At the Crossroads:
The Dietary Supplement Health and Education Act

by Thomas N. Tiedt, Ph.D.

Sprouting from the seeds of many nutritional advances, new directions for nutritional supplementation emerged during the 1970s. Most notably, increasing dietary intake of fiber, antioxidant vitamins, and folic acid revealed that selective dietary enhancements could decrease the risk of complex diseases like cancer, cardiovascular disease, and birth defects. A new therapeutic framework was born—better chronic disease control through better nutrition.

It seemed a good idea in Congress about ten years ago to leapfrog a seemingly cumbersome Food and Drug Administration (FDA) process and grant what the increasingly prominent dietary supplement industry sought—self-regulation without premarket approval of health claims, health warnings, and dosage schedules. A re-defined supplement industry outflanked all the traditional healthcare players, and secured passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA).[1]

The removal of traditional product controls produced a supplement revolution and a novel therapeutic category—herbal medicines marketed as dietary supplements—coincident with consumers' disillusionment about what seemed to be unfulfilled promises of a portfolio of new wonder drugs. For many consumers, traditional medicine did not seem to meet expectations or to support the healthcare cost explosion.

Weird untested blends of new and discarded drugs isolated from plants are now widely promoted (e.g., as "vitamins," soft drinks, and candies—and some as speed products for students and athletes). Every disease and personal shortcoming can be "cured." With powerful consumer appeal, any threat to the availability of these products readily generates a stream of fervent letters and phone calls to FDA and Congress.

Nearly a decade after DSHEA was enacted, this novel law that promised so much appears to be on the rocks. Stories of adulteration and physical injury are skyrocketing. Recurring findings of glass, pesticides, heavy metals, prescription drugs, and undisclosed allergenic substances fuel media coverage about FDA's regulatory reach into this area, and prompt suggestions for mandatory, rather than voluntary, quality control. Adverse health interactions between dietary supplements and traditional medicines and surgical procedures are creating new health problems.

In the months since his appointment, FDA Commissioner Mark McClellan, M.D., Ph.D., has been bringing FDA back into the supplement picture. Dr. McClellan's expertise as an economist and physician appears to be the right skill set for the monumental regulatory tasks at hand; moreover, he comes to FDA with the full endorsement of the dietary supplement industry.

While supplements already are required to comply with federal good manufacturing practices (GMPs) for foods, FDA proposed supplement-specific GMPs in March 2003[2] to mandate the GMPs initially developed by the herbal industry and marketed as industry standards by supplement trade associations since 1995. Long-awaited federal requirements for batch records, raw material, finished product testing, and adverse reaction reporting likely will help reverse consumers' declining respect for dietary supplements and government oversight.

The Office of Inspector General (OIG) of the Department of Health and Human Services (DHHS) also issued a report in March 2003,[3] which will be the impetus to codify labeling requirements that call for more effective adverse reaction warnings, ingredient disclosures, and less confusing health claims. Several years earlier, the OIG had criticized FDA as an inadequate safeguard for consumers flocking to a panoply of experimental dietary supplements.

Why were so many dietary supplement initiatives published in February and March of this year?

The Ephedra Dilemma

One herbal medicine-turned-dietary supplement—ephedra—has overtaken the dietary supplement agenda; its pharmacological profile tests the bounds of what is meant by "dietary" and "nutrition," and what was contemplated in DSHEA.

There are many species of the ephedra plant. Mormons use a North American species lacking pharmacological stimulants, in tea. For dietary supplements, however, the Chinese herbal

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medicine component, *Ephedra sinica*, is used because it contains several ephedra alkaloid drugs, such as ephedrine, phenylpropanolamine (PPA), pseudoephedrine, and norpseudoephedrine. [Note: PPA was removed from the market in November 2000 for causing strokes, heart attacks, and deaths. Norpseudoephedrine is a Schedule IV controlled substance. Ephedra alkaloid/caffeine combinations were banned from over-the-counter (OTC) drugs in 1983. Pseudoephedrine is the only ephedra alkaloid permitted by FDA for internal drug use that does not require physician intervention.]

Ephedra supplements are sold to treat obesity and to increase energy, based on research for an ephedrine/caffeine-containing prescription drug sold in Denmark. [Note: In November 2002, that drug was banned in Denmark due to adverse reaction reports.] The stimulant effects of the ephedra alkaloids generated substantial pharmacological interest in the early 1900s. Because their adverse effects outweighed their benefits, ephedra alkaloids gave way to OTC amphetamine by the 1930s, and to safer (i.e., more selective in their actions) sympathomimetic prescription drugs by the 1960s. On the street, ephedrine and ephedra are common substitutes for illicit methamphetamine and cocaine.

No ephedra alkaloid is nutritional. Nevertheless, ephedra marketers claim that dietary ephedra complies with DSHEA because Chinese ephedra is botanical. Other stimulants and drugs typically are added to ephedra to interfere with physiological defense mechanisms to ephedra alkaloid neurostimulation, and to mask ephedra side effects. Ephedra supplements are widely promoted with fantastic claims, promising cures for obesity, sexual inadequacy, and poor athletic performance.

The promotion of ephedra alkaloids as dietary supplements goes far beyond the limitations imposed on them when they are marketed as drugs. For example, pharmaceutical ephedrine is designed for occasional use only for life-threatening asthma attacks, is not to be used without physician diagnosis of asthma, and use is to be terminated if asthma relief is not achieved within one hour of ingestion. Pseudoephedrine's use as a nasal decongestant is limited to seven days. PPA and norpseudoephedrine are not legitimately sold as OTC drugs because of their health hazards.

Due to the radically expanded types and durations of use of ephedra alkaloids marketed for dietary purposes, ephedra supplements have generated more adverse event reports than those generated for ephedra alkaloid-containing drug products. The ephedra industry acknowledges that perhaps only one percent of adverse events are reported. Thus, 100,000 adverse event reports for ephedra supplements accumulated across several industry and federal databases likely represent millions of actual adverse events, at least thousands of which would be considered serious. A recent study[4] found that ephedra supplements generate the majority of herbal supplement adverse reaction reports to poison control centers, while ephedra supplements represent only a small proportion of herbal supplement sales. Ephedra supplements increase the risk of hemorrhagic stroke nearly 300% when used as directed.[5] The Rand Corporation concluded that the health risks of ephedra supplements outweigh their benefits.[6] In response, DHHS Secretary Tommy Thompson stated, "I would not take this, I would not give it to my family and I don't know why anyone would take these products. Why take the risk?" National Institutes of Health (NIH) and other health agencies agree, and contraindicate dietary ephedra.

The ephedra dilemma and its challenge to DSHEA are illuminated when the ephedra controversy is applied to vitamins, minerals, foods, and drugs (see Table 1). It appears that most herbal supplement claims are inconsistent with DSHEA (see Table 2).

Recently published medical evidence,[7] combined with another ephedra-related death of an athlete in February 2003,[8] elicited an avalanche of media reports. Scores of physicians, pharmacologists, and poison control officials have described the well-known health hazards of ephedra supplements. Following several earlier ephedra health warnings, in February 2003, FDA proposed a "black box" warning to inform consumers that use of ephedra supplements is associated with heart attack, seizure, stroke, and death, and that these risks increase with strenuous exercise and with use of other stimulants such as caffeine.[9]

In a move likely to impact ephedra supplement availability and the future of DSHEA, Representative Greg Walden (R-OR) co-sponsored legislation in March to ban ephedra nationwide. He stated, "It is clear that a consensus is emerging, both in Congress and within the executive branch, that the federal government must do more to protect the public from the potential dangers of this drug. If young healthy athletes like Steve Bechler [who died, in part, due to Xenadrine, according to the medical examiner[10]] can be struck down in the prime of life because of ephedra use, we can only assume that the threat to the larger public is high."[11] Several other members of Congress have announced plans to introduce ephedra and DSHEA legislation, and to conduct congressional safety hearings in order to acquire industry documents and question executives of ephedra-selling companies. Several states are undertaking similar initiatives.

Dietary ephedra's time, and a decade of poor quality herbal supplements, appears to be drawing to a close as a

result of DHHS' views and an invigorated FDA. But, maybe not. According to a recent issue of *Roll Call*, FDA's proposed new ephedra rules and "black box" warnings reflect the ephedra industry's strategy to achieve regulations that will weed out smaller ephedra sellers.[12] Supplement trade associations have prepared letters to legislators and FDA for consumers to sign in order to save ephedra and DSHEA. Members of the National Nutritional Foods Association weaved through Congress on "Natural Foods Day" in March to "educate" legislators with industry's talking points. Energetic lobbying may put DSHEA amendment or repeal back on the back burner.

Significant policy choices are about to be made. Herbal supplements like ephedra either will be banned or will be officially FDA sanctioned for marketing with "black box" label warnings. The latter choice could stimulate the movement toward dietary medicines, and perhaps help botanically-derived drugs bypass the new drug approval process. Furthermore, "black box" warnings of serious adverse reactions would introduce a bold new regulatory scheme for food labeling—a scheme analogous to the label warnings on tobacco products. Either way, significant changes are in store for the dietary supplement industry.

[1] Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in multiple sections of 21 U.S.C.)

[2] *See* 68 Fed. Reg. 12,158 (Mar. 13, 2003).

[3] *See* http://oig.hhs.gov/oei/reports/oei-01-01-00120.pdf and http://oig.hhs.gov/oei/reports/oei-01-01-00121.pdf.

[4] S. Bent, T.N. Tiedt, M.C. Odden & M.G. Shlipak, *The Relative Safety of Ephedra Compared With Other Herbal Products*, 138 ANNALS OF INTERNAL MED. 468 (2003).

[5] L.B. Morgenstern et al., *Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke*, 60 NEUROLOGY 132 (2003).

[6] P.G. Shekelle et al., *Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance*, 289 JAMA 1537 (2003).

[7] *See, e.g.,* Bent at al., *supra* note 4; Morgenstern et al., *supra* note 5; Shekelle et al., *supra* note 6.

[8] Dave Sheinin, *Bechler Tests Implicate Ephedra Use: Stimulant a "Significant Factor" in Pitcher's Death*, WASH. POST, Mar 14, 2003, *available at* www.washingtonpost.com/wp-dyn/articles/A21095-2003Mar13.html.

[9] 68 Fed. Reg. 10,417-20 (Mar. 5, 2003).
In light of the new scientific evidence as well as the comments received in response to the June 1997 proposal, FDA is considering the following warning statement . . . . to appear on the principal display panel of the product:

> WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids . . . .

Id. at 10,418.

[10] Sheinin, *supra* note 8.

[11] Walden Cosponsors Bill to Regulate Sale of Dietary Supplement Ephedra (Mar. 5, 2003), *available at* http://walden.house.gov/press/2003/03Mar/pr0305a03print.htm.

[12] Brody Mullins, *Ephedra Battle Heats Up—Despite Ballplayer's Death, Industry Winning on Hill*, ROLL CALL (THE NEWSPAPER OF CAPITOL HILL), Mar. 12, 2003.

[13] P.A. Vignolo, *The Herbal Street Drug Crisis: An Examination of the Dietary Supplement Health and Education Act of 1994*, 21 SETON HALL LEGIS. J. 200 (1997).

Table 1

If drugs and controlled substances exist in plants, are they dietary supplements?
If the answer is "Yes," then the door is open to many new food products. If not, DSHEA likely will be amended or repealed.

Ephedra attributes will help define the answer.

- Chinese ephedra's dietary use is based on its use as an alcohol substitute sold at bars in the early 1990s.[13]
- *Dietary ephedra is used to treat obesity and its health consequences, and to induce amphetamine-like central nervous system stimulation.*
- According to the Rand Report: 1) risk from ephedra supplements outweigh modest short-term weight loss benefit, 2) ephedra supplements provide no exercise benefit, and 3) several ephedra supplement users experienced strokes, heart attacks, seizures, psychoses, and deaths with no other identifiable cause.
- *In response to the Rand Report, DHHS Secretary Tommy Thompson said, "I would not take this, I would not give it to my family and I don't know why anyone would take these products. Why take the risk?"*
- The owner of the largest ephedra marketer, Metabolife International, is under criminal investigation for possibly wrongly denying the existence of thousands of adverse reaction reports.
- *Several major ephedra marketers have terminated ephedra sales due to safety concerns and declining ability to obtain and afford product liability insurance.*
- 7-Eleven and all military stores terminated all ephedra sales because of their safety hazards.
- *Ephedra is not to be used for more than three months or during exercise.*
- Ephedra supplements are banned by the NFL, NCAA, and International Olympics Committee.
- *Ephedra supplements are contraindicated by NIH, NHLBI, American Dietetic Association, American Obesity Association, American Medical Association, and several other medical and regulatory organizations.*
- Ephedra sales are banned in Suffolk County, NY, and similar legislation is introduced in several states. In California, ephedra sales are banned for those under 18, and similar legislation is introduced in several states.
- *Ephedra supplements are formulated with nonnutritional stimulants, including a federal controlled substance. Ephedra itself is considered a controlled substance in a few states.*
- Scores of physicians and coroners, and ephedra studies, have attributed serious morbidity and mortality to ephedra supplements.
- *In March 2003, FDA proposed a 'black box' label that would require ephedra supplement labels to warn about the risks of serious adverse events.*
- Ephedra alkaloids are List 1 DEA chemicals requiring limits in distribution and reporting requirements.

Table 2

Core Claim Provisions— DSHEA Section 403(r)(6)
A statement for a dietary supplement may be made if – (a) the statement claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient, and (b) the manufacturer of the dietary supplement has substantiation that such statement is truthful and not misleading.