that were displayed and distributed with article were part of the labeling of the article). See also Mark E. Boulding, *The Statutory Basis for FDA Regulation of Scientific and Educational Information*, 4 J. Pharmacy & Law 123, 130 (1995) (noting that the FDA has adopted the position that “bona fide scientific and educational materials could be labeling”)

⁹⁸21 U.S.C. § 321(ff)

⁹⁹Proposed Rule, *Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements*, 68 *Fed. Reg.* 12157 (March 13, 2003).

¹⁰⁰Judith Garrand, *Variations in Product Choices of Frequently Purchased Herbs*, 2003 *ARCH. INT. MED.* 2290, 2290-2295 (2003)

¹⁰¹Robert B. Saper, et. al., *Heavy Metal Content of Ayurvedic Herbal Medicine Products*, 292 *JAMA* 2868, 2868-72 (2004)

¹⁰²See Edzard Ernst, *Harmless Herbs? A Review of the Recent Literature*, 104 *AM. J. MED.* 170, 17074 (1998)

in Germany after liver toxicity.¹⁰³ The pharmacological potency of herbal remedies is also evident in the documented interactions between many popular herbals remedies and traditional drugs.¹⁰⁴ Critics of DSHEA assert that by not providing for clinical testing, DSHEA unleashed herbal remedies into the public without providing an adequate understanding of the potential interactions of drugs and herbal medicines.¹⁰⁵ By not requiring pre-market approval for herbal remedies, DSHEA made an implicit assumption that herbal remedies are safe. Given the pharmacology of herbal remedies, this implicit is suspect, if not contrary to the scientific evidence.

Lastly, while proponents of traditional herbal medicines suggest that the safety of herbal remedies has been demonstrated through thousands of years of human experience and trial and error,¹⁰⁶ DSHEA makes no provisions for whether the herbal remedy is a traditional preparation, and fails to consider the length and quality of prior human experience as a factor in inclusion as a dietary supplement. Even extracts and concentrations of botanicals that far exceed what was safely used in traditional herbal remedies and extracts from herbs with little prior use fall under the DSHEA's dietary supplement definition.

Vioxx and Ephedra – Twin Safety Debacles of Lifestyle Drugs and Herbal Remedies

For both lifestyle drugs and herbal remedies, the regulatory blindspots came into full public view with the

¹⁰³ See Johannes Schulze et. al., *Toxicity of Kava a Case Study*, 10 PHYTOMEDICINE, SUPPLEMENT IV 68, 68-73 (2003)

¹⁰⁴ See Adriane Fugh-Berman, *Herb-Drug Interactions*, 355 LANCET 134, 134-36 (2000)

¹⁰⁵ See Frederick W. Fraunfelder, *The Science and Marketing of Dietary Supplements*, 140 AM. J. OPHTHAL. 302, 303 (2005)

¹⁰⁶ See e.g., Lei, *supra* note 9 at 124-128 (arguing that prevalence of traditional Chinese medicines in Asian countries is proof of its benefits); Huft, *supra* note 12 at 1696-1700

recall of a widely used and popular product. In the case of lifestyles drugs, the recall was of Vioxx by its manufacturer, Merck; for herbal remedies, recall was the FDA's ban of ephedra. And both instances, administrators from the FDA was called to testify in Congressional hearings to explain the efforts of FDA to prevent repeat occurrences.

Vioxx

On September 30, 1994, Merck announced that it was voluntarily withdrawing Vioxx (also known as rofecoxib),¹⁰⁷ a drug approved by the FDA in 1999 for the treatment of arthritis and acute pain.¹⁰⁸ Vioxx is a COX-2 inhibitor and part of family of nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁰⁹ Traditional NSAIDs inhibited both the COX-1 and the COX-2 enzymes, and could cause gastrointestinal bleeding; the numerous deaths and even more hospitalizations were attributable to the side effects.¹¹⁰ By selectively inhibiting of only the COX-2 enzyme, Vioxx could provide the anti-inflammatory and pain relief benefits of traditional NSAIDs, without the gastrointestinal complications.¹¹¹

COX-2 inhibitors arrived on the market near the turn of the millennium; other COX-2 inhibitors, Celebrex and Betrax, both manufactured by Pfizer, gained FDA approval in 1998 and 2001, respectively. The use of COX-2 inhibitors quickly spread. In 1999, an estimated 18% of patients who had visited a doctor reported using a COX-2 inhibitor.¹¹² By 2002, 29% of patients reported using COX-2s.¹¹³ COX-2 inhibitors were no more effective at treating pain and inflammation than traditional NSAIDs but cost significantly more.

¹⁰⁷ See Press Release, Merck & Co., Merck Announces Voluntary Worldwide Withdrawal of VIOXX® (Sept. 30, 2004) available at http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf

¹⁰⁸ See *id.*

¹⁰⁹ See *id.*

¹¹⁰ See Claire Bombardier et. al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 N. Eng. J. Med. 1520, 1520-21 (2000)

¹¹¹ See *id.*

¹¹² See Carolanne Dai et. al., *National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release*, 165 Arch. Intern. Med. 171, 173 (2005)

¹¹³ See *id.*

Despite the cost differentials, COX-2 inhibitors were being used more and more frequently in those least at risk for gastrointestinal complications, i.e. for those who gained the least benefit from COX-2s. In 1999, 35% of the patients using NSAIDs were using COX-2; by 2000, COX-2 accounted for 61% of NSAID use.¹¹⁴

Merck withdrew Vioxx after a large scale study suggested that Vioxx increased the risk of heart attacks.¹¹⁵ Vioxx had been a blockbuster for Merck. In 2003, it accounted for \$2.5 billion, or more than 10% of its \$22.5 billion in sales.¹¹⁶ At the time of its withdrawal, Vioxx was used by an estimated 80 million Americans.¹¹⁷ But the extensive use of Vioxx also meant extensive liability for Merck – Vioxx was estimated to be responsible for over 27,000 heart attacks and deaths.¹¹⁸ After the withdraw of Vioxx, Merck faced numerous lawsuits, 9,650 according to Merck’s 2005 annual report. And perhaps as a bad omen for Merck, in the first lawsuit to reach verdict, the jury found Merck liable for \$253 million in compensatory and punitive damages.¹¹⁹

The Vioxx withdrawal spawned two Congressional Hearings, the first on November 14, 2004 in the Senate (entitled “FDA, Merck and Vioxx: Putting Patient Safety First?”)¹²⁰ and the a second on May 5, 2005, in the House (entitled, “Risk and Responsibility: The Roles of the FDA and Pharmaceutical Companies in Ensuring the Safety of Approved Drugs, Like Vioxx.”)¹²¹ At the Senate hearing, the Deputy Director of

¹¹⁴ See *id.* at 174

¹¹⁵ See Press Release, Merck *supra* note 107

¹¹⁶ Merck Annual Report 2003, 10-K 2, 19 (filed March 10, 2004), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=73184&p=irol-irhome>

¹¹⁷ See Peter Jüni et. al., Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis, 364 *Lancet* 2021, 2021 (2004)

¹¹⁸ See Richard Horton, Vioxx, the implosion of Merck, and aftershocks at the FDA, 364 *Lancet* 1995, 1995 (2004)

¹¹⁹ See Merck Annual Report 2005, 10-K 26, (filed Mar. 13, 2005), available at <http://phx.corporate-ir.net/phoenix.zhtml?c=73184&p=irol-irhome>

¹²⁰ *FDA, Merck and Vioxx: Putting Patient Safety First?*, Hearing Before the S. Comm. on Fin., 108th Cong. (2004) available at <http://www.senate.gov/~finance/sitepages/hearing111804.htm>

¹²¹ *Risk and Responsibility: The Roles of the FDA and Pharmaceutical Companies in Ensuring the Safety of Approved Drugs*,

the Center for Drug Evaluation and Research (CDER), FDA submitted a written statement that declared that FDA planned to publish guidances to “assist pharmaceutical firms in identifying and assessing potential safety risks not only before a drug reaches the market and but also after a drug is already on the market.”¹²² Likewise, at the House hearings, the Acting Director for CDER, FDA, testified to the FDA’s increase in resources at the Office of Drug Safety, the division responsible for postmarketing surveillance.¹²³

In the aftermath of Vioxx, the FDA ultimately requested that Betrax be withdrawn; however, Celebrex still remains on the market.¹²⁴

Ephedra

The safety of ephedra, and of dietary supplements in reached the public spotlight with the death of Steve Bechler in 2003, a 23-years old pitcher for the Baltimore Orioles. Bechler had officially died of heatstroke during spring training, but the coroner found that ephedra likely contributed to his death.¹²⁵ Ephedra is derived from ma huang, an herb used in traditional Chinese medicine for colds and asthma. In the United States, ephedra was marketed for from weight loss to increased energy.¹²⁶

The FDA had raised concerns ephedra in 1997, when it proposed to classify dietary supplements containing ephedra as adulterated if the supplement 1) contained more than eight milligrams of ephedra per serving, 2) suggested a usage of more than eight milligrams per six-hour period or twenty-four milligrams in a day,

Like Vioxx, Hearing Before the H. Comm. Gov’t. Reform 109th Cong. (2005) available at http://frwebgate.access.gpo.gov/cgi-bin/useftp.cgi?IPaddress=162.140.64.128&filename=21483.pdf&directory=/diskb/wais/data/109_house_hearings

¹²²Statement of Sandra Kweder, Deputy Director of the Center for Drug Evaluation and Research, FDA, *FDA, Merck and Vioxx supra* note 120, 6 *available at*, <http://www.senate.gov/~finance/hearings/testimony/2004test/111804sktest.pdf>

¹²³Statement of Steven Galson, Acting Director of the Center for Drug Evaluation and Research, FDA, *Risk and Responsibility supra* note 120 at 37-38.

¹²⁴See <http://www.fda.gov/cder/drug/infopage/cox2/default.htm>

¹²⁵See Reilley M. Dunne, *How Much Regulation Can We Swallow? The Ban on Ephedra and How it may Affect Your Access to Dietary Supplements*, 31 J. LEGIS. 351, 351 (2005)

¹²⁶See *id.* at 358

or 3) contained as caffeine, or other stimulant.¹²⁷ In addition, the proposed rule would have required the label to warn against exceeding the recommended dosage and against use for longer than one week.¹²⁸ The rules had been proposed after the FDA received more than 800 adverse event reaction reports concerning products containing ephedra, with reactions ranging from increased blood pressure and insomnia to heart attack and stroke.¹²⁹

FDA efforts were stymied after the Government Accounting Office (GAO) examined the FDA's proposed rules and concluded that additional research should be conducted.¹³⁰ In particular, the GAO report found that the FDA had relied solely on adverse event reports (AERs) as the basis of its proposed regulation, but that the AERs were often incomplete and inconsistent. In addition, the FDA lack procedures to systematically determine the classification the AERs, and to incorporate the AERs into its decision making.¹³¹ The report concluded that the FDA "needs to provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions that support the proposed dosing levels and duration of use limits."¹³² In response to the GAO report, the FDA modified its proposed regulations, dropping all limitations of dosage but retaining its proposal to ban products containing a combination of ephedra and another stimulant, such as caffeine.¹³³

After additional reports of the dangers of ephedra, a hearing on the Senate Committee on Governmental Affairs was convened on October 2002 (entitled, "Ephedra: Who is Protecting the American Consumer.")¹³⁴

¹²⁷Proposed Rule, Dietary Supplements Containing Ephedrine Alkaloids, 62 Fed. Reg. 30,678 (June 4, 1997)

¹²⁸*See id.*

¹²⁹*See id.* at 30679

¹³⁰Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids, GAO/HEHS/GGD-99-90 (1999)

¹³¹*See id.* at 8-13

¹³²*Id.* at 25.

¹³³Dietary Supplements Containing Ephedrine Alkaloids; Withdrawal in Part, 65 Fed. Reg. 17474 (April 3, 2000) available at <http://www.gao.gov/archive/1999/h299090.pdf>

¹³⁴*Ephedra: Who is Protecting the American Consumers?, Hearing Before the S. Subcomm. Oversight of Gov't Mgmt, Restructuring, & Dist. of Columbia., Comm. On Gov't. Affairs, 107th Cong. (200), available at*

At the hearing, the parents of a sixteen year-old high school basketball player, who had died after using supplements containing ephedra, were called to provide a personal narrative on the dangers of ephedra.¹³⁵ The American Medical Association voiced support for banning ephedra.¹³⁶ The FDA's acting commissioner testified to the difficulty of banning ephedra under DSHEA.¹³⁷ The FDA could remove ephedra by demonstrating that it was unsafe, but the necessary tests had not yet been completed, despite concerns of safety more than five years. Moreover, the commissioner noted that declaring a substance to be an "imminent hazard" was "a long, torturous process... [that] has not been attempted since the middle-1980s, when it failed for the fourth time, with another drug category – prior to [DHSEA]."¹³⁸

The Senate hearings were followed by hearings in the House in July, 2003 (entitled "Issues Relating To Ephedra-Containing Dietary Supplements"), during which executives from Metabolife, a manufacturer of ephedra containing supplements were subpoenaed.¹³⁹ The executives declined to answer, invoking their right against selfincrimination.¹⁴⁰ Representatives for NVE Pharmaceuticals and Cytodyne Technologies, also manufacturers of dietary supplements containing ephedra, asserted that their products were safe when used as directed.¹⁴¹ The FDA Commissioner also testified, and noted that post-marketing regulations based on AERs were the primary regulatory tool for dietary supplements such as ephedra, and that the FDA was still in the process of studying the AERs it had received.¹⁴²

In 2004, more than six years from its initial proposal to restrict ephedra, the FDA was finally able to ban ephedra. In March 2003 the FDA reopened comments for the 1997 proposed rule,¹⁴³ citing a report by the

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_senate_hearings&docid=f:83482.pdf

¹³⁵ See *id.* at 4-7

¹³⁶ *Id.* at 21-22

¹³⁷ *Id.* at 39

¹³⁸ *Id.* at 45

¹³⁹ *Issues Relating To Ephedra-Containing Dietary Supplements, Subcomm. on Oversight & Investigations, Subcomm. Commerce, Trade, and Consumer Protection, H. Comm. Energy and Commerce, 108th Cong., (2003) 9.*

¹⁴⁰ *Id.* at 92-96

¹⁴¹ *Id.* at 120 (statement from NVE Pharm.) and 108 (statement from Cytodyne Tech.)

¹⁴² *Id.* at 233-34, 238-39

¹⁴³ Dietary Supplements Containing Ephedrine Alkaloids; Reopening of the Comment Period, 68 *Fed. Reg.* 10417, 10417, 10417-19 (March 5, 2003)

RAND Corporation.¹⁴⁴ The RAND report analyzed the results of clinical trials published in the medical literature, as well as AERs provided by the FDA and an ephedra manufacturer (Metabolife).¹⁴⁵ The report analyzed AERs and concluded that ephedra was associated with serious events, which included stroke, heart attack, and death. However, the report also noted that: “Scientific studies (not additional case reports) are necessary in order to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events.”¹⁴⁶ The FDA issued the final rule banning ephedra on February 11, 2004, declaring that ephedra presented an unreasonable risk of injury, and was thus adulterated under 21 U.S.C. 342(f)(1)(A).¹⁴⁷

However, the FDA’s regulations banning all ephedra supplements was successfully challenged in *Nutraceutical Corp. v. Crawford*.¹⁴⁸ In *Nutraceutical*, the court found that the FDA’s use of risk-benefit analysis was impermissible as such analysis would shift the burden to the manufacturers of dietary supplements, in contravention of DSHEA.¹⁴⁹ Moreover, its ban of ephedra dietary supplements containing less than ten milligrams of ephedra was impermissible as DSHEA requires dose-specific analysis.¹⁵⁰ To ban all ephedra dietary supplements, the FDA must “prove that any dose amount, no matter how small, presents a significant or unreasonable risk of illness or injury.”¹⁵¹ While *Nutraceutical* is district court case and therefore has limited precedential value, it nevertheless calls suggests the potentially strict limits of the FDA’s powers to regulate dietary supplements.

¹⁴⁴See RAND Corporation, Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects, AHRQ Publication No. 03-E022 (2003) available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/95n-0304-bkg0003-ref-07-01-index.htm>

¹⁴⁵See *id.* at 15-17, 26-30

¹⁴⁶See *id.* at 203

¹⁴⁷See Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 *Fed. Reg.* 6788 (Feb. 11, 2004)

¹⁴⁸364 F. Supp. 2d 1310 (D. Utah 2005)

¹⁴⁹See *id.* at 1317-19

¹⁵⁰See *id.* at 1320

¹⁵¹See *id.*

Regulatory Responses to Vioxx and Ephedra: Post-Market Enforcement

In the wake of Vioxx and Ephedra, reforms were proposed, calling for increased post-marketing surveillance and increased FDA enforcement powers to remove unsafe products from the market. The proposals were made separately for drugs and dietary supplements and were based on different rationales.

Several proposals suggested that the current regulation of drugs had too much inertia. The high barriers to pre-market approval kept too many beneficial drugs from the market, and at the same time, and lack of FDA action postmarketing kept too many harmful drugs on the market.¹⁵² The current regulatory scheme is lacking in its ability to identify adverse effects. The population included in pre-market clinical trials are often the same ones who ultimately use the drug post-marketing.¹⁵³ Moreover, larger populations and longer time spans are necessary to detect many of adverse effects of drugs, especially lifestyle drugs with chronic and frequent usage.¹⁵⁴ The regulation of drugs should lower the hurdles for pre-market approval, so that fewer and smaller scale clinical trials are utilized.¹⁵⁵ In essence, the current drug approval system should shift focus away from pre-marketing approval and towards post-marketing removal.

In the wake of Ephedra, reforms to DSHEA also called for greater post-marketing enforcement.¹⁵⁶ Under DSHEA, post-marketing surveillance has been limited primarily through on self-reporting by consumers

¹⁵²See e.g. Richard A. Epstein, *Symposium - Pharmaceutical Innovation and Cost: An American Dilemma: Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex*, 5 YALE J. HEALTH POL'Y L. & ETHICS 741, 747-50 (2005); Anup Malani & Feifang Hu, *The Option Value of New Therapeutics* (MacClearn Center Conference, University of Chicago, 2004), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=617382; Brian L. Strom, *How the U.S. Drug Safety System Should be Change*, 295 JAMA 2072, 2073-74 (2006);

¹⁵³See Epstein, *supra* note 152 at 750-55; Malani & Hu, *supra* note 152 at 3-6; Strom, *supra* note 152 at 2073

¹⁵⁴See Epstein, *supra* note 152 at 756-57; Strom, *supra* note 152 at 2073

¹⁵⁵See Epstein, *supra* note 152 at 750-55; Malani & Hu, *supra* note 152 at 14-15, Strom, *supra* note 152 at 2073-74

¹⁵⁶See e.g., Debra D. Burke & Anderson P. Page, *Regulating the Dietary Supplements Industry, Something Still Needs to Change*, 1 HASTINGS BUS. L.J. 121, 148-50 (2005); Donald M. Marcus & Arthur P. Grollman, *Botanical Medicines - the Need for New Regulations*, 374 N.E. J. MED. 2073-74 (2002)

and physicians.¹⁵⁷ Manufacturers did not also readily produce reports when requested by the FDA. In the case of ephedra, Metabolife, a manufacturer of ephedra supplements, and its chief executive were indicted for falsifying records provided to the FDA.¹⁵⁸ Several bills were introduced in Congress that would have amended DSHEA to enhance post-marketing surveillance efforts. The Dietary Supplement Information Act would require manufacturers of dietary supplements to register with the FDA,¹⁵⁹ and post-marketing reporting of adverse events.¹⁶⁰ Likewise, the Dietary Supplement Safety Act, would require manufacturers to report adverse event¹⁶¹ and permits the FDA to establish a plan of mandatory surveillance.¹⁶² However, others have suggested that DSHEA already provides the FDA with adequate enforcement remedies. Even DSHEA's defenders, however, seem to agree that increased post-surveillance monitoring is needed; the disagreement is over whether DSHEA or the FDA was the problem. For the defenders, the solution is not to amend DSHEA, but to provide the FDA with the resources necessary for proper enforcement.¹⁶³

The suggestions for post-marketing enforcement were not the only reform proposals in the wake of Vioxx and Ephedra. In addition to proposing to increase the resources for post-marketing surveillance in the wake of Vioxx, the FDA also proposed to re-examine the pre-market approval process.¹⁶⁴ And in the wake of Ephedra, some proposed the repeal of DSHEA.¹⁶⁵ The merits of enhanced post-marketing regulation, are apparent when the changes in the market for lifestyle drugs and herbal remedies. In particular, for lifestyle drugs, pre-market approval is reaching its limits of feasibility, and post-marketing regulations will

¹⁵⁷*Dietary Supplement Safety Act: How is FDA Doing 10 Years Later? Hearing Before Comm. on S. Gov't Affairs, Subcomm. on Oversight of Gov't Mgmt.*, 108th Cong. (2004) (statement of Robert Brackett, Ph.D., Director for Ctr. for Food Safety and Applied Nutrition of the U.S. Food and Drug Admin.), available at <http://hsgac.senate.gov/index.cfm?fuseaction=Hearings.Testimony&HearingID=179&WitnessID=647&IsTextOnly=0> (last visited Mar. 15, 2005).

¹⁵⁸See Department of Justice News Release Summary, <http://www.fda.gov/bbs/topics/news/2004/doj72204.html>

¹⁵⁹108 HR 724, s 416(a)

¹⁶⁰Id. at s 416(b)

¹⁶¹S. 722, 108th Cong. (2003), 416 (b)

¹⁶²Id. s 416 (c)

¹⁶³See Reilley M. Dunne, *How Much Regulation Can We Swallow? The Ban on Ephedra and How it may Affect Your Access to Dietary Supplements*, 31 J. Legis. 351, 377 (2005); see also

¹⁶⁴See Statement of Sandra Kweder, *supra* note 122 at 6

¹⁶⁵See e.g., Peter J. Cohen, *Science, Politics, and the Regulation of Dietary Supplements: It's Time to Repeal DSHEA*, 31 AM. J. L. MED. 175 (2005)

be increasingly necessary. And the converging conceptions of lifestyle drugs and herbal medicines, suggest that post-marketing regulation of herbal remedies is also the optimal regime.

Converging Conceptions for Lifestyle Drugs and Herbal Remedies

Direct to Consumer Advertising and the Market for Lifestyle Drugs

While several factors undoubtedly contribute to the booming market of lifestyle drugs, including the aging of the baby boomer population, the contribution proliferation of DTCA advertising is likely to be significant. The regulation of advertising of prescription drugs is explicitly provided for under the FDCA, which requires that prescription drug advertising must contain a “brief summary relating to side effects, contraindications, and effectiveness”¹⁶⁶ For broadcast advertisements of prescription drugs, the FDA regulations require that the manufacturer disclose the major risks and side-effects of the drug and make an “adequate provision” for disseminating the labeling information to the audience.¹⁶⁷ Prior to 1997, the broadcast advertising had been limited as it could not meet the “adequate provision” requirement.¹⁶⁸ Advertising was limited to “reminders,” which could contain the name of the drug but could not suggestions for use, and “help-seeking” which provided information on a disease or condition, but could not mention the drug. Both were permitted as they were exempted from the “adequate provision” requirement.¹⁶⁹

¹⁶⁶21 U.S.C. § 352(n)

¹⁶⁷21 C.F.R. 202.1(e)(1)

¹⁶⁸Direct-to-Consumer Promotion; Public Hearing, 60 *Fed. Reg.* 42581, 42582-83 (Aug. 16, 1995)

¹⁶⁹*See id.*

In 1997, the FDA changed its regulation of DTCA by publishing a draft of the Guidance for Industry: Consumer-Directed Broadcast Advertising.¹⁷⁰ The guidance was finalized in 1999.¹⁷¹ The guidance provided that the “adequate provision” requirement for broadcast advertising could be met if the broadcast contained a referrals to a physician, a toll-free number and website, and references to print advertising that contained more information.¹⁷² As a result of the change in the FDA’s regulatory stance, prescription drug advertisements have exploded. According to the General Accounting Office (GAO), in 1997, pharmaceutical companies spent \$1.1 billion on DTCA. In 2001, the amount of spending had more than doubled, to \$2.7 billion.¹⁷³ Moreover, the majority of the growth in spending was in television, which accounted for 25% of expenditures in 1997, but accounted for 64% in 2001.¹⁷⁴

The large majority of direct to consumer spending has, predictably been in small number of drugs for chronic conditions – i.e. drugs that can be classified as lifestyle drugs. The top fifteen most heavily advertised drugs accounted for just over half (54%) of the total DTCA. On these, 6 of the drugs were for allergy or asthma, 3 for high cholesterol, 2 for arthritis, and 1 each for acid reflux, depression, obesity, and impotence.¹⁷⁵ The focus of broadcast advertising in lifestyle drugs is perhaps not surprising as lifestyle drugs are particularly suited for the broadcast medium. Lifestyle drugs are targeted a large general population base and the broadcast advertising medium is designed to reach this large, general audience. Moreover, the conditions targeted by such drugs are those that the public generally understands and is able to self-diagnose.¹⁷⁶

¹⁷⁰Notice of Availability, Draft Guidance for Industry; Consumer-Directed Broadcast Advertisements, 62 Fed. Reg. 43171 (Aug. 12,1997)

¹⁷¹Notice of Availability, Guidance For Industry on Consumer-Directed Broadcast Advertisements, 64 Fed. Reg. 43197 (Aug. 9, 1999);

¹⁷²See Guidance For Industry on Consumer-Directed Broadcast Advertisements (1999)

¹⁷³See Government Accounting Office, Prescription Drugs, FDA Oversight of Direct-to-Consumer Advertising Has Limitations GAO-03-177 10 (2002)

¹⁷⁴See *id.*

¹⁷⁵See *id.* at 12; see also Michael S. Wilkes et. al., *Direct-To-Consumer Prescription Drug Advertising: Trends, Impact, And Implications*, 19 HEALTH AFFAIRS 110, 110-127 (2000) (describing trends in DTCA)

¹⁷⁶Devora Mitrany, *Lifestyle Drugs Determining Their Value and Who Should Pay*, 19 PHARMACOECONOMICS 441, 445 (2001)

The overall wisdom of permitting DTCA has been contentious. Proponents argue that such advertising provide a value channel of education for consumers and improves awareness of health conditions, while opponents suggest that it undermines the patient-physician relationship and spurs unnecessary use of prescription drugs.¹⁷⁷ Moreover, First Amendment free speech principles are implicated.¹⁷⁸ However, DTCA has undoubtedly had an effect on both patient and physician behavior. An FDA survey concluded that awareness of drugs and health conditions among patients has been increased by DTCA, prompting patients to seek information on the drugs or health conditions.¹⁷⁹ The FDA's survey focused on patient and physician attitudes and behaviors, rather than on the specific types of prescriptions requested. The potential for DTCA to differentially impact the prescription of lifestyle drugs was suggested in another study that compared patient's requests for prescription in the United States (where DTCA is permitted) and Canada (where DTCA is not permitted). The study concluded that DTCA results in patients requesting specific prescriptions from doctors more often, and that many of the requested prescriptions were for lifestyle drugs.¹⁸⁰

The potential impact of DTCA on spurring demand for prescription drugs is perhaps nowhere better highlighted than by Merck and its advertising of the now recalled Vioxx. In 2000, Vioxx was the most heavily advertised drug, with Merck spending \$160.8 million.¹⁸¹ The amount spent by Merck exceeded the advertising budgets of popular consumer brands such as Pepsi or Budweiser.¹⁸² Sales of Vioxx quadrupled in less than a year, from \$329.5 million in 1999 to \$1.5 billion in 2000.

¹⁷⁷See e.g., Elizabeth A. Almasi et. al., *What Are the Public Health Effects of Direct-to-Consumer Drug Advertising?*, 3 PLoS MEDICINE 284, 284-286 (2006) (summarizing viewpoints of DTCA); Alan F. Homer, *Direct-to-Consumer Prescription Drug Advertising Builds Bridges Between Patients and Physicians*, 289 JAMA 380, 380-82 (1999); Matthew F. Hollon, *Direct-to-Consumer Marketing of Prescription Drugs: Creating Consumer Demand*, 289 JAMA 382, 382-84 (1999).

¹⁷⁸See e.g., George W. Evans & Anold I. Freide, *The Food and Drug Administration's Regulation of Prescription Drug Manufacturer Speech: A First Amendment Analysis*, 58 FOOD DRUG L. J. 364 (2003)

¹⁷⁹See Kathryn J. Aikin et. al, *Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs*, 1-4 (2004) available at <http://www.fda.gov/cder/ddmac/Final%20Report/FRfinal111904.pdf>

¹⁸⁰See Barbra Mintze, *How Does Direct-to-Consumer Advertising (DTCA) Affect Prescribing? A Survey in Primary Care Environments With and Without Legal DTCA*, 16 CANADIAN MED. ASSN. J. 405, 411-12 (2003)

¹⁸¹See The National Institute for Health Care Management Research and Educational Foundation, *Prescription Drugs and Mass Media Advertising*, 2000 2 (2001) available at <http://www.nihcm.org/DTCbrief2001.pdf>

¹⁸²See *id.* at 5

Effects of DTCA on the market for herbal remedies

DTCA has potentially stimulated demand for lifestyle drugs, by medicalizing normal health conditions.¹⁸³ With widespread use and questionable necessity of lifestyle drugs, health insurance companies have balked at coverage for them.¹⁸⁴ Those whose health care plans do not cover their desired drugs, or who do not have health insurance coverage have difficulty satisfying those demands. For many of these people, herbal remedies may be viewed as cheaper alternatives to prescription drugs. Compared to those that have insurance, the uninsured are more likely to use dietary supplements.¹⁸⁵ Moreover, herbal remedies are used for conditions such as, arthritis and allergies, conditions that closely match those targeted by lifestyle drugs.¹⁸⁶ More than half of the respondents in one survey believed that dietary supplements is useful in treating diseases such (61% surveyed), arthritis (53%), depression (52%), and influenza (49%).¹⁸⁷ Moreover, beliefs that herbal remedies can be as potent as drugs are perhaps not unfounded.

The active ingredients in herbal remedies may also be similar or identical to those in prescription drugs. The seeming arbitrariness of the distinction between drugs and dietary supplements was further highlighted in *Pharmanex v. Shalala*.¹⁸⁸ In *Pharmanex*, the FDA challenged the classification of a product named Cholestin as a dietary supplement, contending that the product fell under the definition of “new drug.”¹⁸⁹ Cholestin was made from red yeast and contains, lovastatin, the chemical compound found in Mevacor, a prescription drug used to treat high cholesterol and heart disease.¹⁹⁰ The FDA had asserted that Cholestin

¹⁸³ See e.g., Charles Medawar et. al, *Direct to Consumer Advertising is Medicalising Normal Human Experience*, 324 BRIT. MED. J. 908, 908-09 (2002)

¹⁸⁴ See e.g., Mitrany, *supra* note 176 at 441-48

¹⁸⁵ See Robert J. Blendon et. al, *Americans' Views on the Use and Regulation of Dietary Supplements*, 161 Arch. Internal. Med. 805, 806 (2001)

¹⁸⁶ See Eisenberg, *supra* note 14

¹⁸⁷ See *id.*

¹⁸⁸ 221 F.3d 1151, 1153 (10th Cir. 2000)

¹⁸⁹ See *id.* at 1155-56

¹⁹⁰ See *Pharmanex, Inc. v. Shalala*, 35 F. Supp. 2d 1341, 1344 (D. Utah 1999)

failed to meet the definition of “dietary supplement” under the FDCA. Under DSHEA, a product is excluded from the definition of “dietary supplement” if it contains “an article that is approved as a new drug. . . which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food.”¹⁹¹ Because Mevacor was approved in 1987, prior to the marketing of Cholestin, the FDA considered Cholestin to contain an “article” that was previously approved as a new drug.¹⁹² The issue was one of statutory interpretation – whether “article” under DSHEA referred only to finished drug products or also to individual constituents.¹⁹³ After losing in district court,¹⁹⁴ the FDA prevailed on appeal, with the Tenth Circuit upholding the FDA’s statutory interpretation on the basis of deference administrative agencies.¹⁹⁵ Thus, simple timing differentiates drugs from dietary supplements, driving deep differences not only in regulations, but also in costs.

While the FDA may have been victorious in the short-term in *Pharamanex*, the longer-term implications are less certain. While *Pharamanex* could be interpreted not only as an attempt by the FDA stringently regulate herbal remedies, it could also be perceived as an attempt by the FDA to protect the pharmaceutical industry. Under the Drug User Fee Act, approval for a new drug applications are funded through user fees paid the drug’s manufacturer.¹⁹⁶ The user fees leaves the drug approval process open to the criticism that the FDA has become beholden to those the very pharmaceutical companies that should be regulating.¹⁹⁷ Because dietary supplement manufacturers do not fund the FDA as they do not pay user fees, the FDA could be seen as favoring large pharmaceutical companies to the detriment of consumers and dietary supplement

¹⁹¹21 U.S.C. § 321(ff)(3)

¹⁹²See 35 F. Supp. 2d at 1344

¹⁹³211 F.3d at 1153

¹⁹⁴35 F. Supp. 2d at 1359

¹⁹⁵211 F.3d at 1160

¹⁹⁶Pub. L. No. 102-571, 106 Stat. 4491 (1992)

¹⁹⁷See Vioxx Fears Prompt Call for User Fee Evaluation, 4 Nature Rev. Drug. Discovery 179, 179 (2005); Alexandra Marks, How Drug-Approval Woes Crept Up on FDA, The Christian Science Monitor (Nov. 26, 2004) available at <http://www.csmonitor.com/2004/1126/p02s01-uspo.html>

manufacturers.

This criticism of conflict of interests came to forefront with the Vioxx withdrawal.¹⁹⁸ As the FDA had approved Vioxx, the publicity over the safety of Vioxx predictably and invariably prompted scrutiny into the conduct of the FDA. At the Senate hearings¹⁹⁹ David Graham, associate science director of the Office of Drug Safety at the FDA, prepared a statement in which he declared: “I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference.”²⁰⁰ Graham described the culture in drug approval process as one “views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.”²⁰¹ The comments were carried and amplified by both the Washington Post, which wrote that Graham had allegedly been pressured by his superiors to suppress the results of his study that demonstrated Vioxx increased the risk of heart attacks,²⁰² and the New York Times, which suggested that the FDA attempted to delay Graham’s on the safety of Vioxx.²⁰³

The publicity of 2003 internal survey²⁰⁴ from Department of Health and Human Services only served to bolster concerns about FDA’s oversight into the drug approval process. The conclusions of the survey were seemingly positive, noting “reviewers face workload pressures that increasingly challenge the effectiveness of the process” but that “[t]he enactment of PDUFA III [Public Health Security and Bioterrorism Preparedness Act of 2002, authorizing continued use of user fees] presents significant opportunities to address many of

¹⁹⁸ See *id.*; *Vioxx Fears Prompt Call for User Fee Evaluation* *supra* note 197

¹⁹⁹ Statement of David Graham, *FDA, Merck and Vioxx: Putting Patient Safety First?*, *supra* note 120 available at <http://www.senate.gov/~finance/hearings/testimony/2004test/111804dgttest.pdf>

²⁰⁰ *Id.* at 3

²⁰¹ *Id.*

²⁰² See Marc Kaufman, “FDA Official Alleges Pressure to Suppress Vioxx Findings” THE WASHINGTON POST A23, Oct. 8, 2004

²⁰³ See Gardiner Harris, Drug-Safety Reviewer Says F.D.A. Delayed Vioxx Study, N.Y. TIMES, A1, Nov. 4, 2004

²⁰⁴ FDA’s Review Process for New Drug Applications A Management Review (2003), available at <http://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf>

the findings in this report.”²⁰⁵ In the wake of the Vioxx withdrawal, the contents of the survey were more closely examined. Two public interest groups, Union of Concerned Scientists and Public Employees for Environmental Responsibility filed Freedom of Information requests to obtain public release of the survey results.²⁰⁶ The Washington Post, a month and a half months after the Vioxx withdrawal, noted that the survey hinted at concerns by FDA scientists over the drug approval process. The paper noted that, according to the survey, 36% “of scientists said they were only somewhat confident, or not confident at all, in the FDA’s decisions regarding drug safety,”²⁰⁷ and that 18% of FDA scientists had felt pressured to approve a new drug, “despite reservations about the safety, efficacy, or quality of the drug.”²⁰⁸

Perceptions that the FDA was too closely tied to the pharmaceutical companies that they were supposed to be regulating could only have been exacerbated by the recommendation of a FDA advisory panel to permit COX-2 inhibitors, Celebrex, Betrax, and Vioxx, to remain on the market, even after Merck’s voluntary withdrawal of Vioxx. The panel recommended the COX-2 inhibitors have additional warning labels and limitations on advertising.²⁰⁹ However, the objectivity of the advisory panel was questioned by the New York Times, which found that ten of the thirty-two advisors had ties to the makers of the COX-2 inhibitors.²¹⁰ These ten votes voted nine to one for the continued marketing of Betrax and Vioxx, and the exclusion of these votes would have altered the outcome for these two drugs.²¹¹

One survey suggested that the public confidence in the FDA’s ability to regulate the safety of drugs decreased as a result of the Vioxx withdrawal.²¹² To the extent that Vioxx has also reinforced perceptions of the conflicts of interest in the FDA, many consumers may discount the lack of FDA approval for claims of herbal

²⁰⁵ *Id.* at *iv*.

²⁰⁶ See Marc Kaufman, “Many FDA Scientists Had Drug Concerns, 2002 Survey Shows” A01, THE WASHINGTON POST, Dec. 16, 2004.

²⁰⁷ *Id.*

²⁰⁸ *Id.*

²⁰⁹ See Gardiner Harris, “F.D.A. is Advised to Let Pain Pills Stay on the Market” N.Y. TIMES, Feb. 19, 2005

²¹⁰ See Gardiner Harris and Alex Berenson, “10 Voters on Panel Backing Pain Had Industry Ties” N.Y. TIMES, Feb. 25, 2005

²¹¹ See *id.* The recommendation for Celebrex would not be altered by the exclusion of the ten votes. See *id.*

²¹² See Ipsos Ideas Press Release, Vioxx Recall Hurt American’s Confidence in FDA, Not Prescription Drugs (Mar. 9, 2005) available at http://www.ipsos-na.com/news/client/act_dsp_pdf.cfm?name=mr050309-2.pdf&id=2591

remedies, and view herbal remedies as means to acquiring the benefits of lifestyle drugs –

benefits that through DTCA, they have come to be believed to possible through a “magic pill” – but without the costs.

Lack of Distinction Between Structure / Function and Disease Claims Further Drive

Market Convergence of Lifestyle Drugs and Herbal Remedies

Attempts to differentiate drugs from dietary supplements ironically have further steered herbal remedies towards same market as lifestyle drugs. Since claims establish intended use and intended use determines whether the product will be regulated as a drug, one of the primary benefits that a manufacturer gains from subjecting its product to drug regulation is in the claims that it can make. Drugs may make claims for the cure, treatment, mitigation, or prevention of disease. Dietary supplements are explicitly prohibited from such disease claims, but are permitted to make structure / claims.

Under FDA regulations promulgated in 2000,²¹³ for the purposes of dietary supplement labeling, “disease” is defined as “damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.”²¹⁴ Claims relating to an effect on a specific disease,²¹⁵ characteristics of a disease,²¹⁶ or an

²¹³21 C.F.R. 101.93(g)(2); *see also* Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 Fed. Reg. 1000 (Jan. 6, 2000) (codifying parts of 21 C.F.R. 101) (hereinafter, “Reg. of Struct. / Func.”)

²¹⁴21 C.F.R. 101.93(g)(1)

²¹⁵21 C.F.R. 101.93(g)(2)(i)

²¹⁶21 C.F.R. 101.93(g)(2)(ii)

abnormal condition associated with a disease²¹⁷ will be considered to be disease claims. Moreover, additional factors could cause a claim to be considered a disease claim,²¹⁸ including but not limited to the name of the product,²¹⁹ citations to scientific journals,²²⁰ and the use of certain pictures or symbols.²²¹ The FDA also emphasized that disease claims need not be explicit, but could be implied.²²² A claim is to be evaluated based on an “objective”²²³ assessment that is dependent on “the context and nature of the claim.”²²⁴

Rather than clarifying disease claims, the multi-factor, nebulous standard used by the FDA has resulted in fine and potentially arbitrary distinctions. As part of the promulgation of the final rules, the FDA discussed several examples distinguishing structure/function from disease claims. A claim of treating “joint pain” is a disease claim because “joint pain” is a characteristic of arthritis.²²⁵ However, a claim of “helps support cartilage and joint” would be a structure/function claim.²²⁶ But not all claims of support are permissible. A claim of “helps to maintain normal urine flow in men over 50 years old” is impermissible as it implies the treatment of benign prostatic hypertrophy.²²⁷ Citations to a journal article containing a disease name would not be considered an implied disease claim. However, a prominent placement of the journal could be.²²⁸ A statement that “a good diet promotes good health and prevents the onset of disease” is not a disease claim while “Promotes good health and prevents the onset of disease” is.²²⁹

The FDA’s examples provide the best evidence of the difficulties of drawing the boundary between structure/function and disease claims. However, the conditions targeted by lifestyle drugs are precisely those

²¹⁷21 C.F.R. 101.93(g)(2)(iii)

²¹⁸21 C.F.R. 101.93(g)(2)(iv)

²¹⁹21 C.F.R. 101.93(g)(2)(iv)(A)

²²⁰21 C.F.R. 101.93(g)(2)(iv)(C)

²²¹21 C.F.R. 101.93(g)(2)(iv)(E)

²²²Reg. of Struct. / Func., 65 *Fed. Reg.* at 1013

²²³*Id.* at 1008

²²⁴*Id.* at 1006

²²⁵*Id.* at 1016

²²⁶*Id.* at 1017

²²⁷*Id.* at 1021

²²⁸*Id.* at 1024

²²⁹*Id.* at 1025

conditions for which the distinctions between disease and structure/function are those that are most difficult to draw under the FDA's guidelines. The FDA's definition of disease is premised on "damage to an organ or body" and draws a distinction between "healthy function and preventing or treating abnormal function"²³⁰ "Common conditions associated with natural states or processes that do not cause significant or permanent harm will not be treated as diseases."²³¹ However, many of the conditions targeted by lifestyle drugs are precisely the same "common conditions associated with" aging that is not defined as a disease and would presumably be a structure / function claim. Thus, the claims of dietary supplements (and by inclusion, herbal remedies) can target the very same conditions targeted by lifestyle drugs. At most, one or two minor semantic adjustments to the claim may all that is necessary.

To the extent that disease claims can be differentiated from structure or function claims, the difference is unlikely to be perceived by consumers reading the labels. The FDA has discounted the possibility of subjective interpretations of labels, stating that it "does not believe that market research studies are necessary to provide a reasonable basis for the agency's determinations concerning the meaning of labeling claims. The agency has extensive experience in interpreting such claims."²³² The FDA, however, may be overly optimistic in both the consumers' ability in to decipher labels, as well as its own ability to discern consumer perception. While the FDA has adopted an objective standard,²³³ use of and belief in herbal remedies may be dependent on such subjective factors is personality and degree of social support.²³⁴ Indeed, one study using mock labels to addressing precisely the structure / function versus disease distinction on labels has found that consumers

²³⁰*Id.* at 1019

²³¹*Id.* at 1000

²³²Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 *Fed. Reg.* 1000, 1007-08 (Jan. 6, 2000)

²³³*See id.*

²³⁴*See* Keiko Honda, & Judith S. Jacobson, Use of Complementary and Alternative Medicine among United States Adults: the Influences of Personality, Coping Strategies, and Social Support, 40 *PREVENTIVE MEDICINE* 46, 46-53 (2005)

do not differentiate between structure / function claims and disease claims; rather, consumer interpretation of labels are dependent on the consumer's existing beliefs.²³⁵

Herbal Remedies as the "Poor-Man's" Lifestyle Drug

Lifestyle drugs have redefined the pharmaceutical market by shifting the use of drugs from the treatment disease, to the enhancement or maintenance of the quality of life. DTCA has suggested to the public of the availability of a pill based solution to the enhancement of everyday life. At the same time, in the aftermath of Vioxx, the public may place lower value on FDA approval. Instead, the ability to display publications from scientific journals alongside dietary supplements at the point of sale may be sufficient to convince consumers of the potency of the herbal remedy. Moreover, the structure/function versus disease distinction that has separates drugs from dietary supplements is largely irrelevant in the lifestyle drugs market. The confluence of the effects: DTCA, potential potency of herbal remedies, distrust of the FDA approval process, separating structure/function claims from the types of conditions addressed by lifestyle drugs could all result in herbal remedies becoming the "poor-man" lifestyle drug, used by those who wish to have the effects of lifestyle drugs, but either do not have the means, or do not wish to pay the cost of FDA approve pharmaceuticals.

General Policy Proposal: Shift Regulatory Emphasis from Pre-Market Approval to Post-Marketing Removal

²³⁵See Karen R. France & Paula F. Bone, *Policy Makers' Paradigms and Evidence from Consumer Interpretations of Dietary Supplement Labels*, 39 J. CONSUMER AFFAIRS 27, 47-49 (2005).

The FDCA provides the FDA with regulatory responsibilities for drugs, and dietary supplements, but at the same time, mandates a widely disparate regulatory regime for each. The justification for disparate regulatory treatment is tenuous in light of the converging markets and similar concerns of safety and potency. Moreover, both lifestyle drugs and herbal remedies strain the limits of the pre-marketing approval process. For lifestyle drugs, rare but serious adverse reactions could result in large absolute numbers of consumers being harmed. However, pre-market testing is not feasible due to the practical constraints on the size of clinical trials. For herbal remedies, the complexity of the chemical composition and natural variability in the product may preclude clinical testing at the same standards as single-compound drugs. Post-marketing enforcement provides an alternative to the binary choice of complete elimination from the market of such drugs and the risky and chaotic world of *caveat emptor*.

The difference between lifestyle drugs and herbal remedies can be conceptualized as a difference in the presumption of safety prior to marketing. Both need to satisfy some minimum level of safety prior to marketing. For lifestyle drugs, the hurdle may be met through large, but manageable clinical trials. For herbal remedies, at least traditional herbal remedies, the human experience may be sufficient. For both, however, the initial presumption may be inaccurate. Neither clinical trials nor use by traditional cultures are perfect models of the realities of widespread, frequent, and prolonged use in modern society. The demographics of the users of a particular lifestyle drug or herbal remedy are likely to shift over time, given the discretionary nature of the treatments. Interactions with other drugs or herbal remedies could create complications. The presumption may simply be wrong. Post-marketing enforcement is therefore needed to rectify such situations.

Evaluation of Current Post-marketing Enforcement Provisions for Lifestyle Drugs

For lifestyle drugs, post-marketing efforts are but an extension of the current regulatory regime for drugs. The FDCA already provides the FDA with the authority to conditionally grant approval for a new drug, subject to post-marketing studies and monitoring of adverse event reactions. The FDA, however, has not fully utilized these provisions of the drug regulatory approval process, and has instead, focused on its efforts on pre-market approval. The explanation may be due in part to institutional inertia. The provisions authorizing conditional post-marketing approval were added in 1997 and the FDA did not announce its guidance until 2001.²³⁶ Bureaucratic incentives also undoubtedly come into play. The withdrawal of a drug provides an uncomfortable spotlight on the administrators who authorized approval. Post-hoc, hindsight analysis always paints a poor picture and thus administrators are overly conservative in “type 2” errors (approving an unsafe drug).²³⁷ However, despite these difficulties, the regulatory machinery is in place. What is needed is a change in the mindset of not only FDA administrators, but also public understanding of the impossibility of total safety and the ever potential for harm for all types of drugs. This mindset may gradually be shifting, due to the popularity of lifestyle drugs. Lifestyle drugs highlight the impossibility of absolute safety; as the drug is more widely, frequently, and chronically used, the sizes of clinical trials will need to increase to account for growing heterogeneity. At some point, the pre-market trials will become infeasible.

Evaluation of Current Post-Marketing Removal Provisions for Herbal Remedies

Because, they are classified as dietary supplements, herbal remedies are subject at most to pre-market notification. While the DSHEA provides that a dietary supplement can be prohibited if it “presents a

²³⁶Notice of Availability Draft Guidance for Industry: Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997; 66 *Fed. Reg.* 17912 (April 4, 2001)

²³⁷See Merrill, *supra* note 19 at 1798-99

significant or unreasonable risk of illness or injury,”²³⁸ ephedra has so far been the only dietary supplement banned under this provision.²³⁹ Moreover, the experience with ephedra highlights the difficulties of post-marketing enforcement under DSHEA. Despite initial FDA concerns about ephedra in the mid-1990s, the FDA was unable to issue a final rule banning it until 2004. The use of voluntary AERs (adverse event reports) was problematic as the reports were often inconsistent and incomplete, as both the GAO and the RAND Corporation noted. Moreover, voluntary reporting has known subjective biases and tends to result in underreporting of events.²⁴⁰

The limitations of AERs resulted in the difficulty of the FDA being able to meet its statutory burden of proving that a given herbal remedy is unsafe. *Nutraceutical* holds that the FDA must demonstrate that a given dietary supplement is unsafe at all concentrations in order to ban the dietary supplement completely. Thus, under DSHEA, the FDA’s post-enforcement powers over dietary supplements seem extremely limited.

Specific Proposal: Herbal Remedies Should Be Subject to Low Hurdles for Pre-Marketing Approval but also Low Thresholds for Post-Market Removal

Herbal Remedies Should be Differentiated from Dietary Supplements

The need to regulate herbal remedies as something other than dietary supplements is perhaps self-evident in the definition of dietary supplements. Dietary supplements are defined as “(a) a vitamin, (b) a mineral, (c) an herb or other botanical, (d) an amino acid, (e) a dietary substance for use by man to supplement the diet

²³⁸ 21 U.S.C. § 342(f)

²³⁹ See Hutt., *supra* note 71 at 160-61

²⁴⁰ See Uncertainties in Analyses Underlying FDA’s Proposed Rule on Ephedrine Alkaloids, *supra* note 130 at 35

by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described [above.]”²⁴¹ Herbs and botanicals, often contain a mixture of chemicals, and are thus not well characterized. Vitamins, minerals, and amino acids, by comparison, are typically single-entity compounds. The relative simplicity of vitamins, minerals, and amino acids permits their safety or dangerousness to be readily determinable. Thus, vitamins, minerals, and amino acids are appropriately regulated under DSHEA, as their simplicity permits the FDA to meet its burden of demonstrating a lack of safety for removal. In contrast, the complexity of herbal extracts does not permit for as ready analysis.

Moreover, the standard for removing a dietary supplement from the market, “significant or unreasonable risk of illness or injury”²⁴² is a new standard under DSHEA.²⁴³ *Nutraceutical* is the only case thus far that addresses the definition of this standard. If the FDA’s burden of proof is as high as *Nutraceutical* suggests, the FDA may be required to untangle all of the complexities and multitudes of potential interactions before it is able to satisfy its burden. Given the near endless variety of flora in the world, and the chemical variety present in even a single plant, the FDA is relatively helpless in its ability to police herbal remedies through post-market removal.

Herbal Remedies With Histories of Substantial Prior Human Use May Justify a Lower Threshold for Demonstrating Pre-Market Safety

Herbal remedies, at least under DSHEA, are presumed safe until proven otherwise. For herbal remedies that consist of “new dietary ingredients” all that the manufacturer need do is to submit some evidence of safety to the FDA. The presumption is perhaps not unfounded. Herbal remedies have had long traditions

²⁴¹21 U.S.C. § 321(ff)

²⁴²21 U.S.C. § 342(f)(1)

²⁴³See Hutt, *supra* note 71 at 160

of use in many cultures around the world. The generations upon generations of use would likely screen out many of the more harmful herbal remedies. Indeed, the herbal remedies may have even preceded human civilization. The use of plants as medicines has been observed in chimpanzees, and the medicinal properties of plants may have evolved in conjunction with the evolution of animals.²⁴⁴ Such evolution and selection could provide an additional assurance in that herbal remedies, at least traditional herbal remedies, are relatively benign.

Additional Power for Post-Market Removal of Herbal Remedies Balances the Demands of Protecting Safety with the Demands of Providing Access to Health Care Options

The current regulation of herbal remedies under DSHEA is hampered by both the lack of pre-marketing hurdles that permits dangerous products such as ephedra on the market, and at the failure to give adequate power to the FDA to remove such products from the market. Additional hurdles prior to marketing is not the ideal solution, as such hurdles could also keep herbal remedies that have proven safe histories from the market. In addition, the use of herbal remedies as substitutes for lifestyle drugs suggests that the requirement of pre-marketing would be ineffective, as the scale and scope of the clinical trials necessary to demonstrate safety and efficacy necessary to detect rare but serious adverse events would exceed feasibility. For traditional herbal remedies, those that have had substantial prior human use, such preclinical testing is also likely unnecessary. Providing FDA with the flexibility to remove unsafe products from the market would balance the competing needs for safety and for access to beneficial remedies by enabling the FDA to rectify situations where the presumption of safety of a herbal remedy is unfounded.

Implementation Issues

Implementation is the greatest difficulty with a post-marketing removal system. Post-marketing regulation

²⁴⁴See Benjamin L. Hart, *The Evolution of Herbal Medicine: Behavioural Perspectives*, 70 ANIM, BEHAV. 975, 975-85 (2005)

had been the original scheme for the regulation of food and drugs under the 1906 Act. The proposed regulatory scheme therefore seems to be the regurgitation of an old, failed idea. Such regulation would require active surveillance for adverse events reporting, which is subject to the numerous biases and gaps. Moreover, post-marketing removal would likely require a substantial expansion of FDA resources and thus draw criticism of the ever greater expansion and intrusion of government into the affairs of private individuals, and with the result of cumbersome constraints on individual autonomy and choice.

The implementation barriers are substantial, and are also critical to the feasibility of a post-marketing regulatory regime. However, the barriers are not insurmountable. With better communication networks, such as the internet, coupled the advent of computerized data processing, and statistical analysis, the adverse reporting system has the potential to be ever more sensitive in detecting rare events and deciphering the bias and statistical noise. The resource issues can potentially be addressed by requiring manufacturers of herbal remedies to pay for regulation through user fees, analogous to the user fees in the approval process for new drugs. These fees could be criticized for their effect in limiting smaller businesses from the market for herbal remedies. However, given the limited liability of corporations, some size limitation may be necessary to provide incentives for self-policing of the safety herbal remedies. Larger corporations will be less likely to be judgment proof and thus would take greater precautions to insure the safety of their product, as failure to do could subject them to tort liability. Manufacturers who wish to assert the safety of herbal remedies should be able to substantiate their believes with their capital.

An Additional Reason for Greater Post-Marketing Removal Power for Herbal Remedies:

Unlocking the Value of Herbs

Traditional Herbal Medicines Show Great Promise in the Treatment of Disease

At the most basic level, traditional herbal medicines provide rich sources for new compounds that can be used in initial screening step of drug discovery process. Pharmaceutical companies are under the constant pressure to identify bioactive chemical compounds that may serve as drugs.²⁴⁵ The plants used in the traditional medicines are theorized to have evolved to produce bioactive compounds; as plants are stationary, they are heavily reliant on chemicals to ward off predators, and to otherwise interact with their environment.²⁴⁶ Furthermore, The history of medicine is replete with examples of powerful drugs that have been developed from or derived from plants, including narcotics such as cocaine and opium,²⁴⁷ as well as anti-cancer agents such as taxol.²⁴⁸ Indeed, up to one fourth of all prescription drugs are chemical compounds have been derived from botanicals.²⁴⁹ The drug discovery process could be further enhanced by leveraging existing knowledge of traditional herbal medicines. Such knowledge could further narrow the scope of the search for drug compounds, as the conditions treated by the traditional medicine may suggest the target areas of an herbal compound and therefore may provide a lead on for particular diseases.²⁵⁰

In addition to serving as a source for new drug compounds, traditional herbal medicines can potentially

²⁴⁵See e.g., Bhushan Patwardhan, World Health Organization Report: Traditional Medicine: Modern Approaches for Affordable Global Health 121-123 (2005) available at <http://www.who.int/intellectualproperty/studies/B.Patwardhan2.pdf> (describing the need for pharmaceutical companies to identify new compounds for drug targets)

²⁴⁶See e.g., Hart, *supra* note **Error! Bookmark not defined.** at 981-85

²⁴⁷See Padwardhan, *supra* note 245 at 112

²⁴⁸See Gordon M. Cragg, David J. Newman, *Plants as a Source of Anti-Cancer Agents*, 100 J. ETHNOPHARM. 72, 72-75 (2005)

²⁴⁹See Charles R. McManis, *The Interface Between International Intellectual Property and Environmental Protection*, 76 WASH. U. L. Q. 255, 273 (1998)

²⁵⁰Huft *supra* note 12 at 1700-03

be used to treat diseases directly. The precise identity of the active compounds or compounds, and the mechanism through which the compounds act have often not been determined. Indeed, the effect of the medicine may not depend on the action of a single compound, but on the combined effects of multiple compounds. Furthermore, the plant used may not contain the active compound, but its precursor; or the active compound may be a product of the preparation of the medicine or a metabolite of the precursor compound.²⁵¹ Moreover, despite the lack of scientific characterization of some traditional medicines, the use of traditional medicines itself could suggest that issues of safety and efficacy have been resolved through the thousands of years of experience with the plants.

Failure of DSHEA to Harness the Potential of Traditional Herbal Medicines

On its face, DSHEA was a success for herbal remedies. After the passage of DSHEA, manufacturers could bring their product to market, without having to undergo the extensive and expensive pre-market approval process for drugs. However, DSHEA proved to be a double edged sword for the development of herbal remedies and medicines. Even if a manufacturer could have profitably subjected an herbal remedy to the drug approval process, the availability of an alternative path to market meant that not only did performing the necessary clinical trials to obtain approval have to be profitable, but also that sale of the remedy as drug was more profitable than sale as a dietary supplement.

FDA's Attempts to Adapt Drug Regulation to Herbal Remedies

The FDA has attempted to facilitate the use of herbals and botanicals as drugs by adapting the regulations

²⁵¹ See World Health Organization, Guidelines for the Appropriate Use of Herbal Medicines, 8.1.2 (1998); Guideline for Industry, Botanical Products 5 (2004) available at <http://www.fda.gov/cder/guidance/4592fnl.pdf>

of drugs to address some of the realities of herbal medicines. The FDA's efforts include adjusting the criteria for inclusion in an OTC monograph to explicitly consider botanical drugs, publishing a guidance for industry that interprets the requirements of for pre-market approval under a NDA for botanicals, and establishing the Botanical Review Team to review the INDs for botanical drugs.

The FDA promulgated 21 C.F.R. 330.14 in 2002, which provided for the explicit consideration of botanical products in an OTC monograph. The regulation defines "botanical drug substance" as "a drug substance derived from one or more plants, algae, or macroscopic fungi, but does not include a highly purified or chemically modified substance derived from such a source."²⁵² Moreover, the regulation requires that the information useful for the characterization the botanical product be provided as part of the petition for inclusion in a OTC monograph. The information requirements includes (a) botanical ingredient, including growing conditions, supplier, harvest location and conditions, (b) qualitative descriptions such as name, appearance, physical and chemical properties, and known active constituents, (c) quantitative descriptions such as chemical constituents, and known active constituents, (d), type of manufacturing processes, and (e) further processing.²⁵³

Of more practical significance than the explicit approval of considering botanical products in OTC monographs is the consideration of foreign marketing experience. When the FDA established the OTC Drug Review in 1972, it considered only drug's marketing history within the United States in determining whether the drug had been used for a material extent or time.²⁵⁴ Therefore, a traditional herbal medicine would have been considered a "new drug" even if it had long history of use as a medicine in its native country or in other countries. The FDA began to consider the inclusion of foreign marketing experience in the 1980s ,after lobbying efforts by European manufacturers of sunscreen, dental ingredients, and herbal products.²⁵⁵ The

²⁵²21 C.F.R. 330.14(a)

²⁵³21 C.F.R. 330.14(c)(4)

²⁵⁴See Pinco, *supra* note 40 at 107.

²⁵⁵See Pinco, *supra* note 40 at 108.

FDA finally proposed to amend regulations to permit foreign marketing experience in 1996,²⁵⁶ issuing the final rule in 2002.²⁵⁷ The use of foreign marketing experience can potentially provide a means for herbal medicines to gain legitimacy without the added costs of clinical trials as the drug approval process in other countries have validated and regulated herbal remedies as drugs. Data from the experiences of the herbal remedy the those countries could therefore potentially be used to satisfy the GRAS/E and marketed for a material time / extent eligibility requirements for inclusion into the OTC Drug review process.

Two years after the OTC Drug review process was effectively opened for herbal remedies, the FDA, in 2004, published the Guidance for Industry, Botanical Product (the Guidance).²⁵⁸ The Guidance's explicit purpose is to describe the FDA's current thinking on and recommendations for the approval of drugs based on botanical products. As with all FDA guidances, it does not establish generally legally binding requirements. The Guidance defines "botanical product" to include plant materials, algae, macroscopic fungi, or any combinations of botanical products, but excludes material from genetically modified botanical species, fermentation products, highly purified substances, parts from animals, and vitamins and minerals. The Guidance highlighted the eligibility of botanical products for inclusion in the OTC monograph system. However, the primary contribution of the Guidance, was in clarifying the application of the NDA requirements to botanical products.

For the requirements of the IND, the Guidance notes that ensuring a consistent manufacturing process poses challenges in botanical products not present in a single compound drug. The raw botanical material is often not completely characterized and is susceptible to contamination or deterioration. The clinical investigator

²⁵⁶See 61 *Fed. Reg.* 51625

²⁵⁷See 67 *Fed. Reg.* 3060.

²⁵⁸See Guidance for Industry, Botanical Products, *supra* note 251

therefore should have appropriate quality controls for the botanical raw material.²⁵⁹ Furthermore, while identification of the active constituent is not necessary in the initial investigations, spectral analysis, chromatic fingerprinting, and/or strength by dry weight should be used to insure batch consistency.²⁶⁰ Ideally, a single source or batch should have sufficient quantities of the botanical product to sustain all the early investigations; bridging studies should be used if multiple batches are unavoidable.²⁶¹

While drugs derived from botanical products face increase quality control burdens, the requirements for pre-clinical toxicity studies are somewhat lessened for Phase I and II studies.²⁶² The Guidance notes that for orally ingested botanical products with prior human experience, pre-clinical testing for pharmacology and toxicity may not be needed.²⁶³ Botanical products that have been lawfully marketed as dietary supplements in the United States and without known safety concerns generally would not require additional pharmacological and toxicity studies.²⁶⁴ Furthermore, for such botanical products, the Guidance suggests that would be little need for initial typical pilot Phase I studies, but instead “strongly encourage[s]” the sponsor to pursue more definitive trials to determine effectiveness.²⁶⁵ Even for products that have not been legally marketed in the United States, the Guidance suggests that fewer safety trials may be necessary if there is sufficient prior human experience.²⁶⁶

In contrast to Phase I and II studies, Phase III studies should be accompanied by additional toxicity data,

²⁵⁹ See *id.* at 10-11

²⁶⁰ See *id.* at 11

²⁶¹ See *id.* at 11-12

²⁶² See *id.* at 13

²⁶³ See *id.* at 13

²⁶⁴ See *id.* at 17

²⁶⁵ See *id.* at 18

²⁶⁶ See *id.* at 25-26

regardless of whether the biological product has been lawfully marketed as a dietary supplement in the United States or elsewhere.²⁶⁷ Furthermore, the burden characterizing and insuring the quality of the biological product is fully borne in Phase III. While Phase I and II studies require only a rudimentary description of the biological product, such as a description of the plant raw material and method of preparation,²⁶⁸ Phase III studies are to be accompanied by a detailed documentation, including certification of the harvest time and location of the plant raw material, descriptions of the processing of the raw material, spectral analysis, chromatic fingerprinting, biological assays, analysis of heavy metals and pesticide residues.²⁶⁹

To facilitate review and approval of botanical drugs, the FDA established the Botanical Review Team in 2003, as a division of the FDA's Center for Drug Evaluation and Research (CDER).²⁷⁰ In addition, in June, 2004, the FDA published policies and procedures for the review botanical drugs as guidelines for the team.²⁷¹ The guidelines noted that botanical drugs have special features such as "complex mixtures, lack of a distinct active ingredient, substantial prior human uses," that "require consideration during the review processes."²⁷² The stated goals of the Botanical Review Team include serving as the expert resource within the CDER all in issues related to botanical drugs, participating in the application and approval of all botanical drugs, and coordinating with external groups to develop the knowledge and understanding of botanical drugs.²⁷³ The Botanical Review Team thus suggests the FDA's desire to adapt its NDA process for botanical drugs by providing specialized consideration for them.

²⁶⁷ See *id.* at 27

²⁶⁸ See *id.* at 13-16

²⁶⁹ See *id.* at 28-32

²⁷⁰ See Mark Blumenthal, *Botanical Products Team Established by FDA to Review New Products*, 58 HERBALGRAM 17 (2003) available at <http://www.herbalgram.org/iherb/herbalgram/articleview.asp?a=2520>

²⁷¹ Office of New Drugs, Center for Drug Evaluation and Research, *Review of Botanical Drug Products, Manual of Policies and Procedures*, 6007.1 (June 7, 2004)

²⁷² See *id.* at 1

²⁷³ About the Botanical Review Team, <http://www.fda.gov/cder/Offices/ODE-V.BRT/default.htm>

The Failure of the FDA's Herbal Efforts

The FDA's attempts to encourage the submission of herbal supplements for approval as drugs have largely failed. While the Guidance notes that several botanical products, cascara, psyllium, and senna, have been included in the OTC Drug Review,²⁷⁴ these cited botanicals were included in the OTC Drug Review prior to the efforts of FDA to incorporate botanical products into OTC monographs. The FDA also acknowledged that none of the currently marketed prescription drugs are botanical products.²⁷⁵

The failure of the FDA's attempts is not surprising. As a result of DSHEA, A manufacturer of traditional herbal medicines is confronted with a regulatory scheme offering a bi-polar choice, between having its products regulated as drugs or as dietary supplements. The choice then is stark. Drugs are subject to FDA pre-market approval with the manufacturer bearing the burden for safety and effectiveness; dietary supplements are subject only to pre-market notification. Drugs require the manufacturer to conduct extensive, multi-phase clinical trials; dietary supplements require only that the manufacturer have "substantiation" of the claims.

The costs of drug development are staggering, due in large part of meeting the requirements to obtain FDA approval. One estimate places the direct costs to bring a single drug to market have been estimated at over \$400 million.²⁷⁶ An average of than 7.5 years elapses between initial clinical trials and FDA approval.²⁷⁷

When the costs are capitalized to account for the length of the approval process, the estimated costs exceed

²⁷⁴ See Guidance for Industry, Botanical Products, *supra* note 251 at 6

²⁷⁵ See Botanical Review Team, http://www.fda.gov/cder/Offices/ODE_V_BRT/botanicalDrug.htm

²⁷⁶ See Joseph A. Dimasi et. al, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166(2003)

²⁷⁷ See *id.* at 164-165

\$800 million.²⁷⁸ Phase I alone costs an average of \$15.2 million; the average Phase III study costs \$86.3 million. In addition to the costs is the risk: only 31.4% of compounds entering Phase I complete Phase III. Another study has suggested that the cost is even higher, at \$863 million, but found that costs vary substantially from under half a billion to over \$2 billion, depending on the disease and the pharmaceutical company.²⁷⁹

While the costs are already enormous for traditional, single chemical entity pharmaceuticals, the costs could be even higher for non-purified herbal extracts under the FDA's Guidance for Industry. To obtain approval, the manufacturer would have to ensure consistency and quality by ultimately conducting chemical characterizations of markers. Given the effect of variability in soil conditions, harvesting, and storage, among other factors, bioassays chemical characterizations are likely not feasible, especially if the active chemical compound is unknown.²⁸⁰ With the additional requirements for herbal medicines, the development of a drug from an herbal extract is more complex and thus more expensive than development from a single chemical entity. While the FDA's objective in setting for the Guidance was to encourage the development of new herbal drugs, it's effect was to most likely do the exact opposite.

The combined effects of a the extensive regulation as drugs and the minimal regulation as dietary supplements has ensured that traditional herbal medicines would rarely be developed into full-fledged drugs, but rather, would mostly be relegated to the nebulous realm of dietary supplements.

²⁷⁸ See *id.* at 166

²⁷⁹ See Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development, Is it Really \$802 Million?*, 25 HEALTH AFFAIRS 420, 427 (2006)

²⁸⁰ Peter Goldman, *Herbal Medicines Today and the Roots of Modern Pharmacology*, 135 ANN. INTERN. MED. 594, 596(2001)

Intellectual Property Concerns of Herbal Remedies

The initial fixed costs of drug development are coupled with the relatively low marginal costs of the production of the drug. Even if there were no regulatory costs to drug development, substantial search costs would need to be expended to research and identify effective drugs. Given the relative ease with which a competitor can free-ride off the research and development by merely copying a drug, manufacturers must rely on patent protection to capture the benefits stemming from their research and to compensate them for their initial expenditures. Without such protection, drug development would be unprofitable, as the manufacturer will be unlikely to capture sufficient benefits to recoup their research investment.

In the case of herbal remedies, the patent protection afforded for herbal medicines is substantially weaker than for traditional chemical compounds. Patents can be granted for “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement.”²⁸¹ Patents, however, are unavailable for products of nature.²⁸² Thus, a manufacturer of an herbal remedy would not be able to patent the underlying plant from which the remedy is made. Herbal remedies, however, are not automatically excluded from all patent protection. The precise contours of what is a product of nature has not been established.²⁸³ Thus, a manufacturer could potentially genetically modify the herb in order to patent it. Even if the plant itself cannot be patented, the method of extracting the chemicals can be.²⁸⁴ And the patent may also be granted for the use of the extract – i.e. treatment of a specific disease.²⁸⁵ However, while there is some patent protection for herbal remedies, the degree of protection is less than that for a new chemical

²⁸¹ 35 U.S.C. § 101(a)

²⁸² *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)

²⁸³ *See id.* at 310 (strain of oil-eating bacteria was found not to be a product of nature as genetic engineering had altered its characteristics sufficiently such that the bacteria were markedly different from any found in nature); *cf. Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948)

²⁸⁴ *See e.g., Kuehsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701, 705 (7th Cir. 1910)

²⁸⁵ *See e.g.*, 21 C.F.R. 314.53(b)

compound because unlike the chemical compound, the plant itself may not be patentable. A competitor may therefore be able to circumvent the patent protections by utilizing a different method of processing the plant, or suggesting its use for another condition.

An additional hurdle for herbal remedies exists in the novelty requirements for patentability. The novelty requirement denies the issuance of a patent if the invention had been “described in a printed publication” in any country.²⁸⁶ Because many traditional herbal remedies have long histories of use, and the remedies may already be previously be published and thus fail to meet the novelty requirement. A patent for an herbal remedy therefore stands a greater risk for being invalidated on the basis, as a competitor may be able to shift through old medicinal texts to find a prior publication. Again, the precise contours of the bar to patentability on account of prior publication are uncertain.²⁸⁷ And the degree of overall patent protection for herbal remedies is debatable.²⁸⁸ However, the greater uncertainty of patent protection entails greater risks for manufacturers of herbal remedies. To compensate for these greater risks, manufacturers require a greater reward from their investment.

The issue of the patentability of traditional herbal medicines also raises the question of the ownership of traditional herbal medicines. The commercialization of drugs based on traditional herbal medicines has recently raised legal, ethical, and moral concerns of “biopiracy” - the exploitation of the natural resources of other cultures and countries.²⁸⁹ Concerns of biopiracy can be addressed through such mechanisms as such as assigning any patent rights to the country of origin of the traditional medicine, or providing for

²⁸⁶35 U.S.C. § 102(a)-(b)

²⁸⁷See *e.g.*, Huft, *supra* note 12at 1718-21

²⁸⁸See Liz Hanellin, *Note, Protecting Plant-Derived Drugs: Patents and Beyond*, 10 CARDOZO ARTS & ENT. L.J. 169, 189 (1991) (arguing that current patent protection is insufficient for plant derived medicines); cf. 12at n9 (suggesting that patent laws provides patent protection for plant-derived medicines)

²⁸⁹See *e.g.*, David Conforto, *Traditional and Modern-Day Biopiracy: Redefining the Biopiracy Debate*, 19 J. ENVTL. L. & LITIG. 357, 357-68 (2004) (describing biopiracy)

joint ownership of the whatever patents over the herbal remedy.²⁹⁰ However, such measures entail both transactions costs, e.g. negotiations with foreign governments, and as operational costs, e.g., royalties for the license to manufacture and market drugs derived from traditional herbal medicines.

Regulatory Proposals for Herbal Remedies

Due to the high hurdles to drug approval, and the potential for lowered returns from diminished patent protection, several articles have suggested an alternative regulatory scheme for herbal medicines. Some have suggested that the FDA lower the standards for the approval of traditional herbal medicines, as herbal medicines have meaningful differences, including substantial history of prior human use and complex and synergistic chemical constituents that are not readily amenable to analysis under current clinical trial designs.²⁹¹ Others have pointed to European nations as models for reform, where herbal drugs are evaluated and approved by a separate department creates the specialization and expertise necessary to evaluate the safety and efficacy of herbal-based drugs.²⁹² Still others call for a more active FDA role in determining the safety and effectiveness of herbal remedies, with the FDA establishing advisory boards to review the safety

²⁹⁰ See e.g., *id.* at 389-91 (describing partnership with third-world governments as a solution to biopiracy); Huft *supra* note 12 at 1721-29 (describing the possibility of joint-ownership for traditional herbal remedies between indigenous peoples and Western corporations)

²⁹¹ See e.g., Lei, *supra* note 9 at 136-39 (proposing that the FDA lower its approval hurdle for herbal drugs based on traditional medicines); Debra D. Burke & Anderson P. Page, *Regulating the Dietary Supplements Industry: Something Still Needs to Change*, 1 HASTINGS BUS. L.J. 121, 145-50 (2005) (suggesting that dietary supplements manufacturers conduct Phase I testing prior to marketing)

²⁹² See e.g., Edgar R. Cataxinos, *Regulation of Herbal Medications in the United States: Germany Provides a Model for Reform*, 1995 UTAH L. REV. 561, 590-92 (1995) (proposing the FDA adopt the German regulatory process for herbal medicines); Pinco, *supra* note 40 at 108-111 (comparing European and U.S. regulations of botanical medicines); Scott Martin, *Unlabelled Drugs as U.S. Health Policy; Canada Provides a Model for Reform* 9 ARIZ. J. INT'L & COMP. L. 545, 569-71 (1992) (describing the Canadian regulation of herbal medicines)

of herbals, in the same way that the OTC Drug Review Process evaluated the safety of existing OTC drugs.

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Proposals for treating herbal medicines separately from traditional, singlecompound entities, of course, presupposes that there is a difference between “nature” and “synthetic.” This distinction is untenable in some circumstances, as many of the chemical compounds used in modern drugs are identical to those found in plants. Indeed, plants produce powerful and illegal narcotics such as cocaine and opium. The lowering of pre-marketing standards could create consumer confusing by providing hierarchies of safety, with not only a “gold” standard of FDA approval, but also a “silver” and “bronze.”²⁹⁴ In addition, reducing the scientific rigor of clinical trials would only serve to impede the scientific understanding of herbal medicines. If anything, the scientific studies will be more uncertain, and the complexities of herbal medicines will remain unexplored.

The issue has been cast as one of weighing consumer protection and consumer choice, between preventing the consumer from acting on potentially inaccurate assumptions of the safety of “natural” or “traditional” products and permitting the consumer to judge for him or herself. While there will always tension between protection and choice, there is perhaps greater room for compromise when post-marketing options are also considered. Concerns arising from lowered pre-marketing approval hurdle can be partially alleviated by permitting a more aggressive post-marketing removal. Some premarketing approval hurdle may still be necessary, such as basic toxicity studies in animals. However, the use of aggressive-post marketing removal

²⁹³Cary E. Zuck, *Herbal Remedies Are Not Dietary Supplements: A Proposal For Regulatory Reform*, 11 HASTINGS WOMEN'S L.J. 29, 49-57 (2000)

²⁹⁴See Margaret Gilhooley, *Herbal Remedies and Dietary Supplements, the Boundaries of Drug Claims and Freedom of Choice*, 49 FLA. L. REV. 665, 717-20 (1997)

will insure the proper balance between safety and access, and leverage the potentially thousands of years of experience that traditional cultures have had with herbal remedies.

Aggressive post-market approval could also resolve the intellectual property barriers to the research and development of herbal drugs. Removal of herbal remedies need not be based on issues of safety alone. The FDA could perhaps be permitted to award the manufacturers who first characterize the active compounds or convincingly demonstrate the safety and efficacy of a herbal drug (perhaps to the degree of rigor necessary to gain approval as a single-compound entity) the exclusive right to market the drug, and remove of other herbal drugs containing crude preparations of the active compound. In the alternative, the FDA could perhaps require competing manufacturers to license from the discoverer, in order to continue marketing. Such a regime would provide for the incentive to conduct research and gain better scientific understanding of an herbal remedy. Moreover, if the herbal drug was developed from a traditional herbal medicine, the centralization of property rights in a manufacturer would create a pool of funds that could be more easily shared with the origin of the traditional medicine and thereby address concerns of biopiracy.

Conclusions

Under the current statutory scheme of the FDCA is hampered by its emphasis and focus at the point of marketing. The regulation of drugs in the FDCA has been one of shifting emphasis on the hurdle necessary to permit marketing. With the 1906 Act, the hurdle was non-existent. After the inadequacy of enforcement of the 1906 became apparent, the 1938 FDCA Act erected the hurdle of a pre-notification. The 1962 amendments raised the hurdle yet higher, by requiring pre-market notification.

The history of the FDA has neglected post-marketing removal as a regulatory solution. When the FDA attempted to bring vitamins and minerals into the purview of pre-market approval by classifying potent formulations as drugs or food additives, Congress reacted, perhaps harshly, by enacting DSHEA, which created a polar regulatory scheme between drugs and dietary supplements.

The desirability of greater post-marketing regulation was perhaps further highlighted by the safety recalls of Vioxx and Ephedra. Despite stark differences in regulatory regimes, one common lesson from the recalls was the need for greater postmarketing activity. The desirability of post-marketing regulations for lifestyle drugs and herbal remedies is further suggested by their converging markets. Lifestyle drugs have created demand for the treatment of widespread and chronic conditions that lie at the boundary of therapy and enhancement. Herbal remedies have also gained widespread popularity and may have come to be viewed as a cheaper substitute for lifestyle drugs.

The widespread use of lifestyle drugs, both in the breadth of the population as well as the frequency and duration has demonstrated the limits of pre-market approval clinical trials in coping rare but severe adverse

side effects. The only solution is for greater post-marketing regulation. The parallel growth of the use of herbs for similar conditions as lifestyle drugs suggests the conceptual differences between lifestyle drugs and herbal remedies are minor. The difference is one of presumption at prior to marketing, with a lifestyle drug being presumed safe only after clinical trials have been conducted, and a herbal remedy assumed safe, especially if it has been used by a traditional culture. However, for both, the relatively high degree of error in the initial presumptions suggests the need for aggressive post-marketing enforcement to rectify those errors.

The current drug regulations are adequate and adaptable to increasing postmarketing enforcement for lifestyle drugs. However, herbal remedies require a different regulatory category, one with lower pre-marketing hurdles than drugs, but also a lower threshold for post-marketing removal. Such a regulation system could also have the added benefit of addressing the issue of the intellectual property of natural herbal medicines, and thus remove a significant impediment to unlocking their full value.