

ROUTING SLIP
GENERATED BY: HF-40
DATE: FEB 01, 2002

FDA CONTROL NUMBER: 02 607

TRACER #: OS #: 0201020018

DATE OF CORRESPONDENCE: 01/31/02

DATE INTO FDA: 02/01/02

TO: TOMMY G THOMPSON, SECRETARY, HEALTH AND HUMAN SERVICES

FROM: SIDNEY M WOLFE, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

SYNOPSIS: SWIFT - COMMENTS ON PETITION, DOCKET NO. 01P-0396, FOR FDA TO BAN
EPHEDRA AND DIETARY SUPPLEMENTS CONTAINING SYNTHETIC EPHEDRINE
ALKALOIDS (REF: TRAC # 01 4527).

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COORDINATION:

SIGNATURE REQUIRED: DEPUTY SECRETARY, HHS

REFERRALS FROM HF-40

ASSIGNED TO	ACTION	DUE DATE
HF-40 CRAWFORA	PREPARE RESPONSE FOR SIGNATURE	02/15/02

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

From: **Sidney Wolfe** *OS#:* **020120020018**
Organization: **Public Citizen** *Date on Letter:* **1/31/02**
City/State: **Washington DC** *Date Received:* **2/1/02**
On Behalf Of: *Type:* **Major Organization**

Subject: **Expresses grave concerns regarding the failure to ban the food supplement ephedra and those dietary supplements containing synthetic ephedrine alkaloids**

Assigned to: **FDA** *Dep.ES:* **Dick Eisinger**
PC: **Tom Kuchenberg** *Date Assigned:* **2/1/02**
Action Required: **Dep Sec Sig** *Date Reassigned:*
Reply Due Date: **2/15/02**

Info Copies To: **Kuchenberg, Thomas (HHS/OS); SWIFT, ASL; SWIFT, ASPA; SWIFT, COS; SWIFT, DEP; SWIFT, ESS; SWIFT, OGC; SWIFT, OIG; SWIFT, SEC**

Interim (YIN): **No** *Date Interim Sent:*

Comments:

File Index: **PO-4-6** *CCC:* **Elaine Gross**



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From: SID WOLFE, AMER ARDATI

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Joan Claybrook, President

Tommy Thompson, Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

January 31, 2002

Dear Secretary Thompson,

Despite your oft-professed concern for food safety, your Department has been grossly negligent in protecting Americans from what is clearly the most dangerous drug that masquerades as a food supplement, ephedra. More than seven months ago, last June, Canadians were alerted by an advisory from their government "warning consumers not to use products containing the herb Ephedra."¹ Health Canada based its decision to release the advisory, in part, on the United States' FDA adverse event reports. Public Citizen, along with noted Clinical Pharmacologist Dr. Ray Woosley, of the University of Arizona, petitioned you on September 5th to ban all ephedra supplements. More recently, on January 9th, the Canadian government called for a recall of all "Ephedra/ephedrine products with labeled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects."²

We now have evidence that you are not only failing to protect Americans by banning a chemical that has more reports of deaths, heart attacks, strokes, cardiac arrhythmias, hypertension and seizure than all other food supplements combined, but that you have failed to seize at least 10 products made by at least nine dietary supplement manufacturers who are selling products that illegally contain synthetic ephedrine alkaloids under the guise of being legitimate dietary

¹ Health Canada. Advisory not to use products containing Ephedra or ephedrine. [Advisory] June 14th, 2001. http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_67e.htm

² Health Canada. Health Canada requests recall of certain products containing Ephedra/ephedrine. [Advisory] January 9th, 2002. http://www.hc-sc.gc.ca/english/protection/warnings/2002/2002_01e.htm

Ralph Nader, Founder

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supplements.³ These products are being sold by their manufacturers over the Internet. Although the FDA has recognized that this practice is unacceptable and has recently taken action to seize such adulterated dietary supplements, the sale of similarly illegal products remains widespread.⁴

The inclusion of synthetic compounds in dietary supplements is expressly prohibited by the Food, Drug and Cosmetic Act (FDCA), which limits supplement ingredients to those that are concentrates, metabolites, constituents, or extracts of dietary substances.⁵ Accordingly, Dennis Baker, the Associate Commissioner for Regulatory Affairs, has clearly stated in a letter to the Drug Enforcement Administration (DEA) that the FDCA prohibits the adulteration of ephedrine alkaloid dietary supplements with synthetic ephedrine compounds.⁶ More recently in a letter responding to Representative Henry Waxman's inquiry regarding FDA's position on synthetic ephedrine alkaloids in dietary supplements, Associate Commissioner for Legislation Melinda Plaisier stated that the:

FDA has concluded that synthetically produced ephedrine alkaloids are not "dietary ingredients" as defined in 21 USC §321 (ff)(1)...FDA has further concluded that products containing synthetic ephedrine alkaloids do not fall under the dietary supplement regulatory scheme and should be regulated as drugs.⁷

Under this interpretation of the FDCA, the FDA has recently taken action against E'OLA International and its contract manufacturer Nature's Energy, Inc, by seizing their adulterated product, Amp II Pro Drops, and the bulk Ephedrine HCl used to manufacture it.⁸

³ Ephedrine alkaloids include: ephedrine, pseudoephedrine, methylephedrine, norephedrine, and norpseudoephedrine. Norephedrine (also known as phenylpropanolamine - PPA) was recently banned by the FDA. These compounds are able to elicit physiological responses similar to sympathetic nervous system catecholamines and are hence known as sympathomimetics. These compounds are known to increase the risk for hypertension, stroke and heart attacks.

⁴ FDA Talk Paper "U.S. Marshals Seize Unapproved Drug in FDA Case." October 31st, 2001. The FDA announced the seizure of 140,000 bottles of dietary supplements containing synthetic ephedrine and the bulk ephedrine used for production purposes from Biogenics, Inc. of St. George, Utah.

⁵ 21 USC 321(ff) (1)

⁶ Baker, Dennis E. Letter to Laura Nagel, Deputy Assistant Administrator for the Office of Diversion Control of the Drug Enforcement Administration. June 21st, 2001.

⁷ Plaisier, Melinda K. Letter to Representative Henry Waxman. October 31st, 2001.

⁸ FDA Talk Paper, *op cit*.

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In its complaint requesting product seizure against E'OLA, the FDA asserts that synthetic Ephedrine HCl cannot be considered a legitimate dietary supplement ingredient because it is a new drug that was not marketed as a dietary supplement prior to its approval in 1948.⁹ This court-proven argument invariably holds true for other synthetic ephedrine alkaloids such as PPA and pseudoephedrine.¹⁰

Our research has found nine manufacturers who are overtly producing and marketing ten dietary supplements that contain synthetic ephedrine alkaloids.¹¹ These are:

Product	Manufacturer
Adrenalin	Genapharm http://www.genapharm.com/Adrenalin.asp
Ephedrine 25	Scientifically Advanced Nutrition, Corporation http://www.sann.net/epbysan.html
Hollywood Cuts	Scientifically Advanced Nutrition, Corporation http://www.sann.net/holbysan.html
Lipodryl II	Thermolife http://www.thermolife.com/Prducts-Lipodryl.html
Ephedrol	Thermal Plus http://www.thermalplus.com/ephedrol.htm
Phenylkinetics	21st Century Nutritionals / Synergy Nutritionals http://www.21centurysports.com/weight_loss.htm
Overdrive	7th Millennium Nutrition http://www.diabetestea.com/diabetestea/shortoverdrive.html
Adipokinetix	Syntrax http://www.syntrax.com/
Alphadrine	Pro-Muscle http://www.promuscle.com/alphadrine.htm
Meta-Burn Extreme	Metabolic Response Modifiers http://www.metabolicresponse.com/detail.asp?ID=80

⁹ Warner, Paul M. United States complaint filed with United States District Court for the District of Utah, Central Division. October 22nd, 2001 (Civil No. 2:01CV-820C). The complaint cites 21 USC 321 (ff) (3) (B) which prohibits the marketing of new drugs in dietary supplements. 21 USC 321 (ff) (3) (A) does not apply to Ephedrine HCl because it was not marketed as a dietary supplement prior to its approval as a new drug in 1948.

¹⁰ Pharmanex v. Shalala, 221 F.3d 1151 (2000); here the court states "that approval of active ingredients is integral to the overall new drug approval process," and concludes that the term "an article that is approved as a new drug" 21 USC 321 (ff) (3) (B) applies to both final drug products and their ingredients. Therefore active ingredients of approved drugs may not be used in the production of dietary supplements unless they meet the criteria of 21 USC 321 (ff) (3) (A).

¹¹ See attached table for more details.

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These companies are specifically advertising their products as "pharmaceutical grade" and consistently make strong efforts to distinguish them from herbal based ephedrine alkaloid dietary supplements. For example, the company which manufactures Overdrive warns potential ephedrine alkaloid dietary supplement consumers to "be sure that the product [they] purchase contains only pharmaceutical grade ingredients and not herbal derivatives."¹² Given that the FDA has determined that synthetic drugs are not legitimate ingredients for dietary supplements, and since Ephedrine HCl and PPA are defined as drugs, these products should also be seized on the basis of being unapproved new drugs.¹³

In addition to being unapproved new drugs, most of these alleged dietary supplements also can not be legally sold as over-the-counter (OTC) drugs due to their content of both caffeine and ephedrine alkaloids. The combination of caffeine with any other stimulant was prohibited for OTC drugs in 1983. Moreover, the FDA specifically singled out the combination of ephedrine alkaloids and caffeine as unacceptable due to their potential for misuse and abuse.¹⁴ Therefore, even if these products were to fulfill the requirements for sale under the OTC monographs for Ephedrine HCl or PPA, most of them would be subject to seizure for inappropriately combining said stimulants with caffeine.

Furthermore, many of these adulterated dietary supplements contain the drug PPA, which the FDA is in the process of banning.¹⁵ The FDA decided to remove PPA from the market due to the results of the Yale Hemorrhagic Stroke Project, which found an association between PPA use and hemorrhagic stroke. Legitimate PPA OTC drugs have been voluntarily withdrawn in anticipation of FDA's final rule revoking all New Drug Applications and Abbreviated New Drug Applications for PPA. Unfortunately, ephedrine alkaloid dietary supplement consumers are still at risk for PPA induced stroke due to the gross negligence of supplement producers who insist on peddling this dangerous drug.

Not even the porous regulations proposed by the dietary supplement industry for ephedrine alkaloid dietary supplements would allow for the use of

¹² <http://www.diabetestea.com/diabetestea/overdrive.html>

¹³ Warner; Paul M. *op cit*. These products are considered drugs under the definition of drugs as articles intended for the diagnosis, cure, mitigation, treatment, or prevention of disease in man. In this case, the supplements are marketed as weight-loss drugs. They are new drugs because the safety and efficacy of these drugs have not been evaluated, and hence they must apply for approval. 21 USC 321 (g)(1)(c) *also* 321 (p) *and* 355 (b).

¹⁴ Federal Register 48(224):52513 November 18, 1983

¹⁵ Federal Register 66(157):42665 August 14, 2001

synthetically derived alkaloids or their salts as ingredients.¹⁶ Though industry claims to voluntarily adhere to these proposed regulations, it appears that it is unable to reign in manufacturers who choose to endanger consumers. This should alert you to the need for clear and unequivocal regulations for dietary supplement production and use. However, we expect that the Dietary Supplement Health and Education Act of 1994 does not currently grant the FDA the authority to promulgate effective regulations that would sufficiently protect the public health.

Besides the legal reasons for why these drugs should be seized, it is worth noting that ephedrine alkaloid dietary supplements are inherently dangerous products regardless of the source of alkaloids. In our petition dated September 5th, 2001 we asked you to initiate a ban on ephedrine alkaloid dietary supplements, and to issue an immediate advisory to consumers asking them to stop using these products.¹⁷ In our petition we analyzed recently updated data from the FDA's Center for Food Safety and Applied Nutrition's Special Nutritionals Adverse Event Monitoring System, that show that ephedrine alkaloid dietary supplements are associated with more reports of death, myocardial infarction, cardiac arrhythmia, hypertension, stroke and seizure than all other dietary supplements combined. In the interval between January 1993 and February 2001 there were:

- 3308 adverse events for all dietary supplements, of which 1398 (42%) are associated with ephedrine alkaloid dietary supplements (EADS)
- 137 reports of death, 81 (59%) associated with EADS
- 38 reports of myocardial infarction/heart attack, 32 (84%) associated with EADS
- 98 reports of cardiac arrhythmias, 62 (63%) associated with EADS
- 144 reports of hypertension, 91 (63%) associated with EADS
- 85 reports of stroke, 69 (81%) associated with EADS
- 121 reports of seizure, 70 (58%) associated with EADS

In addition to seizing the ten drug products mentioned in this letter, the broader goal of banning all ephedrine alkaloid dietary supplements demands your immediate attention.

¹⁶ The American Herbal Products Association, the Consumer Healthcare Products Association, the National Nutritional Foods Association and the Utah Natural Products Alliance. Citizen Petition to the FDA. October 25th, 2000 (FDA Docket # 95N-0304/CP2). The petitioners propose that "neither finished consumer goods nor raw materials used in their manufacture are to contain any synthetically derived ephedrine alkaloids or their salts." Moreover, they suggest that industry has already "effectively" implemented a voluntary program for ephedra and that it has been adopted by "virtually all major manufacturers and distributors of ephedra products."

¹⁷ Public Citizen Health Research Group and Raymond Woosley. Petition to the Secretary of Health and Human Services. September 5th, 2001. (FDA Docket # 01P-0396)

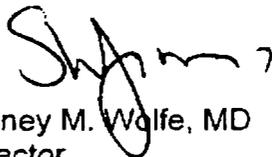
The sale of these dangerous products over the Internet is a cause for added concern. By forgoing the physical limitations of the traditional marketplace these products are readily accessible to minors who may not be fully aware of the abuse and injury potential of these dangerous drugs. The marketing techniques used on a majority of these websites promotes usage of these products for the indications of weight loss and energy enhancement. Coupling these indications with explicit language describing these drugs as synthetic chemicals surely promotes substance abuse. In fact, the makers of Hollywood Cuts explicitly state that the ingredient "1R, 2S Norephedrine [PPA] is a close cousin to the pharmaceutical "amphetamine."¹⁸ Also, the presence of both caffeine and ephedrine alkaloids increases the abuse potential of these drugs. The scientific literature shows that the combination of ephedrine and caffeine at individually sub-threshold quantities are synergistically able to produce an effect that is similar to that of amphetamine, an illegal drug.¹⁹ Therefore, we believe that sale of these alleged dietary supplements over the Internet increases the risk of substance abuse, especially by minors and young adults.

In summary, we have compiled a list of nine manufacturers who are publicly selling ten mislabeled drugs in the United States over the Internet. These products and the materials used to manufacture them are subject to seizure under the laws and regulations detailed above. Failure to act swiftly and decisively in this matter as required by law and to ban all ephedra alkaloids will result in a continuation of the harm and injury of dietary supplement consumers nationwide and will emphasize how fraudulent your concerns about food safety are.

Sincerely,



Amer K. Ardati
Research Associate
Public Citizen Health Research Group



Sidney M. Wolfe, MD
Director
Public Citizen Health Research Group

¹⁸ <http://www.sann.net/holbysan.html> [emphasis in original]

¹⁹ Young, R.; Gabryszuk, M.; Glennon, R. A. (-)Ephedrine and caffeine mutually potentiate one another's amphetamine-like stimulus effects. *Pharmacology Biochemistry and Behavior*, 1998; 61:169-73

Product	Manufacturer	Ephedrine HCl Content	Norephedrine HCl (Phenylpropanolamine-PPA) Content	Other	Descriptors
Adrenalin	Genapharm PO Box 2558 Ceder Park, TX 78641 888 471-7733 http://www.genapharm.com/Adrenalin.asp	10 mg	20 mg	100 mg Caffeine 3.4 mg Yohimbine HCl	"[A]ll alkaloid pharmaceutically manufactured fat-burning compound." "This product is not for sale in Texas!"
Ephedrine 25	Scientifically Advanced Nutrition, Corporation 4230 Del Rey Ave. # 458 Marina Del Rey, CA 90292 818 772-0500 http://www.sann.net/epbysan.html	25 mg	None	None	"100 Pharmaceutical Grade Tablets contain 25 mg of pure Ephedrine Alkaloid."
Hollywood Cuts	Scientifically Advanced Nutrition, Corporation 4230 Del Rey Ave. # 458 Marina Del Rey, CA 90292 818 772-0500 http://www.sann.net/holbysan.html	None	25 mg	100 mg Caffeine 2.75 mg Yohimbine HCl	"1R, 2S Norephedrine is a close cousin to the pharmaceutical "amphetamine." [emphasis in original]

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Lipodryl II	Thermolife 720 El Camino Real #101 Belmont, CA 94002 877 874-2262 http://www.thermolife.com/ Products-Lipodryl.html	None	25 mg	200 mg Caffeine 40 mg Aspirin 2.75 Yohimbine HCl	"real pharmaceutical grade Ephedrine HCL and pure Caffeine not herbal substitutes"
Ephedrol	Thermal Plus 900 Greenbank Rd. Suite 522 Nepean, Ontario K2J-4P6 http://www.thermalplus.com/ /ephedrol.htm	12.5 mg	None	Citrus Aurantium (4% synephrine) 125 mg Ma Huang (6% ephedrine) 200 mg Kola Nut (50% caffeine) 400 mg White Willow Bark (15% salicin) 105 mg	"Ephedrine HCL [sic] - pharmaceutical grade"
Phenylkinetics	21st Century Nutritionals / Synergy Nutritionals 745 Hollywood Blvd. N.W., Ft. Walton Beach FL 32548 888 802-5419 http://www.21centurysports. com/weight_loss.htm	None	25 mg	90 mg Caffeine 2.75 mg Yohimbine HCl	"Due to its ephedrine content this product should not be used by individuals who have been hospitalized for asthma or are taking asthma medication."

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<p>Overdrive</p>	<p>7th Millennium Nutrition P.O. Box 2206 Stow, Ohio 44224 877 832-9369 330 689-0666 http://www.diabetestea.com/diabetestea/shortoverdrive.htm http://www.diabetestea.com/diabetestea/overdrive.html</p>	<p>10 mg</p>	<p>15 mg</p>	<p>90 mg Caffeine 3.4 mg Yohimbine HCl</p>	<p>"ephedrine HCL, Caffeine and Yohimbine HCL [sic] in just the right amounts--so good, in fact, that it significantly surpassed the standards set at clinical trials." "As a final note, please be sure that the product you purchase contains only pharmaceutical grade ingredients and not herbal derivatives. As of now, there is only one company that makes a stack which contains Yohimbine HCL, Ephedrine HCL and Caffeine. Fortunately, this product is of the highest quality."</p>
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<p>Adipokinetix</p>	<p>Syntrax Syntrax Innovations, Inc. P.O. Box 1593 Cape Girardeau, MO 63702 888 321-2348 http://www.syntrax.com/</p>	<p>None</p>	<p>25 mg</p>	<p>100 mg Caffeine 3 mg Yohimbine HCl</p>	<p>"contains the highly potent thermogen, IR, 2S Norephedrine HCl. This compound is the most potent thermogenic ephedrine alkaloid."</p>
<p>Alphadrine</p>	<p>Pro-Muscle 888 646-7867 http://www.promuscle.com/alphadrine.htm</p>	<p>None</p>	<p>Positive</p>	<p>Contains Caffeine and Yohimbine HCl</p>	<p>"exact combination of IR, 2S Norephedrine HCl, Yohimbine HCl, and Caffeine. This is a great thermogenic for those who do not like that "wired" feeling from Ma Huang (Ephedrine)."</p>
<p>Meta-Burn Extreme</p>	<p>Metabolic Response Modifiers 236 Calle Pintero San Clemente, CA 92673 949 369-6641 http://www.metabolicresponse.com/detail.asp?ID=80</p>	<p>None</p>	<p>25 mg</p>	<p>90 mg Caffeine 2.75 mg Yohimbine HCl 25 mg Forskolin 5 mg Naringin</p>	<p>"thermogenic formula that combines the most potent stimulants that are available today" "IR, 2S-norephedrine and Yohimbine supercharge the body's energy production"</p>