



Better Health
Through Responsible
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April 29, 1998

Dockets Management Branch (HFA-305)
Food and Drug Administration, Rm. 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

5773

Re: International Drug Scheduling; Convention on Psychotropic Substances;
Dihydroetorphine; Ephedrine; Remifentani; Isomers of Psychotropic Substances
-- Docket No. 98N-0148, 63 Fed. Reg. 13258, additional NDMA comments

Dear Sir or Madam:

On March 18, 1998, the Food and Drug Administration (FDA) published the above-referenced notice requesting comments concerning abuse potential, actual abuse, medical usefulness, and trafficking of dihydroetorphine, ephedrine, and remifentani. The notice stated that this information would be considered in preparing a U.S. response to a World Health Organization (WHO) notification.

The Nonprescription Drug Manufacturers Association (NDMA) is the national association representing manufacturers and distributors of nonprescription, or over-the-counter (OTC), medications. NDMA provided comments to the notice on April 17, 1998. After reviewing comments on the docket from the Drug Enforcement Administration, which call for a response, and based on subsequent information concerning the WHO notification, we submit these additional comments.

The United Nations (UN) Convention on Psychotropic Substances -- the Convention at issue under which WHO is considering ephedrine -- has a clear focus on the risks and benefits of substances themselves, not on their possible use as precursor chemicals.¹ In contrast, the UN

98N-0148

¹See UN Convention on Psychotropic Substances, Article 2, para. 4.

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Convention Against the Illicit Traffic focuses on precursors.² Ephedrine is already included in this latter convention.³ The precursor focus matches well with the approach taken by the U.S. government, as discussed in detail in NDMA's April 17 comments.

The Drug Enforcement Agency (DEA) comments of April 17, 1998 to FDA similarly focus on precursor use of ephedrine, and thus are not pertinent to the matter at issue. For example, DEA notes that they have found that ephedrine is used as precursor material for the clandestine manufacture of controlled substances.⁴ "Ephedrine is one of the primary precursors used in the illicit manufacture of methamphetamine and methcathinone. As such, it contributes to the public health risk associated with *these* substances."⁵ DEA goes on to describe the mechanisms in place for preventing the diversion of legitimately produced chemicals.⁶ As noted in our April 17 comments, NDMA supported passage of the three laws which make up the mechanisms DEA describes, and we have worked extensively with DEA on implementation. Further, legitimate ephedrine-containing products have not been a significant portion of the diversion DEA references.

FDA has already concluded that ephedrine is generally recognized as safe and effective for OTC use when taken as directed and when appropriately labeled.⁷ While FDA proposed in 1995 to reclassify ephedrine products as not generally recognized as safe and effective for

²See UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

³UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Annex Table I.

⁴DEA letter to Dockets Management Branch, FDA, April 17, 1998, enclosure "Ephedrine: Evidence of Abuse," 1 (Docket 98N-0148, C5).

⁵*Id.* (emphasis added)

⁶*Id.* at 1-3.

⁷21 C.F.R. Parts 341 and 346 (concerning use as a bronchodilator and an anorectal drug product, respectively).

nonprescription use, such a move remains a proposal, not a final determination.⁸ In addition, this association urged FDA to abandon the proposal, noting that legitimate combination ephedrine products have not been associated with abuse problems cited by the agency.⁹ Indeed, at an August 28, 1996 public hearing an FDA official confirmed that there have not been serious adverse events associated with these legal OTC products that would justify an abuse finding.¹⁰ The association also pointed out that any asserted diversion of the products -- even if true, which has not been shown -- does not provide a legal basis for FDA to revoke the products' status as generally recognized as safe and effective. Finally, NDMA requested an FDA hearing in connection with the proposal if it were to move forward.¹¹

An assessment recommending that ephedrine be scheduled or controlled under the UN Convention on Psychotropic Substances would run counter to established U.S. policies and would thwart the intent of Congress that ephedrine-containing nonprescription medicines be available to consumers -- not on controlled substance schedules. The Comprehensive Methamphetamine Act, U.S. state laws to limit diversion, DEA enforcement tools against diversion, FDA and FTC enforcement tools against illegal claims, and the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances -- all of these are already in place to protect the safety of American consumers and other consumers around the world.

Thank you for considering our views.

Sincerely,



David C. Spangler
Vice President - International
& Assistant General Counsel

⁸See 60 Fed. Reg. 38643, Proposed Amendment of Monograph for OTC Bronchodilator Drug Products.

⁹NDMA letter to Dockets Management Branch, FDA, September 27, 1995, at 17. (Copy attached.)

¹⁰See FDA Food Advisory Committee transcript, volume II, Wednesday, August 28, 1996, at 116-7 (quoting Dr. Michael Weintraub, Director, Office of Drug Evaluation V, FDA).

¹¹Id. at 18.

Attachment: NDMA letter to Dockets Management Branch, Food and Drug Administration,
September 27, 1995

cc: Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA
Nicholas P. Reuter, Office of Health Affairs, FDA

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NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

September 27, 1995

Dockets Management Branch (HFA-305)
Food and Drug Administration, Rm. 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Re: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Monograph for OTC Bronchodilator Drug Products; Docket No. 95N-0205; 60 Fed. Reg. 38643; NDMA Comments and Request for Hearing

Dear Sir or Madam:

On July 27, 1995, FDA published the above-referenced notice of proposed rulemaking to amend the Final Monograph for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify them as not generally recognized as safe and effective (GRAS/E) for OTC use.

The Nonprescription Drug Manufacturers Association (NDMA) is the national association representing manufacturers and distributors of nonprescription, or over-the-counter (OTC), medications. NDMA members account for over 95% of retail OTC drug sales in the United States. NDMA has been active in every aspect of the FDA's OTC Drug Review program. NDMA has also been active in anti-drug abuse and chemical diversion prevention activities, both at the federal and state levels. NDMA worked directly with the Drug Enforcement Administration (DEA) to develop the "legal drug exemption" language for the Domestic Chemical Diversion Control Act of 1993 (DCDCA) (which amended the Chemical Diversion and Trafficking Act of 1988 (CDTA)) to provide DEA with the power to prevent

diversion of ephedrine for illicit drug manufacture without unduly restricting legitimate commerce, which DEA agreed was not a source of illegally produced controlled substances. NDMA has also worked cooperatively over the past two years with state authorities to develop reasonable responses to ephedrine problems.

Summary

As a principal basis for its proposed action, FDA relies on the request of the DEA to restrict OTC availability of ephedrine because of ephedrine diversion to illicit manufacture of controlled substances. However, legitimate ephedrine-containing combination products have a long history of safety and effectiveness, and are valuable for consumers who use them to alleviate mild symptoms of asthma in accordance with labeled conditions. FDA does not have authority under the FDC Act to ban safe and effective drug ingredients because of illegal diversion. Pursuant to the CDTA and the DCDCA, diversion control is the responsibility of the DEA, which may not ban affected ingredients. Rather, DEA may require records and reports about manufacturing and distribution of chemicals. FDA is not authorized to enforce the DCDCA by use of a method -- ban of an ingredient -- that Congress has not given DEA. If FDA's rationale for removing ephedrine from the Monograph stands, there will also be profound implications for drugs containing pseudoephedrine and phenylpropanolamine (PPA), which are also precursor chemicals subject to DEA diversion controls. DEA says there is "massive diversion" of pseudoephedrine now, and that it intends to take steps to counter the problem. Armed with FDA's action to ban ephedrine on diversion grounds, DEA can be expected to request similar FDA action to address asserted pseudoephedrine problems. PPA

could also be targeted, on the basis that OTC drugs "may" become subject to diversion to clandestine labs. FDA thereby becomes an unauthorized agent of the DEA, and effectively cedes to DEA part of its statutory mission to decide whether otherwise safe, effective and properly labeled OTC drugs should be available to the public. FDA appears to be unaware of the legal and policy implications in proposing this action. The Federal Register proposal mentions neither pseudoephedrine nor PPA; the agency dismissed the issue when it was raised by NDMA's extension request letter, insisting that "this proposal affects ephedrine ingredients only. The proposed amendment does not affect the current OTC marketing status of pseudoephedrine or phenylpropanolamine in any manner." 60 Fed. Reg. 44787 (August 29, 1995).

FDA also cites abuse of ephedrine products promoted for illegal uses as a basis for its proposed action. DEA has stated repeatedly that legitimately labeled combination ephedrine-containing products marketed by NDMA member companies have not been associated with either abuse or diversion to illicit drug production. The diversion problem rested with single ingredient ephedrine tablets, which are now controlled under the DCDDCA. With respect to abuse of ephedrine products, FDA should use its ample enforcement authority to take action against products marketed for unapproved uses and against the companies who make them. Banning legal GRAS/E OTC products that consumers have found helpful for approved uses is an inappropriate regulatory response to the abuse of products promoted for illegal uses.

Finally, FDA states that its action against ephedrine is based on conclusions reached by the Pulmonary-Allergy and Nonprescription Drugs Advisory Committees during their November 14, 1994, joint meeting. The Committees, however, never addressed the question

of whether FDA should revoke ephedrine's monograph status. The Committees therefore never engaged in a reasoned analysis of the issue, and they did not, as FDA asserts, reach a "consensus" regarding ephedrine's OTC availability.

To ensure a full exploration of the issues presented by the proposal, NDMA requests a formal evidentiary public hearing pursuant to 21 CFR Part 12. In the alternative, NDMA requests a public hearing before the Commissioner pursuant to 21 CFR Part 15. The grounds for the request are described below.

I. FDA lacks legal authority to remove a GRAS/E ingredient from OTC status on the basis of diversion concerns.

Under the FDC Act, a drug that is GRAS/E for use under the conditions in the labeling is legally available for marketing. 21 U.S.C. § 321 (p). FDA has made a determination that ephedrine and certain ephedrine combination drug products are GRAS/E and properly labeled for OTC use, and that determination has been codified in a Final Monograph.¹ Ephedrine has a long and well-established safety and effectiveness record for its intended use as a nonprescription bronchodilator. Legitimate ephedrine-containing products have provided safe and effective relief to mild asthmatics for decades. FDA says DEA has reported that OTC marketing status and broad distribution of OTC ephedrine products is hindering its efforts to prevent diversion of ephedrine to illicit drug manufacture. 60 Fed. Reg. 38644. No evidence from DEA is presented in support of the statement.

¹21 C.F.R. Part 341.

GRAS/E status contemplates a determination by qualified experts that a drug is safe and effective “for use under the conditions prescribed, recommended or suggested in the labeling” 21 U.S.C. § 201 (p). Nothing in the FDC Act allows use of diversion concerns as an element of a GRAS/E determination. Nor does the FDC Act authorize FDA to remove an ingredient from an OTC Monograph in order to restrict the ingredient's possible diversion for unintended uses.² The desire to prevent diversion was the rationale for FDA's attempt to restrict methadone distribution, which was squarely rejected in American Pharmaceutical Ass'n v. Weinberger, 377 F.Supp. 824 (D.C.D.C. 1974); aff'd per curiam, 530 F.2d 1054 (D.C. Cir. 1976). In that case, FDA regulations purported to restrict methadone distribution to direct shipments from the manufacturer to certain drug treatment programs and approved pharmacies, in order to help reduce the likelihood of diversion. FDA based its action on its construction of the term “safe” under the FDC Act, which the agency asserted should be interpreted not only with reference to the inherent qualities of the drug but also in the sense of the drug's being secure from possible misuse. The court rejected this interpretation, finding that the term “safe” is used in the statute in conjunction with the phrase “for use under the conditions prescribed, recommended, or suggested in the proposed labeling” of the drug. The court concluded that “safe” was only intended to refer to a determination of the inherent safety or lack thereof of the drug under consideration when used for its intended purpose. Once FDA has cleared a drug for marketing for whatever uses the Commissioner deems appropriate, said

²See 21 U.S.C. § 503(b) for permissible bases for designating a drug as prescription only.

the court, the question of permissible distribution of the drug, when the drug is a controlled substance, is “clearly within the jurisdiction of the Justice Department To allow the challenged portions of the methadone regulations to stand, therefore, would be to abrogate the collective judgment of Congress with regard to the appropriate means of controlling unlawful drug diversion” 377 F. Supp. 824, 830 (D.C.D.C. 1974).

- II. FDA reliance on diversion control considerations to ban a GRAS/E product is contrary to Congressional intent to make diversion control subordinate to preserving the availability of safe, effective, and properly labeled legal drugs.

Under the Chemical Diversion and Trafficking Act (CDTA) of 1988,³ amended by the Domestic Chemical Diversion Control Act (DCDCA) of 1993,⁴ Congress established a scheme to enable DEA to keep track of certain transactions involving precursor chemicals that could be diverted for use in the clandestine manufacture of illicit drugs. Each “regulated person”⁵ (including a manufacturer, distributor, importer, or exporter of a listed chemical) who engages in a “regulated transaction”⁶ (distribution, receipt, sale, import, or export) of a “threshold amount”⁷ of a listed chemical is required to register with DEA,⁸ to keep records of the

³P.L. 100-690, 21 U.S.C. § 801 nt.

⁴P.L. 103-200.

⁵21 U.S.C. § 802 (38).

⁶Id. § 802 (39) (A).

⁷Id.

⁸21 U.S.C. § 822.

transactions for four years, and to make them available for DEA inspection and copying.⁹ Annual reports must be filed with DEA by manufacturers of listed chemicals.¹⁰ Oral and written reports must be made to DEA at the earliest practicable opportunity about transactions involving extraordinary quantities of listed chemicals, uncommon methods of payment, unusual or excessive loss of listed chemicals, or other suspicious circumstances.¹¹ Failure to keep a record or to file a report can result in civil penalties of up to \$25,000. Knowing and/or repeated violations can be prosecuted criminally and subject the person to one to two years imprisonment in addition to monetary fines.¹²

Over twenty chemicals are included in the diversion law as listed precursor chemicals, including three -- ephedrine, phenylpropanolamine (PPA), and pseudoephedrine -- that are used in legal OTC drugs.¹³ To assure that valuable OTC drugs would continue to be readily available to the public, and that manufacturers and distributors of these drugs would not be burdened with unnecessary record keeping and reporting requirements, Congress included an exemption from the requirements described above for transactions involving finished drug products containing the listed chemicals, if the drug products may be lawfully distributed in the United States under the FDC Act.¹⁴ This is known as the "legal drug exemption." Due to

⁹21 U.S.C. § 830.

¹⁰21 U.S.C. § 830 (b)(2).

¹¹21 U.S.C. § 830 (b)(1).

¹²21 U.S.C. § 842.

¹³21 U.S.C. § 802 (34).

¹⁴21 U.S.C. § 802 (39) (A)(iv).

diversion of single ingredient ephedrine drug products, the diversion law was amended in 1993 by the DCDCA to remove the legal drug exemption for single ingredient ephedrine drug products and combination drug products containing ephedrine and insignificant amounts of another active ingredient.¹⁵ However, other, legitimate combination ephedrine drug products continued to be covered by the legal drug exemption because they were not involved in the diversion problem. The Attorney General has statutory authority to take action to revoke the legal drug exemption for other drug products containing listed precursor chemicals, including combination ephedrine products, but she may only do so based on a rulemaking proceeding that is subject to strict evidentiary and procedural standards, as described below.

By including the “legal drug exemption” in the CDTA in 1988 and preserving it in the DCDCA in 1993, Congress plainly viewed the FDA mission of making safe, effective, and properly labeled products available to the public to be the paramount value, with diversion concerns to remain subordinate to that mission.¹⁶ FDA’s use of diversion control as a dispositive factor in removing all ephedrine products from the Final Monograph, however, stands the Congressional scheme on its head. There are no reports that legitimate OTC combination ephedrine products have been associated with diversion. Rather, DEA speculates that clandestine laboratories “may” turn to combination drug products containing ephedrine

¹⁵Id.

¹⁶“The first challenge is to find a method to control the diversion of legal chemicals without affecting the commerce of valuable and legal over-the-counter products. * * * The NDMA raised concerns . . . [that the law not] unduly regulate legitimate pharmaceutical manufacturers whose products were not being diverted to the production of illicit drugs. * * * [Its] concerns [are] valid and crucial to the best possible solution.” 139 Cong. Rec. S10808-10 (daily ed. July 29, 1992) (statement of Sen. Gorton).

and guaifenesin. 60 Fed. Reg. at 38643. (Emphasis added.) As discussed below, this speculation could not serve as a legal basis for DEA to remove the legal drug exemption for combination ephedrine products so as to make them subject to record keeping and reporting requirements, yet FDA proposes to ban OTC ephedrine combination products in misplaced reliance on it.

The CDTA and DCDCA do not empower DEA to ban precursor chemicals, only to require certain documentation about their manufacture and distribution. The documentation requirements do not apply to products subject to the legal drug exemption. DEA, in turn, may only revoke the legal drug exemption from legitimate combination ephedrine products and other legal drugs that contain listed precursor chemicals based on a rulemaking in which the Attorney General has considered factors including the scope, duration, and significance of the diversion. 21 U.S.C. § 814 (a) and (b). She must specifically limit the designation of the drugs whose legal drug exemption is removed to the "most particularly identifiable type" of drugs for which there is evidence of diversion. *Id.* § 814 (c). Finally, even where she has removed the legal drug exemption for a specific group of drugs, the DCDCA provides that upon application by a manufacturer of a specific drug product, the exemption must be reinstated for the particular product if it is packaged, marketed, and distributed in such a way as to prevent diversion. *Id.* § 814 (d)(1)-(2). This underscores the Congressional determination that potentiality of diversion was considered to be insufficient to revoke the legal drug exemption for legitimate drugs. Congress decided such drugs should remain freely available to the public to the maximum extent possible and without imposing unnecessary record keeping and reporting burdens on the affected companies.

The DCDCA retains the legal drug exemption for ephedrine combination drug products that are legally marketed under the FDC Act because they have not been associated with illegal diversion. DEA has confirmed that no legitimate OTC drug products have been involved in ephedrine diversion to clandestine laboratories.¹⁷ To determine otherwise, and justify a determination that legitimate combination ephedrine products should no longer be subject to the legal drug exemption, Congress required DEA to meet both procedural and evidentiary standards. The FDA proceeding is an evasion of the procedural requirements mandated by Congress that DEA engage in notice and comment rulemaking. Moreover, on the factual record, it is apparent that DEA could not satisfy the DCDCA evidentiary requirements of 21 U.S.C. § 814 to revoke the legal drug exemption for legitimate combination ephedrine products. FDA has no authority to enforce the DCDCA through an FDC Act ingredient ban. Even if FDA could be argued to have such authority, it surely could not do so on grounds that fail to meet DCDCA standards for revocation of the legal drug exemption.

In addition, at least twenty states have undertaken legislative or regulatory actions to prevent ephedrine diversion or misuse. NDMA has worked closely with 17 of them in this effort. These states have also confirmed to NDMA that no legitimate OTC drug products have been involved in ephedrine diversion or abuse. Accordingly, they have been willing to exempt

¹⁷See e.g., Letter to FDA Commissioner Kessler from DEA Administrator Bonner (September 29, 1993), in FDA Public Administrative File for the Proposed Amendment of the Final Monograph for OTC Bronchodilator Drug Products (Docket No. 95N-0205).

legitimate OTC products from ephedrine restrictions, recognizing that such products should be available to consumers who find them useful for FDA-approved use as bronchodilators.¹⁸

- III. FDA action on ephedrine based on diversion control grounds will have serious consequences for OTC drugs containing pseudoephedrine and PPA, and for FDA's position as the preeminent drug approval agency.

FDA reports DEA's comment that "the OTC marketing status and broad distribution of these [ephedrine-containing] products is hindering efforts to prevent . . . illicit use of ephedrine" for diversion to clandestine laboratories. 60 Fed. Reg. 38644. Ephedrine is used in only a few NDMA member company OTC combination drug products, however, they have been relied upon for decades by mild asthmatics who use them safely and effectively to alleviate symptoms of asthma. FDA removal of ephedrine from the Monograph to prevent its availability for illicit diversion would deprive these consumers of useful ephedrine-containing medicines, and would deny the affected companies the right to market legitimate products.¹⁹

FDA's action will also have profound consequences for companies who market OTC drugs containing pseudoephedrine and PPA. Along with ephedrine, pseudoephedrine and PPA are also listed as precursor chemicals subject to the DCDCA. 21 U.S.C. § 802 (34)(I) and

¹⁸See Attachment A. NDMA has worked closely with state authorities in Arkansas, Florida, Illinois, Indiana, Louisiana, Michigan, Missouri, Nebraska, New Mexico, New York, Ohio, Oklahoma, Oregon, South Dakota, Texas, Washington, and Wisconsin.

¹⁹FDA's removal of ephedrine from the OTC bronchodilator monograph is unlikely to have any meaningful effect on the supplies of ephedrine for diversion to clandestine manufacture of illicit drugs. Ephedrine is also sold directly to the public as a dietary supplement (both as ephedrine and as ma huang), and thus remains available for diversion to illicit drug manufacture.

(K). Pseudoephedrine is one of the most widely used ingredients in OTC drugs, and PPA is also pervasively used in OTCs. We estimate that the two ingredients are found in at least one thousand legally marketed OTC drugs, including combination and single ingredient formulations. Together, the ingredients account for approximately \$1.5 billion in annual OTC retail sales in the United States.

FDA removal of ephedrine from the OTC marketplace will not solve the diversion problem.²⁰ Clandestine laboratory operators can be expected to turn to other precursor chemicals if ephedrine supplies diminish. In fact, at an April 1995 meeting with NDMA, DEA claimed that there was "massive diversion" of pseudoephedrine to clandestine labs due to the success of DEA ephedrine controls.²¹ DEA said that the problem is "nationwide," and that both bulk pseudoephedrine powder as well as finished drug tablets in large quantity packages are involved.²² NDMA is also aware that DEA met with drug wholesalers in February 1995²³

²⁰See also note 19, *supra*.

²¹At the April meeting, DEA gave NDMA copies of the attached "NOTICE," which DEA said it was broadly distributing to importers, laboratories, and others. (Attachment B.) DEA said that no legitimate OTC drug products have been involved in the diversions.

²²DEA declined to provide details to NDMA at the April 1995 meeting. NDMA filed a Freedom of Information Act request in May seeking information on pseudoephedrine seizures associated with clandestine synthesis of illicit drugs, for the period March 1994 to May 1995. In its August 8, 1995 response, DEA reported 58 seizures of pseudoephedrine in 7 states (California, Arizona, Nevada, Idaho, Illinois, Minnesota, and Missouri), the overwhelming majority (41) occurring in California. Twenty-six of the seizures were reported to have occurred in 1994, and 22 in the first five months of 1995. The seizures reportedly involved both pseudoephedrine powder and tablets, the latter predominantly in bottles of 500 or 1000 count. DEA identified the quantities seized in about one third of the reported cases. No seizures were reported to involve legitimate OTC drug products.

²³"Regulatory Affairs Groups Meets With DEA to Discuss Issues, Trends," Government Update (National Wholesale Druggists' Association, February 1995).

and with pseudoephedrine importers in June 1995 and gave those groups the same reports about major pseudoephedrine diversion. DEA has also made statements to the general press about the asserted problem.²⁴ Arkansas is considering regulatory action to limit the OTC sale of pseudoephedrine because DEA reported a seizure of the ingredient at a clandestine methamphetamine laboratory in the state.²⁵ On July 11, 1995, the DEA Office of Diversion Control disseminated a report, "The Licit and Illicit Utilization of Pseudoephedrine."²⁶ DEA reiterated that with increased control over OTC ephedrine products and other ephedrine controls,²⁷ "clandestine laboratory chemists are acquiring large quantities of pseudoephedrine for use as a precursor in the synthesis of methamphetamine."²⁸ The report says that "OTC pseudoephedrine is a direct substitute for ephedrine in the synthesis of methamphetamine," and that:

"All OTC dosage forms of pseudoephedrine (including film coated, sustained release, and combination products in tablet or capsule form) are suitable for use in the clandestine synthesis of methamphetamine. An investment of \$638 to \$7960 (depending upon dosage form and package size purchased) would be

²⁴See e.g., Greensboro News & Record, July 17, 1995 (New York Times News Service).

²⁵Proposed Rule to Place Ephedrine, its Salts, Optical Isomers and Salts of Isomers in Schedule V of Arkansas Controlled Substances List, Arkansas Department of Health, promulgated pursuant to Ark. Code Ann. § 5-64-201, effective September 1, 1995. [Because the proposed rule would include all isomers of ephedrine, pseudoephedrine is included.] The rule was later withdrawn due to technical problems, but Arkansas plans to revisit the matter in October.

²⁶Attachment C. The DEA report was provided to Arkansas officials by Douglas Snyder, Drug Enforcement Administration, September 1, 1995.

²⁷Id. at 12.

²⁸Id. at 1.

sufficient to purchase enough pseudoephedrine to manufacture 500 grams of methamphetamine with street value of up to \$70,000.”²⁹

Internationally, the United Nations Commission on Narcotic Drugs met in the Spring of 1995. DEA proposed and took the lead in the development of a Draft Resolution which declares that there is “worldwide diversion of vast quantities of ephedrine and pseudoephedrine from licit manufacture and trade to be used for the illicit manufacture of methamphetamine,” and urges that all Governments take necessary actions to prevent diversion of the substances.³⁰

It appears that FDA is unaware of the asserted pseudoephedrine problem. The July 27 Federal Register proposal includes no mention of it. In its August 29 Federal Register notice extending the comment period, FDA dismisses NDMA’s statement (in its August 4, 1995 extension request letter) that pseudoephedrine and PPA could be affected, insisting that neither ingredient is affected by the proposal “in any manner.” 60 Fed. Reg. 44787 (August 29, 1995). Nor does the FDA docket file for the instant proceeding include any of this pseudoephedrine information. Nevertheless, as the above account shows, if FDA removes ephedrine from the Monograph, DEA can be expected to request that FDA next place restrictions on pseudoephedrine-containing products, and FDA arguably will have obliged itself to do so by reason of its ephedrine action.

²⁹Id. at 11.

³⁰Advance Copy, Draft Version, Draft Resolution V: “Measures to strengthen international cooperation to prevent diversion of substances listed in Table I of the United Nations Convention against illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 and used in the illicit manufacture of stimulants and other psychotropic substances.” (April 24, 1995) (Attachment D).

The Pulmonary-Allergy and Nonprescription Drugs Advisory Committees also recognized this problem. One committee member stated that even if ephedrine is taken off the market, “we would . . . find ourselves back here next year with a very similar problem . . . [T]he people who are now marketing ephedrine . . . will be back with phenylpropanolamine or pseudoephedrine . . . ”³¹ Contrary to FDA’s assertion in the Federal Register proposal, the Committees did not reach a “consensus” that ephedrine should be removed from the OTC market. Indeed, the Committees were never specifically asked whether ephedrine’s monograph status should be revoked. At most, the members “expressed concern about abuse and illicit diversion.” 60 Fed. Reg. at 38644.

FDA’s approach has no apparent limits, since FDA’s proposal to remove ephedrine combinations from the Monograph is responsive to DEA’s concern that clandestine labs “may” turn to combination ephedrine drugs if single ingredient ephedrine drugs are unavailable.³² PPA is also listed as a precursor chemical in the DCDCA. It “may” become subject to diversion, and on that ground, FDA presumably could propose Monograph restrictions on PPA-containing OTC drug products.

By making Monograph changes at DEA’s request, FDA surrenders authority to the DEA to decide whether otherwise safe, effective and properly labeled OTC drugs should be

³¹See Transcript of Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary-Allergy Advisory Committee (November 14, 1994) at 265 (Public Administrative File for the [Instant] Proposed Amendment of the Final Monograph for OTC Bronchodilator Drug Products, Docket No. 95N-0205).

³²NDMA reiterates that this standard would be insufficient under the DCDCA and the CDTA for DEA to control the products.

available to the public. FDA abandons its statutory mission to provide safe and effective drugs to the public, and subordinates itself to the DEA. This disserves the public, and is contrary to Congressional intent in the FDC Act and the DCDCA. DEA has no authority to ban or otherwise restrict marketing of otherwise safe, effective, and properly labeled drugs. By banning ephedrine because DEA says there are diversion control problems or that such problems “may” occur, FDA becomes an unauthorized agent of DEA, indirectly enforcing the DCDCA using tools that Congress has not granted to DEA directly. FDA thereby loses its status as the preeminent drug approval agency.

IV. Illegal promotion of ephedrine products for unapproved uses calls for FDA enforcement action, not the ban of legal products.

Ephedrine as marketed in legitimate NDMA combination drug products has a long and well-established safety and effectiveness profile. These products have provided relief for consumers who find them valuable for mild symptoms of asthma. They have not been associated with either abuse or diversion. FDA reports that some companies promote ephedrine-containing products for use as stimulant, weight control, and muscle enhancement products, which has resulted in “extensive and extremely dangerous misuse and abuse.” 60 Fed. Reg. at 39644. Products offered for these uses are in violation of the FDA Final Monograph and the FDC Act. FDA has ample enforcement authority to proceed against the illegal products and the companies who market them, through seizure, injunction, and criminal prosecution. 21 U.S.C. §§ 332, 333, and 334. The agency should undertake a program of vigorous enforcement action against them, especially in view of FDA’s statement that the

products pose a public health risk for young people and others. 60 Fed. Reg. at 38644. The FDA's Public Administrative File for the instant rulemaking includes several examples of blatantly illegal ephedrine promotional materials that were forwarded to the FDA by state agencies. Ephedrine drug product advertisements promising relief for "weight loss," "fatigue," and "sleep problems" are actionable by FDA.

The Federal Trade Commission, with whom the FDA has a close working relationship, also has jurisdiction under Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45, to take action against companies who illegally promote ephedrine products for unapproved uses. FDA can request that the FTC undertake an investigation or regulatory action against these companies. However, banning legal ephedrine products because of illegal promotion of other ephedrine products is an inappropriate regulatory response that would unnecessarily deprive the public of useful OTC medicines and deny legitimate companies the right to continue to market them.

V. Conclusion

NDMA urges FDA to abandon its proposal to remove ephedrine from the Final Monograph. Legitimate combination ephedrine products have not been associated with either abuse or diversion problems cited by the agency. Abuse of illegally promoted ephedrine-containing products should be addressed through FDA enforcement, not by banning legal products. Diversion control is not a legal basis for FDA to remove otherwise GRAS/E and properly labeled OTC products from the Final Monograph. Diversion control is the responsibility of the DEA pursuant to the CDTA and the DCDCA, using the tools Congress

provided in the those laws. FDA may not indirectly enforce the DCDCA for the DEA using methods not authorized by Congress. Moreover, FDA action against ephedrine in response to DEA diversion control considerations would make FDA subordinate to the DEA. It would establish a precedent with serious consequences for thousands of OTC products containing pseudoephedrine and PPA, and for the status of the FDA as the preeminent drug approval agency.

In order for the issues presented by the agency's proposal to be fully examined in an evidentiary forum, NDMA requests a formal evidentiary public hearing pursuant to 21 CFR Part 12. In accordance with 21 CFR § 10.30, there is no requirement for an environmental impact assessment in conjunction with this hearing request. As discussed above, the economic impact of the agency's proposed action would be substantial not only for legitimate marketers of ephedrine-containing OTC products, but also for the future marketing of pseudoephedrine- and PPA-containing products. The undersigned further certifies that, to her best knowledge and belief, this request includes all information and views on which the request relies, and that it includes representative data and information which are unfavorable to the request. NDMA requests in the alternative that the Commissioner exercise his discretion to hold a public hearing pursuant to 21 CFR Part 15.

Thank you for your consideration of our views.

Sincerely yours,

Eve E. Bachrach
Vice President - Associate General Counsel
and Secretary

- Attachments: A -- Status of State Ephedrine Restrictions
- B -- DEA Notice re Pseudoephedrine Drug Products
- C -- "The Licit and Illicit Utilization of Pseudoephedrine (A Background Paper)," DEA Drug and Chemical Evaluation Section, Office of Diversion Control, July 11, 1995
- D -- United Nations International Narcotics Control Board Advance Copy, draft version, Draft Resolution V

cc: William E. Gilbertson, Pharm.D. (HFD-810)

A:AFDA-EPH.828



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