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# **Pharmacy Compounding Advisory Committee**

## **Public Meeting**

**May 6-7, 1999**

**Volume 1**

**Introduction**

**Advisory Committee Conference Room, 1066  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852**

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# Pharmacy Compounding Advisory Committee

May 6-7, 1999  
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### Drug Substances Nominated for the Bulks List

The Volumes 2 and 3 contain documentation regarding each of the bulk drug substances nominated for inclusion on the list of bulk drugs acceptable for pharmacy compounding that will be discussed at the meeting. Most of the documentation was compiled by the review divisions responsible for these drugs.

#### Volume 2

Dinitrochlorobenzene  
Diphenylcyclopropanone  
Squaric Acid Dibutyl Ester  
4-Aminopyridine and 3,4-diaminopyridine

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Mild Silver Protein  
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Betahistine Dihydrochloride  
Cyclandelate  
Hydrazine Sulfate

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## **DRAFT AGENDA**

### Objective:

The committee will review ten drug substances that are being considered to be used in pharmacy compounding that do not have a United States Pharmacopeia or National Formulary monograph and are not components of FDA-approved drugs.

### Day 1: Thursday, May 6, 1999

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**8:30 a.m. Call to Order/General Introductory Remarks** *Dr. Randy Juhl*  
*Chair, Pharmacy Compounding Advisory Committee*

Conflict of Interest *Mr. Igor Cerny*  
*Advisors and Consultants Staff, CDER*

9:00 a.m. Introductory Remarks *Ms. Jane Axelrad*  
*Associate Director for Policy, CDER*

**9:30 a.m. Dermatological Products**  
Dinitrochlorobenzene  
Diphenylcyclopropenone  
Squaric Acid Dibutyl Ester

*Representatives from the*  
*Division of Dermatologic and Dental Drug Products*

*Dr. Katherine Laessig*  
*Medical Officer*  
*Division of Antiviral Drug Products*

*Dr. Bill Rosenberg*  
*University of Tennessee*  
*American Academy of Dermatology*

**10:30 a.m. Break**

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*Medical Officer*  
*Division of Antiviral Drug Products*

*Dr. Bill Rosenberg*  
*University of Tennessee*  
*American Academy of Dermatology*

**10:30 a.m. Break**

# Pharmacy Compounding Advisory Committee

May 6-7, 1999 Meeting

## **DRAFT AGENDA (cont)**

10:45 a.m. Open Public Hearing

11:15 a.m. Discussion and Vote on Dermatological Products

**12:00 p.m. Lunch**

**1:00 p.m. Neuropharmacological Drug Products**

*Dr. John Feeney  
Medical Officer*

*Division of Neuropharmacological Drug Products*

4-aminopyridine

*Dr. Chris Bever  
University of Maryland*

*Presentation from Accorda*

3,4-diaminopyridine

*Dr. Donald Sanders  
Duke University*

*Presentation from Jacobus*

**3:00 p.m. Break**

3:15 p.m. Open Public Hearing

3:45 p.m. Discussion and Vote on Neuropharmacological Drug Products

**5:00 p.m. Adjourn**

# Pharmacy Compounding Advisory Committee

May 6-7, 1999 Meeting

## **DRAFT AGENDA (cont)**

Day 2: Friday, May 7, 1999

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- 8:30 a.m. Call to Order** *Dr. Randy Juhl*  
*Chair, Pharmacy Compounding Advisory Committee*
- 8:40 a.m. Mild Silver Protein** *Dr. Wiley Chambers*  
*Supervisory Medical Officer*  
*Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products*
- 9:00 a.m. Open Public Hearing
- 9:20 a.m. Discussion and Vote on Mild Silver Protein
- 9:30 a.m. Monosodium Aspartate** *Dr. Raymond Lipicky*  
*Division Director*  
*Division of Cardio-Renal Drug Products*
- 9:40 a.m. Open Public Hearing
- 9:50 a.m. Discussion and Vote on Monosodium Aspartate
- 10:00 a.m. Break**
- 10:15 a.m. Cyclandelate and Betahistine Dihydrochloride** *Dr. John Feeney*  
*Medical Officer*  
*Division of Neuropharmacological Drug Products*
- 10:40 a.m. Open Public Hearing
- 11:10 a.m. Discussion and Vote on Cyclandelate and Betahistine Dihydrochloride
- 12:00 p.m. Lunch**

# Pharmacy Compounding Advisory Committee

May 6-7, 1999 Meeting

## **DRAFT AGENDA (cont)**

**1:00 p.m.    *Hydrazine Sulfate***

*Dr. Saul Malozowski  
Medical Officer  
Division of Metabolic and Endocrine Drug Products*

*Dr. Charles L. Loprinzi  
Principal Investigator  
Videotaped Presentation*

*Mary McCabe  
National Cancer Institute*

**2:45 p.m.    *Break***

**3:00 p.m.    *Open Public Hearing***

**3:30 p.m.    *Discussion and Vote on Hydrazine Sulfate***

**5:00 p.m.    *Adjourn***



**PHARMACY COMPOUNDING ADVISORY COMMITTEE  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**CHAIR**

Randy P. Juhl, Ph.D.  
09/30/02  
School of Pharmacy, Office of the Dean  
University of Pittsburgh  
1103 Salk Hall  
Pittsburgh, Pennsylvania 15261

**EXECUTIVE SECRETARY**

Igor Cerny, Pharm.D.  
Advisors and Consultants Staff  
Food and Drug Administration, HFD-021  
5600 Fishers Lane  
Rockville, Maryland 20857  
(301) 827-6762 Fax: (301) 827-6776  
E-mail: Cerny@cder.fda.gov

**MEMBERS**

Judith Martin Riffée, R.Ph. 1639 N.W. 11 <sup>th</sup> Road Gainesville, Florida 32610	09/30/00	Christopher T. Rhodes, Ph.D. Professor of Applied Pharmaceutical Sciences University of Rhode Island Kingston, Rhode Island 02881	09/30/02
William J. Rodriguez, M.D., Ph.D. Chairman, Department of Infectious Diseases Children's National Medical Center 111 Michigan Avenue, N.W. Washington, D.C. 20010	09/30/00	William J. Rusho, R.Ph. Professor of Pharmacy Practice Department of Pharmacy Services University of Utah Hospitals and Clinics 50 North Medical Drive, Room A050 Salt Lake City, Utah 84132	09/30/02
Tony Welder, R.Ph. Dakota Pharmacy, Post Office Box 835 717 East Main Avenue Bismarck, North Dakota 58501	09/30/00	Lawrence Trissel, F.A.S.H.P. Director, Clinical Pharmaceutics Research Program Division of Pharmacy University of Texas, M.D. Anderson Cancer Center 1515 Holcombe Boulevard, Room B1-4302 Houston, Texas 77030	09/30/02
Loyd V. Allen Jr., Ph.D. Editor-In-Chief International Journal of Pharmaceutical Compounding 122 North Bryant Edmond, Oklahoma 73034	09/30/01	<b>Consumer Representative</b> Rose-Ellen M. Hope, R.Ph. 1355 S. Water Silverton, Oregon 97381	09/30/02
Carmen A. Catizone, M.S., R.Ph. National Association of Boards of Pharmacy 700 Busse Highway Park Ridge, Illinois 60068	09/30/01	<b>Industry Representative (Non-voting)</b> David Liebman, R.Ph. Kaye's Pharmacy 6913 Belair Road Baltimore, Maryland 21206	09/30/00
Elizabeth I. McBurney, M.D. Clinical Professor Louisiana State University School of Medicine P.O. Drawer 2179 1051 Gause Boulevard, Suite 460 Slidell, Louisiana 70458	09/30/01	<b>Industry Representative (Non-voting)</b> Joan M. LaFollette, R.Ph. Bristol-Myers Squibb Company Director, Worldwide Regulatory Affairs - CMC 311 Pennington - Rocky Hill Road, Room 306 Pennington, New Jersey 08534	09/30/01
Sarah L. Sellers, Pharm.D. 316 Beech Cove Dr. Grimesland, NC 27837	09/30/01		
Garnet E. Peck, Ph.D. Department of Industrial and Physical Pharmacy School of Pharmacy and Pharmacal Sciences Purdue University West Lafayette, Indiana 47907	09/30/02		

~~(B) by redesignating subparagraphs (B) and (C) as subparagraphs (A) and (B), respectively.~~

~~(2) Section 503(b)(3) (21 U.S.C. 353(b)(3)) is amended by striking section 502(d) and".~~

~~(3) Section 102(9)(A) of the Controlled Substances Act (21 U.S.C. 802(9)(A)) is amended—~~

~~(A) in clause (i), by striking "(i)"; and~~

~~(B) by striking "(ii)" and all that follows.~~

**SEC. 127. APPLICATION OF FEDERAL LAW TO PRACTICE OF PHARMACY COMPOUNDING.**

(a) AMENDMENT.—Chapter V is amended by inserting after section 503 (21 U.S.C. 353) the following:

21 USC 353a.

**\*SEC. 503A. PHARMACY COMPOUNDING.**

"(a) IN GENERAL.—Sections 501(a)(2)(B), 502(f)(1), and 505 shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding—

"(1) is by—

"(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

"(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

"(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

"(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between—

"(i) the licensed pharmacist or licensed physician; and

"(ii)(I) such individual patient for whom the prescription order will be provided; or

"(II) the physician or other licensed practitioner who will write such prescription order.

"(b) COMPOUNDED DRUG.—

"(1) LICENSED PHARMACIST AND LICENSED PHYSICIAN.—A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician—

"(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—

"(i) that—

"(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

"(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

"(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d);

"(ii) that are manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i)); and

"(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

"(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

"(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

"(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

"(2) DEFINITION.—For purposes of paragraph (1)(D), the term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

"(3) DRUG PRODUCT.—A drug product may be compounded under subsection (a) only if—

"(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

"(B) such drug product is compounded in a State—

"(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

"(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

“(c) ADVERTISING AND PROMOTION.—A drug may be compounded under subsection (a) only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

“(d) REGULATIONS.—

“(1) IN GENERAL.—The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A), the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

“(2) LIMITING COMPOUNDING.—The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

“(e) APPLICATION.—This section shall not apply to—

“(1) compounded positron emission tomography drugs as defined in section 201(ii); or

“(2) radiopharmaceuticals.

“(f) DEFINITION.—As used in this section, the term ‘compounding’ does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling.”

(b) EFFECTIVE DATE.—Section 503A of the Federal Food, Drug, and Cosmetic Act, added by subsection (a), shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act.

~~SEC. 128. REAUTHORIZATION OF CLINICAL PHARMACOLOGY PROGRAM.~~

~~Section 2 of Public Law 102-222 (105 Stat. 1677) is amended—~~

~~(1) in subsection (a), by striking “a grant” and all that follows through “Such grant” and inserting the following: “grants for a pilot program for the training of individuals in clinical pharmacology at appropriate medical schools. Such grants”; and~~

# Proposed Rules

Federal Register

Vol. 64, No. 4

Thursday, January 7, 1999

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 216

[Docket No. 98N-0182]

#### List of Bulk Drug Substances That May Be Used in Pharmacy Compounding

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing a new regulation which will identify the bulk drug substances that may be used in pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the act) even though such substances are neither the subject of a current United States Pharmacopeia (USP) or National Formulary (NF) monograph nor a component of an FDA-approved drug. FDA's development and publication of this bulk drugs list is statutorily required by the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).

**DATES:** Submit written comments on or before March 23, 1999.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Robert J. Tonelli, Center for Drug Evaluation and Research (HFD-332), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-7295.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

President Clinton signed the Modernization Act (Pub. L. 105-115) into law on November 21, 1997. Section 127 of the Modernization Act, which added section 503A to the act (21 U.S.C. 353a), clarifies the status of pharmacy

compounding under Federal law. Under section 503A of the act, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) The adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug or abbreviated new drug applications).

To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements. One of these requirements, found in section 503A(b)(1)(A) of the act, restricts the universe of bulk drug substances that a compounder may use. Section 503A(b)(1)(A) provides, in relevant part, that every bulk drug substance used in compounding: (1) Must comply with an applicable and current USP or NF monograph, if one exists, as well as the current USP chapter on pharmacy compounding; (2) if such a monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug;<sup>1</sup> or (3) if a monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug, it must appear on a list of bulk drug substances that may be used in compounding (i.e., the bulk drugs list being proposed in this rulemaking). The term "bulk drug substance" is defined in FDA regulations at 21 CFR 207.3(a)(4) to mean "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances" (see section 503A(b)(1)(A) of the act).

<sup>1</sup> To identify such FDA-approved drugs, compounders can consult the publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation," commonly referred to as the "Orange Book."

##### II. Criteria for Bulk Drug Substances

According to section 503A(d)(2) of the act, the criteria for determining which substances should appear on the bulk drugs list "shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary of Health and Human Services may identify." The FDA, after consulting with the USP and the Pharmacy Compounding Advisory Committee, is proposing to use the following four criteria: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

In evaluating candidates for the bulk drugs list under these criteria, the agency proposes to use a balancing test. No single one of these criteria will be considered to be dispositive. Rather, the agency will consider each criterion in the context of the others and balance them, on a substance-by-substance basis. In deciding whether a particular substance is appropriate for inclusion on the list.

Under the first criterion, the chemical characterization of the substance, FDA will consider each substance's purity, identity, and quality. Based on attributes such as the substance's chemical formula, melting point, appearance, and solubilities, FDA will determine whether the substance can be identified consistently based on its chemical characteristics. If a substance cannot be well characterized chemically, this criterion will weigh against its inclusion on the proposed bulk drugs list because there can be no assurance that its properties and toxicities when used in compounding would be the same as the properties and toxicities reported in the literature and considered by the agency.

Under the second criterion, FDA will consider the safety issues raised by the use of each substance in general pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the bulk drugs list will have been thoroughly investigated in well-controlled animal toxicology studies, or that there will be well-controlled clinical studies to substantiate their safe use in humans.

**DEPARTMENT OF HEALTH AND  
HUMAN SERVICES****Food and Drug Administration****Pharmacy Compounding Advisory  
Committee; Notice of Meeting**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

*Name of Committee:* Pharmacy Compounding Advisory Committee.

*General Function of the Committee:* To provide advice and recommendations to the agency on FDA's regulatory issues.

*Date and Time:* The meeting will be held on May 6 and 7, 1999, 8:30 a.m. to 5 p.m.

*Location:* CDER Advisory Committee Conference Room 1066, 5630 Fishers Lane, Rockville, MD.

*Contact Person:* Igor Cerny, or Tony Slater, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7001, or by e-mail at CERNY@CDER.FDA.GOV, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12440. Please call the Information Line for up-to-date information on this meeting.

*Agenda:* The committee will discuss and provide FDA with advice about the agency's development and publication of a list of bulk drug substances that may be used in pharmacy compounding that do not have a United States Pharmacopeia or National Formulary monograph and are not components of FDA-approved drugs. Specifically, the committee is likely to address the following drug substances as candidates for the bulk drugs list: 4-aminopyridine, 3,4-diaminopyridine, betahistine dihydrochloride, chloramine-T, cyclandelate, dinitrochlorobenzene, diphenylcyclopropenone, hydrazine sulfate, mild silver protein, monosodium aspartate, pentylenetetrazole, peruvian balsam, and squaric acid dibutyl ester.

*Procedure:* Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by April 23, 1999. Oral presentations from the public will be scheduled between approximately 10:30 a.m. to 11 a.m. for dinitrochlorobenzene, diphenylcyclopropenone, and squaric acid dibutyl ester, and between approximately 2:45 p.m. and 3:15 p.m. for 4-aminopyridine, 3,4-diaminopyridine, and betahistine dihydrochloride on May 6, 1999; and between approximately 10:15 a.m. and 10:45 a.m. for mild silver protein, cyclandelate, and monosodium aspartate, and between approximately 2:45 p.m. and 3:15 p.m. for hydrazine sulfate on May 7, 1999. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before April 23, 1999, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 16, 1999.

**Michael A. Friedman,**

*Deputy Commissioner for Operations.*

[FR Doc. 99-10076 Filed 4-19-99; 11:05 am]

BILLING CODE 4160-01-F

Thus, in evaluating list candidates, the agency is likely to have at its disposal either none or very little of the type or quality of information that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances, then, the agency will rely on information about each substance's acute toxicity, repeat dose toxicity, and other reported toxicities, including mutagenicity, teratogenicity, and carcinogenicity. The agency will also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the toxicity criterion, FDA may also consider the availability of alternative approved therapies when the toxicity of a particular substance appears to be significant. The existence of alternative approved therapies is likely to weigh against inclusion on the proposed list because the risks of using a substance with significant toxicities is more likely to outweigh the benefits when approved alternative therapies are available.

Under the third criterion, the historical use of the substance in pharmacy compounding, FDA will consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, and how widespread its use has been. This criterion will weigh in favor of list inclusion for nominated substances that have enjoyed longstanding and widespread use in pharmacy compounding for a particular indication. Evidence of both widespread and longstanding use will be viewed by the agency as indicative of the substance's perceived usefulness and acceptance in the medical community. Fraudulent or "quack" remedies, on the other hand, will be less likely to be included on the list as a result of this criterion because the practice of compounding such drugs is not expected to be sufficiently prevalent and longstanding.

Under the fourth criterion, FDA will consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, if any such evidence exists. When drugs go through the new drug approval process, they are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the act. FDA recognizes that few, if any, of the candidates for the bulk drugs list will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the agency will take

into account whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use, or reports of one or more trials demonstrating effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was shown not to be effective for a particular use (negative effectiveness data).

When evaluating a bulk drug substance used to treat a less serious illness, FDA will generally be more concerned about the safety of the substance than about its effectiveness. Thus, the absence of effectiveness data, or the existence of mere anecdotal reports, will be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance used to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are alternative approved therapies. In those cases, the absence of effectiveness data, or the presence of negative effectiveness data, will weigh more heavily in FDA's balancing of the relevant criteria.

### III. FDA Development of a Bulk Drugs List

#### A. Methodology

Although the Modernization Act directs FDA to develop a list of bulk drug substances for use in pharmacy compounding, it does not specify how candidates for the list should be identified. In a notice published in the *Federal Register* of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In response to this request, FDA received nominations for 41 different drug substances. The nominations came from Abbott Laboratories, the American Academy of Dermatology, the Texas Pharmacy Association, the North Carolina Board of Pharmacy, Moss Pharmacy and Nutrition Center, the University of Texas MD Anderson Cancer Center, the International Academy of Compounding Pharmacists, Baxter Healthcare Corp., Scottsdale Skin & Cancer Center Ltd., Dermatology Associates, and Neil Brody, M.D.

Ten of the nominated substances (clotrimazole, fluocinonide, hydrocortisone, hydroquinone, mechlorthamine, pramoxine, quinacrine hydrochloride, salicylic acid, tretinoin, and triamcinolone) are the subject of a USP or NF monograph or

are components of FDA-approved drugs. As such, they already qualify for use in pharmacy compounding under section 503A(b)(1)(A)(i) of the act (assuming they satisfy all other applicable requirements of the act). Therefore, FDA dismissed these substances as list candidates and will not address them further in this proposed rulemaking. An additional substance (sulfadimethoxine) was eliminated as a list candidate after being withdrawn by its sponsor at the inaugural meeting of the Pharmacy Compounding Advisory Committee. It too will not be addressed further in this proposed rulemaking.

The remaining 30 nominations were appropriate list candidates and were evaluated based on a balancing of the four criteria identified in section II of this document: (1) The chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.<sup>2</sup>

The information that FDA assessed under each of the evaluation criteria was obtained from journal reports and abstracts from reliable medical sources, including peer reviewed medical literature. This information is available for viewing at the Dockets Management Branch (address above) under Docket No. 98N-0182. Some of this information was submitted in support of the nominations. The remainder FDA gathered through independent searches of medical and pharmaceutical data bases. FDA did not review any raw data.

The nature, quantity, and quality of the information assessed by FDA varied considerably from substance to substance. In some cases there was very little data. For example, the agency found only two relevant journal articles concerning thymol iodide. For other substances, such as taurine and sodium butyrate, reports in the literature were more plentiful and sometimes comprised hundreds of articles. In those cases, the agency reviewed a limited sample of the available literature sources.

Because FDA's assessment of the nominated substances was far less rigorous and far less extensive than the agency's ordinary evaluation of drugs as part of the new drug approval process,

<sup>2</sup> In making its evaluations, the agency did not consider whether any of the nominated substances are manufactured by an establishment registered under section 510 of the act (see 21 U.S.C. 353a(b)(1)(A)(ii)). This registration requirement is one of a number of other conditions that must be satisfied to qualify for the applicable compounding exemptions.

the inclusion of a drug substance on the proposed bulk drugs list should not, in any way, be equated with an approval, endorsement, or recommendation of the substance by FDA. Nor should it be assumed that substances on the proposed list have been proven to be safe and effective under the standards normally required to receive agency approval. In fact, any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA-approved, or otherwise endorsed by FDA generally or for a particular indication, will cause such drug to be misbranded under section 502(a) of the act.

On October 14 and 15, 1998, FDA consulted with the Pharmacy Compounding Advisory Committee, created under section 503A(d)(1) of the act about the contents of this proposed rule (see 63 FR 47301, September 4, 1998). The discussion included the criteria FDA proposes to use to evaluate candidates for the bulk drugs list and the nominations that FDA has already received.<sup>3</sup> In general, the advisory committee agreed with the approach taken by the agency in evaluating the nominated bulk drug substances and the agency's tentative conclusions regarding whether these substances should be included on the bulk drugs list. The agency has taken into consideration all of the advisory committee's recommendations in developing this proposed rule, and the agency intends to continue to consult with the Pharmacy Compounding Advisory Committee in evaluating future candidates for the bulk drugs list.

After evaluating the comments on this proposed rule, FDA is proposing to issue the bulk drugs list as a final rule which will be codified in the Code of Federal Regulations (CFR). The final version of the rule may include all, or only some, of the substances proposed for inclusion on the list in this proposal, depending on the comments received. Individuals and organizations will be able to petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published. Amendments to the list will be proposed through rulemaking.

With regard to nominated substances discussed in this proposed rulemaking (substances proposed for inclusion on the proposed list and substances that have been nominated but are still under consideration by the agency), FDA intends to exercise its enforcement discretion regarding regulatory action

during the pendency of this proposed rulemaking. For further information on this subject, see the guidance for industry entitled "Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act" (see 63 FR 64723, November 23, 1998).

#### *B. Nominated Drug Substances Being Proposed for Inclusion on the Bulk Drugs List*

Under section 503A(d)(2) of the act, FDA is proposing that the following 20 drug substances, which are neither the subject of a current USP or NF monograph nor components of FDA-approved drugs, be included in the list of bulk drug substances that may be used in compounding under the exemptions provided in section 503A of the act (sections 501(a)(2)(B), 502(f)(1), and 505). When a salt or ester of an active moiety is listed, e.g., diloxanide furoate, only that particular salt or ester may be used. Neither the base compound nor other salts or esters of the same active moiety qualify for section 503A of the act's compounding exemptions, unless separately listed.

The following bulk drugs list is being proposed in § 216.23 of title 21 of the CFR. (Section 216.23 will be included in new part 216, which is currently intended to include all FDA regulations whose primary purpose is implementation of the pharmacy compounding provisions found in section 503A of the act):

*Bismuth citrate.* Bismuth citrate is well characterized chemically. It has been used extensively in compounded products for short-term treatment of several gastrointestinal disorders, including *Helicobacter pylori*-associated ulcers. At doses reported in the literature for these indications, bismuth citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of bismuth citrate's effectiveness for these indications is also reported in the literature.

*Caffeine citrate.* Caffeine citrate is well characterized chemically. As a central nervous system stimulant, caffeine citrate has been used extensively and for many years in compounded products to treat apnea in premature infants. At doses reported in the literature for this indication, caffeine citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of caffeine citrate's effectiveness for this indication is also reported in the literature.

*Cantharidin.* Cantharidin, which is well characterized chemically, is a substance obtained from the Chinese blister beetle, among other beetle species, that has been used topically in the treatment of warts and molluscum contagiosum, often in patients with compromised immune systems. Limited anecdotal evidence of cantharidin's effectiveness for these indications is reported in the literature. Although cantharidin is an extremely toxic substance, it is apparently used only in the professional office setting and not dispensed for home use. Because of cantharidin's toxicity, FDA is proposing to include it on the bulk drugs list for topical use in the professional office setting only.

*Choline bitartrate.* Choline bitartrate is well characterized chemically. It has been used to treat Alzheimer's-type dementia. It has also been used to treat infantile colic. At doses reported in the literature for these indications, choline bitartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of choline bitartrate's effectiveness for these indications is also reported in the literature. Additionally, FDA has previously established that choline bitartrate is generally recognized as safe, as a dietary supplement, when used in accordance with good manufacturing practices (see 21 CFR 182.8250 (45 FR 58837, September 5, 1980)).

*Diloxanide furoate.* Diloxanide furoate is well characterized chemically. It has been used to treat parasitic diseases such as intestinal amoebiasis. At doses reported in the literature for these indications, diloxanide furoate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of diloxanide furoate's effectiveness for these indications is also reported in the literature.

*Dimercapto-1-propanesulfonic acid.* Dimercapto-1-propanesulfonic acid (DMPS), a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of DMPS's effectiveness for this indication is also reported in the literature.

<sup>3</sup> A transcript of the advisory committee meeting may be found at the Dockets Management Branch (address above) under Docket No. 98N-0182.



**Ferric subsulfate.**<sup>4</sup> Ferric subsulfate is well characterized chemically. It has been used as a topical hemostatic agent to control bleeding associated with minor surgical procedures, biopsies, and minor gynecological surgery involving the cervix. At doses reported in the literature for this indication, ferric subsulfate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric subsulfate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

**Ferric sulfate hydrate.** Ferric sulfate hydrate is well characterized chemically. It has been used topically as a hemostatic agent to control bleeding from dermatological and dental procedures. At doses reported in the literature for these indications, ferric sulfate hydrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of ferric sulfate hydrate's effectiveness for this indication is also reported in the literature. However, because the literature is limited to topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

**Glutamine.** Glutamine, the most abundant free amino acid found in the human body, is well characterized chemically. Glutamine is involved in a wide variety of metabolic processes, including regulation of the body's acid-base balance. For years, glutamine has been used in compounding as a supplement in parenteral nutrition regimens in adults. At doses reported in the literature for this use, glutamine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of glutamine's effectiveness for this indication is also reported in the literature.

**Guaiaicol.** Guaiaicol is well characterized chemically. It has been used for decades in compounded products as an expectorant. At doses reported in the literature for this indication, guaiaicol appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited

anecdotal evidence of guaiaicol's effectiveness for this indication is also reported in the literature.

**Iodoform.** Iodoform is well characterized chemically. It has been used for the control of acute epistaxis (nosebleeds) and as a paste for dental root fillings. Iodoform has tested positive in in vitro mutagenicity assays and in an in vitro transformational assay in mammalian cells. However, in 2-year bioassays conducted by the National Toxicology Program, iodoform was found to be noncarcinogenic in rats and mice. At doses reported in the literature for these indications, iodoform appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of iodoform's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the topical and intradental use of this substance, FDA is proposing to include it on the bulk drugs list for topical and intradental use only.

**Metronidazole benzoate.** Metronidazole benzoate, which is well characterized chemically, has been used to treat parasitic diseases such as amoebiasis and giardiasis. The base of this substance (metronidazole) is an FDA-approved drug which has a bitter taste. The benzoate salt apparently renders metronidazole tasteless, however, so metronidazole benzoate is sometimes prescribed instead of the metronidazole base to increase patient compliance, especially in children. Serious adverse reactions associated with the use of metronidazole benzoate have not been commonly reported, and limited anecdotal evidence of its effectiveness is reported in the literature. Although the agency is proposing to include metronidazole benzoate on the bulk drugs list, it is specifically seeking public comment on metronidazole benzoate's solubility and appropriate dosing, as questions about these issues have been raised in the literature.

**Myrrh gum tincture.** Myrrh is a gum resin obtained from the stem of *Commiphora molmol* and other species of camphora. Myrrh is a mixture of many substances and has not been well characterized chemically. Myrrh has been used in its natural form and as a tincture to treat inflammatory disorders of the mouth and pharynx. The preparation reviewed by FDA is the tincture, which, at doses reported in the literature for those indications, appears to be relatively nontoxic. Serious adverse reactions associated with the use of myrrh gum tincture have not been

commonly reported. Limited anecdotal evidence of myrrh gum tincture's effectiveness for those indications is also reported in the literature. Because the literature is limited to the topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

**Phenindamine tartrate.** Phenindamine tartrate is well characterized chemically. It is an antihistamine that has been used to treat hypersensitivity reactions including urticaria (hives) and rhinitis (nasal inflammation). At doses reported in the literature for this indication, phenindamine tartrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Additionally, in developing the over-the-counter monograph for antihistamine drug products, FDA previously established that phenindamine tartrate, under the conditions established in the monograph (including particular labeling and dosage limits), is generally recognized as safe and effective for over-the-counter antihistamine use (see 21 CFR 341.12; 57 FR 58356, December 9, 1992). Limited anecdotal evidence of phenindamine tartrate's effectiveness as an antihistamine is reported in the literature.

**Phenyltoloxamine dihydrogen citrate.** Phenyltoloxamine dihydrogen citrate, a structural isomer of diphenhydramine, is well characterized chemically. It has been used as an antihistamine. At doses reported in the literature for this indication, phenyltoloxamine dihydrogen citrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of phenyltoloxamine dihydrogen citrate's effectiveness as an antihistamine is reported in the literature.

**Piracetam.** Piracetam, a derivative of the amino acid gamma-amino butyric acid, is well characterized chemically. Piracetam is believed by some to enhance certain cognitive skills, and has been used to treat Down's syndrome, dyslexia, and Alzheimer's disease, among other cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of piracetam's effectiveness for these indications is reported in the literature.

**Sodium butyrate.** Sodium butyrate is a short chain fatty acid that is well characterized chemically. It has been

<sup>4</sup> Both ferric subsulfate solution and ferric subsulfate powder were nominated for inclusion on the bulk drugs list. FDA combined them under one entry for ferric subsulfate.

used rectally in an enema formulation to treat several inflammatory bowel conditions, including ulcerative colitis and diversion colitis. At doses reported in the literature for these indications, sodium butyrate appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of sodium butyrate's effectiveness for these indications is also reported in the literature. However, because the literature is limited to the use of sodium butyrate rectally in an enema formulation, FDA is proposing to include it on the bulk drugs list for use in this dosage form and route of administration only.

**Taurine.** Taurine, an amino acid with several important physiological functions, including a role in bile acid conjugation, is well characterized chemically. It has been used for years in compounding as a component in parenteral nutrition solutions for infants and adult patients. At doses reported in the literature for this use, taurine appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of taurine's effectiveness for this indication is also reported in the literature.

**Thymol iodide.** Thymol iodide is well characterized chemically. It has been used as a topical agent for its absorbent, protective, and antimicrobial properties. At doses reported in the literature for these indications, thymol iodide appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of thymol iodide's effectiveness for these indications is also reported in the literature. FDA notes, however, that it was able to identify only two relevant articles concerning this substance. Because the literature is limited to the topical use of thymol iodide, FDA is proposing to include it on the bulk drugs list for topical use only.

**Tinidazole.** Tinidazole is a chemically well-characterized derivative of 5-nitromidazole. It has been used, often in conjunction with diloxanide furoate, which also appears on this proposed list, to treat parasitic diseases such as amoebiasis and giardiasis. At doses reported in the literature for these indications, tinidazole appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of tinidazole's effectiveness for these indications is also reported in the literature.

#### *C. Nominated Drug Substances Still Under Consideration for the Bulk Drugs List*

The following 10 drug substances were nominated for inclusion on the proposed bulk drugs list. However, for the reasons described in section III.C of this document, they are still under review by the agency:

**4-Aminopyridine.** The drug substance 4-Aminopyridine (4-AP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. It has been used to treat several neurological disorders, including Lambert-Eaton myasthenic syndrome, multiple sclerosis, and Alzheimer's disease. It also has been used to reverse the effects of nondepolarizing muscle relaxants. At doses reported in the literature, the side effects of 4-AP for most patients do not appear to be serious. However, there have been some reports of seizures associated with the use of 4-AP. FDA would like more information about the historical use, safety, and effectiveness of 4-AP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about 4-AP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

**Betahistine dihydrochloride.** Betahistine dihydrochloride is a chemically well characterized histamine analog. Formerly marketed as Serc tablets, betahistine dihydrochloride was approved by FDA to treat the symptoms of vertigo in patients with Meniere's disease. In 1970, however, FDA withdrew approval of the new drug application for Serc tablets because they were found to lack substantial evidence of effectiveness for this approved indication (see 35 FR 17563, November 14, 1970). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include betahistine dihydrochloride on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

**Cyclandelate.** Cyclandelate, which is well characterized chemically, is a vasodilator that was formerly approved by FDA for two indications: (1) Treatment for intermittent claudication caused by arteriosclerosis obliterans, and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multi-infarct or

Alzheimer's type. Cyclandelate was formerly marketed in Cyclospasmol capsules and tablets, which were removed from the market for lack of effectiveness for these approved indications (see 61 FR 64099, December 3, 1996). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include cyclandelate on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

**3,4-Diaminopyridine.** The drug substance 3,4-Diaminopyridine (DAP), which is well characterized chemically, is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. DAP has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis. At doses reported in the literature, DAP appears to be well tolerated and its toxicity appears to be dose related. There have been reports of seizures with its use, however, and DAP is contraindicated in patients with epilepsy. FDA would like more information about the historical use, safety, and effectiveness of DAP before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about DAP before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

**Dinitrochlorobenzene.** Dinitrochlorobenzene (DNCB), which is well characterized chemically, has been used in the treatment of recurrent melanoma and as a skin sensitizer to estimate immune system competency. It also has been used topically in the treatment of warts. Limited anecdotal evidence of DNCB's effectiveness for these indications is reported in the literature. DNCB is a highly toxic substance that may be fatal if inhaled, swallowed, or absorbed through skin. High concentrations of DNCB are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin. At the inaugural meeting of the Pharmacy Compounding Advisory Committee, the nominator of this substance withdrew it as a list candidate, but several members of the committee recommended that it still be considered. The Pharmacy Compounding Advisory Committee then voiced concerns about the safety of the

substance and expressed a desire for more information about it before making a recommendation to the agency. FDA agrees and, therefore, is requesting public input about the historical use, safety, and effectiveness of DNCB, as well as any other information that would be relevant to the agency's consideration of DNCB for the bulk drugs list.

*Diphenylcyclopropenone.*

Diphenylcyclopropenone, which is well characterized chemically, has been used for the topical treatment of extensive alopecia areata. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

*Hydrazine sulfate.* Hydrazine sulfate is well characterized chemically and has been used to treat cachexia in cancer patients. The substance, however, is extremely toxic. Multiple exposures to hydrazine sulfate have caused liver and kidney damage, gastrointestinal damage, convulsions, and coma, among other conditions. Hydrazine sulfate is also considered by the International Agency for Research on Cancer to be a potential carcinogen to humans. In at least two clinical studies, hydrazine sulfate was shown to have no effect, or even a negative effect, on patients who received it. FDA would like more information about the historical use, safety, and effectiveness of hydrazine sulfate before deciding whether to propose it for inclusion on the bulk drugs list. The Pharmacy Compounding Advisory Committee similarly expressed a desire for more information about hydrazine sulfate before making a recommendation about its status to the agency. FDA is soliciting public input on these and any other issues that are relevant to the agency's consideration of this substance for the bulk drugs list.

*Pentylentetrazole.*

Pentylentetrazole, which is well characterized chemically, was approved by FDA for use in the treatment of senile confusion, depression, psychosis, fatigue, and debilitation, as well as for the relief of dizzy spells, mild behavioral disorders, irritability, and functional memory disorders in elderly patients. Pentylentetrazole was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness for these approved indications (see 47 FR 19208, May 4, 1982). FDA will

consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include pentylentetrazole on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

*Silver protein mild.* Mild silver protein is well characterized chemically. It has been used to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. At doses reported in the literature for these indications, mild silver protein appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. When mild silver protein is administered internally, however, it can cause serious untoward side effects, including argyria, a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs (see 61 FR 53685, October 15, 1996). At this time, FDA is deferring a decision on this substance because questions were raised at the inaugural meeting of the Pharmacy Compounding Advisory Committee about its efficacy. FDA is soliciting public input on this issue and any other issues that are relevant to the agency's consideration of mild silver protein for the bulk drugs list.

*Squaric acid dibutyl ester.* Squaric acid dibutyl ester, which is well characterized chemically, is a contact sensitizer that has been used as a topical treatment for alopecia areata and warts. The nomination of this substance was not received by FDA in time to permit a full discussion of it at the October 1998 meeting of the Pharmacy Compounding Advisory Committee. A decision about this substance is therefore being deferred until after FDA has had an opportunity to consult the Pharmacy Compounding Advisory Committee about it at a future meeting.

#### IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select

regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities if the proposed rule is expected to have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any 1 year by State, local and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in the Executive Order and these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order. As discussed below, the agency certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. Also, because the rule is not expected to result in any annual expenditures, FDA is not required to prepare a cost/benefit analysis under the Unfunded Mandates Reform Act.

FDA is proposing to amend its regulations to include a list of bulk drugs that may be used in pharmacy compounding under certain conditions even though such substances are neither the subject of a USP or NF monograph nor components of FDA-approved drugs. FDA has requested and received nominations for bulk drugs to be included on this list. Twenty of the nominated substances are being proposed for inclusion, which means they would be eligible for use in pharmacy compounding under the exemptions provided by section 503A of the act. As a result, there would be no loss of any sales, or other economic impact, for compounded drug products containing these 20 substances.

FDA has proposed to include some of these substances on the list with a restriction on their route of administration or a requirement that the resulting compounded drug product be for professional office use only. As FDA is unaware that any of these drug substances are currently used in compounding outside of the proposed restrictions, the agency does not expect these restrictions to result in decreased sales of any compounded drug product.

Further, this regulation is not anticipated to impose any other compliance costs on bulk drug manufacturers or compounding pharmacies.

Ten additional nominated substances, while not being proposed for inclusion on the bulk drugs list, are still under review by the agency. As explained more fully in the guidance for industry entitled "Enforcement Policy During Implementation of section 503A of the Federal Food, Drug, and Cosmetic Act" (see notice of availability, 63 FR 64723, November 23, 1998), FDA intends to exercise its enforcement discretion regarding these 10 substances. In short, FDA does not intend to take regulatory action against a drug product that has been compounded with one of these substances while the substance is being evaluated during the pendency of this rulemaking proceeding, as long as the compounding complies with the other effective requirements in section 503A of the act and does not appear to present a significant safety risk.

Although usage or sales data for the nominated drug substances is limited, the agency further concludes that even if any of the 10 deferred drug substances were, in the future, to be excluded as candidates for the bulk drugs list, the economic impact would not be significant, particularly not for any substantial number of pharmacies or other small entities. The quantity demanded of these 10 drugs appears to be relatively small, especially when compared to the total number of prescription drugs dispensed annually in the United States. In addition, if any of the 10 substances were ultimately excluded from the list, sales of alternatives to the excluded drugs would be expected to reduce the economic impact of such exclusion.

At the October 1998 meeting of the Pharmacy Compounding Advisory Committee, a representative of the International Academy of Compounding Pharmacists (IACP) presented usage and sales data for four of the deferred substances: 3,4-DAP, 4-AP, hydrazine sulfate, and mild silver protein. According to the IACP representative, the drug substances 3,4-DAP and 4-AP are currently being used in compounding to treat patient populations estimated at 1,000 and 10,000 patients, respectively; hydrazine sulfate is currently being used to treat between 5,000 and 10,000 patients annually; and the annual production of mild silver protein is approximately 9 kilograms. FDA does not have a firm estimate of the number of patients being treated with mild silver protein, but estimates it to be several thousand.

Similarly, FDA does not have usage or sales data for the six other deferred drug substances, but estimates that their usage is also relatively low. The agency invites comments and data on any projected loss of sales or other compliance costs directly attributable to this proposal.

If a rule is expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize these impacts. Section 503A of the act specifically directs FDA to develop a list of bulk drug substances that may be used in pharmacy compounding. The agency received nominations from the public for 41 bulk drugs to be included on this list. All the nominations are either proposed for inclusion on the list or are still under review. The agency therefore certifies that this proposal will not have a significant economic impact on a substantial number of small entities. The agency invites public comment and data on these issues, specifically the number and size of the bulk drug manufacturers and compounding pharmacies that sell any of the deferred substances, or drug products containing them, and any sales data on these compounded drug products.

The Unfunded Mandates Reform Act requires (in section 202) that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of FDA's list of bulk drug substances for use in pharmacy compounding is not expected to result in any expenditure of funds by State, local and tribal governments or the private sector. Because the proposed rule is not expected to result in any mandated expenditures, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

#### VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### VII. Request for Comments

Interested persons may, on or before March 23, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that

individuals may submit one copy. Comments are to be identified with docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

#### List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be added as follows:

1. Part 216 is added to read as follows:

#### PART 216—PHARMACY COMPOUNDING

##### Subpart A—General Provisions [Reserved]

##### Subpart B—Compounded Drug Products Sec.

216.23 Bulk drug substances for use in pharmacy compounding.

216.24 [Reserved]

Authority: 21 U.S.C. 351, 352, 353a, 355, 371.

##### Subpart A—General Provisions [Reserved]

##### Subpart B—Compounded Drug Products

#### § 216.23 Bulk drug substances for use in pharmacy compounding.

(a) The following bulk drug substances, which are neither the subject of a current United States Pharmacopeia or National Formulary monograph nor components of the Food and Drug Administration approved drugs, may be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

Bismuth citrate.

Caffeine citrate.

Cantharidin (for topical use in the professional office setting only).

Choline bitartrate.

Diloxanide furoate.

Dimercapto-1-propanesulfonic acid.

Ferric subsulfate (for topical use only).

Ferric sulfate hydrate (for topical use only).

Glutamine.

Guaiacol.

Iodoform (for topical and intradental use only).

Metronidazole benzoate.

Myrrh gum tincture (for topical use only).

Phenindamine tartrate.

Phenyltoloxamine dihydrogen citrate.

Piracetam.

Sodium butyrate (for rectal enema use only).

Taurine.  
Thymol iodide (for topical use only).  
Tinidazole.

(b) FDA balances the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section: The chemical characterization of the substance; the safety of the substance; the historical use of the substance in pharmacy compounding; and the available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists.

(c) Based on evidence currently available there are inadequate data to establish substantial evidence or general recognition of the safety or effectiveness of any of the drug substances set forth in paragraph (a) of this section, for any indication.

#### § 216.24 [Reserved]

Dated: December 29, 1998.

William K. Hubbard,  
Associate Commissioner for Policy  
Coordination.

[FR Doc. 99-277 Filed 1-6-99; 8:45 am]

BILLING CODE 4160-01-F

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Parts 52 and 81

[FL-75-1-9806b; FRL 6196]

#### Designation of Areas for Air Quality Planning Purposes Florida: Redesignation of the Duval County Sulfur Dioxide Unclassifiable Area to Attainment

AGENCY: Environmental Protection  
Agency (EPA).

ACTION: Proposed rule.

**SUMMARY:** On January 28, 1997, the Florida Department of Environmental Protection (DEP) submitted a request for redesignation to attainment for sulfur dioxide (SO<sub>2</sub>) in Duval County, Florida. The redesignation request included five years of quality assured monitoring data which showed no exceedances of the National Ambient Air Quality Standards (NAAQS) for SO<sub>2</sub>. Duval County was originally designated as an unclassifiable area in 1978 due to lack of adequate monitoring data. Sufficient data have now been collected to make affirmative declaration of attainment status. The EPA is redesignating Duval County from unclassifiable to attainment for SO<sub>2</sub> and approving three permits that provide SO<sub>2</sub> emission reductions.

In the Final Rules Section of this Federal Register, EPA is approving the

Florida State Plan submittal as a direct final rule without prior proposal because the Agency views this as a noncontroversial submittal and anticipates that it will not receive any significant, material, and adverse comments. A detailed rationale for the approval is set forth in the direct final rule and incorporated herein. If no significant, material, and adverse comments are received in response, to this rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this action.

**DATES:** Comments must be received in writing by February 8, 1999.

**ADDRESSES:** All comments should be addressed to Scott Martin at the EPA Regional Office listed below. Copies of the documents relevant to this proposed rule are available for public inspection during normal business hours at the following locations. The interested persons wanting to examine these documents should make an appointment with the appropriate office at least 24 hours before the day of the visit.

Environmental Protection Agency,  
Region 4, Air Planning Branch, 61  
Forsyth Street, SW, Atlanta, Georgia  
30303-3104.

Florida Department of Environmental  
Protection, Twin Towers Office  
Building, 2600 Blair Stone Road,  
Tallahassee, Florida 32399-2400.

**FOR FURTHER INFORMATION CONTACT:**  
Scott Martin at (404) 562-9036.

**SUPPLEMENTARY INFORMATION:** See the information provided in the Direct Final action which is located in the Rules Section of this Federal Register.

Dated: November 10, 1998.

A. Stanley Meiburg,  
Acting Regional Administrator, Region 4.  
[FR Doc. 99-230 Filed 1-6-99; 8:45 am]

BILLING CODE 8560-50-M

## FEDERAL COMMUNICATIONS COMMISSION

### 47 CFR Part 90

[WT Docket No. 96-86; DA 98-2588]

#### The Development of Operational, Technical and Spectrum Requirements for Meeting Federal, State and Local Public Safety Agency Communication Requirements Through the Year 2010, Establishment of Rules and Requirements for Priority Access Service

AGENCY: Federal Communications  
Commission.

ACTION: Proposed rule; extension of time  
for comments.

**SUMMARY:** This document extends the time to file comments concerning the Commission's *Third Notice of Proposed Rule Making* ("Third Notice") adopted on August 6, 1998. Comments on the *Third Notice* were due on or before January 4, 1999, and Reply Comments were due on or before February 1, 1999. Because of the many petitions for reconsideration and clarification filed in response to the *First Report and Order* ("First Report") in this proceeding and the close proximity of the deadlines for responding to these petitions and the *Third Notice*, the Commission extended the time to file comments.

**DATES:** Comments are due on or before January 19, 1999, and reply comments are due on or before February 18, 1999.

**ADDRESSES:** Federal Communications  
Commission, Office of the Secretary,  
Publications Branch, Room TW-B204,  
The Portals II, 445 12th St., SW,  
Washington, D.C. 20554.

**FOR FURTHER INFORMATION CONTACT:**  
Peter Daronco or Michael Pollak, at the  
Public Safety & Private Wireless  
Division, (202) 418-0680.

**SUPPLEMENTARY INFORMATION:** This is a summary of the Commission's *Order* in WT Docket No. 96-86, adopted on December 23, 1998, and released on December 24, 1998, (DA 98-2588). The full text of the *Order* is available for inspection and copying during normal business hours in the FCC Reference Center, Room 239, 1919 M St., NW, Washington, DC 20554. The complete text of this decision may also be purchased from the Commission's duplicating contractor, International Transcription Services, 1231 20th Street, NW, Washington, DC 20036, 202-857-3800. Alternative formats (computer diskette, large print, audio cassette and Braille) are available to persons with disabilities by contacting

Olefin polymers	Density	Melting Point (MP) or softening point (SP) (Degrees Centigrade)	Maximum extractable fraction (expressed as percent by weight of the polymer) in <i>N</i> -hexane at specified temperatures	Maximum soluble fraction (expressed as percent by weight of polymer) in xylene at specified temperatures
<p>* 3.7 Ethylene/propylene copolymers, meeting the identity described in paragraph (a)(3)(i) of this section, containing not less than 80 mole-percent of polymer units derived from ethylene and having a minimum viscosity average molecular weight of 95,000 as determined by the method described in paragraph (d)(5) of this section, and a minimum Mooney viscosity of 13 as determined by the method described in paragraph (d)(6) of this section. Ethylene/propylene copolymers described in this item 3.7 are to be used only in blends with other olefin polymers complying with this section, at levels not to exceed 30 percent by weight of the total polymer blend, and in contact with food only of types identified in § 176.170(c) of this chapter, Table 1, under Types I, II, III, IV-B, VI, VII, VIII, and IX. Additionally, optional adjuncts permitted for use in olefin copolymers complying with item 3.4 of this table may be used in the production of this copolymer. *</p>	<p>* Not less than 0.86 *</p>	<p>*  *</p>	<p>*  *</p>	<p>*  *</p>

\* \* \* \* \*  
Dated: February 23, 1999.

Janice F. Oliver,

Deputy Director for Systems and Support,  
Center for Food Safety and Applied Nutrition.

[FR Doc. 99-5520 Filed 3-5-99; 8:45 am]

BILLING CODE 4160-01-F

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 216**

[Docket No. 98N-0655]

**List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending its regulations to include a list of drug

products that may not be used for pharmacy compounding under the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. The list has been compiled under the new statutory requirements of the Food and Drug Administration Modernization Act of 1997 (Modernization Act).

**DATES:** This rule is effective on April 7, 1999.

**FOR FURTHER INFORMATION CONTACT:** Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers

Lane, Rockville, MD 20857, 301-594-2041.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

Section 127 of the Modernization Act (Pub. L. 105-115), which added section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. Section 503A(b)(1)(C) of the act provides that the licensed pharmacist or licensed physician does not "compound a drug product that appears on a list published by the Secretary in the *Federal Register* of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective." Section 503A(d)(1) of the act requires that the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective be issued as a regulation and that an advisory committee be consulted in the rulemaking process.

In the *Federal Register* of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the list of drug products that have been withdrawn or removed from the market because they were unsafe or not effective. The primary focus of that initial proposed rule and this final rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may initiate rulemaking to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective or to update the list as new information becomes available to the agency regarding products that were removed from the market because they were unsafe. The proposed rule was presented to the Pharmacy Compounding Advisory Committee at a meeting held on October 14 and 15, 1998 (see the *Federal Register* of September 4, 1998 (63 FR 47301)). The committee did not have any adverse comments on the proposed rule and did not suggest any changes.

##### II. Comments on the Proposed Rule

FDA received comments from consumers, pharmacists, a medical doctor, a pharmaceutical manufacturer,

a pharmaceutical manufacturers' organization, and a committee representing the plaintiffs in a drug product liability class action suit.

1. Two comments questioned FDA's shortening the comment period from 75 to 45 days.

As FDA stated in the preamble to the proposed rule (63 FR 54082 at 54087 to 54088), the agency believes that a shorter comment period was warranted to expedite this rulemaking proceeding because the compounding of many of the drug products on the list would present a serious threat to the public health. Many of the drug products have caused death or life-threatening conditions. Some of the drugs on the list are believed to cause cancer, while others were shown to be toxic to the liver and other organs.

2. One comment objected to the wording of the first sentence of proposed § 216.24, which says "The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective." The comment expressed concerns that the finding that a drug was withdrawn from the market by the manufacturer because it was not safe or effective might be used in a product liability lawsuit against the manufacturer who voluntarily withdrew the drug product from the market. The comment also expressed concerns that fear of having the finding used against them might discourage manufacturers from voluntarily withdrawing drug products when concerns about the drug product's safety and effectiveness have developed.

The agency does not believe it is necessary to change the wording of § 216.24 in response to this comment. Compounding pharmacists and physicians are the intended audience for this rule. The purpose of § 216.24 is to provide these compounders a list of drugs that they may not compound under section 503A of the act. This list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.

For the purposes of this rule, FDA has determined that it is not necessary to deviate from the statutory language found in section 503A(b)(1)(C) of the act, which prohibits compounders from compounding "a drug product that appears on a list published by [FDA] in the *Federal Register* of drug products that have been withdrawn or removed from the market because such drug products or components of such drug

products have been found to be unsafe or ineffective."

The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

3. A large number of comments objected to drug products containing adrenal cortex being placed on the list. One of the comments included a photocopy of an article from the November issue of the magazine *Nutrition & Healing*. This article apparently is the source of much of the content of many of the comments. None of the comments provided any information about the removal of adrenal cortex extract from the market, other than the unsupported statements that the removal of adrenal cortex extract was economically motivated. These comments included unsupported statements that adrenal cortex extract has never been associated with a death or serious adverse event (except for a series of adverse events in 1996 and 1997 associated with contaminated adrenal cortex extract) and that adrenal cortex extract is safer and more effective than the synthetic adrenocortical steroids that have replaced it in medical use. The comments also asserted, without presenting any scientific data or historical information to support the assertion, that FDA acted improperly in directing the removal of drugs containing adrenal cortex from the market because the low levels of corticosteroids found in the drugs presented a substantial risk of undertreatment of serious conditions.

FDA's concerns about the safety of adrenal cortex extract have grown stronger since the drug product was removed from the market in 1978. Adrenal cortex extract is derived from the cortex adrenal glands of domestic food animals, including cattle. In 1986 the disease bovine spongiform encephalopathy (BSE) was identified in cattle. BSE has been found to be epidemic in Great Britain and present in Western Europe and Oman. Hundreds of thousands of cattle have either died or been destroyed as a result of BSE infection. Since that time strong evidence has been developed associating ingestion of tissues from

BSE-infected cattle with the development of new variant Creutzfeldt-Jakob disease (nvCJD) in humans. A patient taking a drug derived from the adrenal cortex of a BSE-infected cow would be running an unacceptable risk of contracting nvCJD. Due to the destruction of BSE-infected cattle and other controls (see the **Federal Register** of August 29, 1994 (59 FR 44591)), the chances of a patient getting nvCJD from adrenal cortex extract are low. However, there is still a risk involved in taking adrenal cortex extract, and that risk must be taken very seriously in light of the fact that nvCJD appears to always be fatal.

Concerning the comments that FDA acted improperly in removing drugs containing adrenal cortex from the market because of a substantial risk of undertreatment of serious conditions, FDA's action was investigated by the General Accounting Office and found to be proper (see "By the Comptroller General, Report to the Honorable Barry M. Goldwater, Jr., House of Representatives of the United States: Adrenal Cortical Extract Taken Off Drug Market" (HRD-81-61, 1981)).

For the reasons stated previously, FDA is keeping drug products containing adrenal cortex on the list of drugs that may not be compounded under section 503A of the act.

4. One comment strongly supported the inclusion of drug products containing dexfenfluramine hydrochloride and fenfluramine hydrochloride on the list.

5. One comment pointed out that there is a hearing request pending before the agency regarding the withdrawal of approval of the applications for neomycin sulfate in sterile vials for injection (see the **Federal Register** of December 6, 1988 (53 FR 49232)) and another pending request for a hearing regarding the withdrawal of approval of the applications for neomycin sulfate for prescription compounding (see the **Federal Register** of December 6, 1988 (53 FR 49231)). A petition for stay of action regarding the two actions mentioned above and regarding a labeling guideline for neomycin sulfate for prescription compounding (see the **Federal Register** of April 15, 1988 (53 FR 12662)) is also pending before the agency.

Because of the complex administrative record on neomycin sulfate currently before the agency and because of the public health need to expedite implementation of this rule, FDA is postponing final action on listing all parenteral drug products containing neomycin sulfate. Parenteral drug products containing neomycin

sulfate may be added to the list at a later date.

### III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed in the paragraphs below, the agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this final rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. The agency is not aware of any routine use of these drug products in pharmacy compounding and received no significant data in response to the request in the preamble to the proposed rule for the submission of comments on this issue and current compounding usage data for these drug products. Additionally, FDA did not receive any comments on compliance costs and loss of sales due to this rule or current compounding usage data for the drug products listed in this rule at the Pharmacy Compounding Advisory Committee meeting held on October 14 and 15, 1998.

Unless an agency certifies that a rule will not have a significant economic

impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action in order to comply with section 503A of the act. This provision specifically directs the FDA to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act. The drug products on this list were manufactured by many different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes those drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this final rule will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any loss of sales due to this rule. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than \$5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before it finalizes any rule requiring any expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any 1 year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of \$100 million annually. Because the agency does not estimate any annual expenditures due to the final rule, FDA is not required to



perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

#### V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is added to read as follows:

#### PART 216—PHARMACY COMPOUNDING

##### Subpart A—General Provisions [Reserved]

##### Subpart B—Compounded Drug Products

Sec.

216.23 [Reserved]

216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

##### Subpart A—General Provisions [Reserved]

##### Subpart B—Compounded Drug Products

#### § 216.23 [Reserved]

#### § 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

*Adenosine phosphate*: All drug products containing adenosine phosphate.

*Adrenal cortex*: All drug products containing adrenal cortex.

*Azaribine*: All drug products containing azaribine.

*Benoxaprofen*: All drug products containing benoxaprofen.

*Bithionol*: All drug products containing bithionol.

*Bromfenac sodium*: All drug products containing bromfenac sodium.

*Butamben*: All parenteral drug products containing butamben.

*Camphorated oil*: All drug products containing camphorated oil.

*Carbetapentane citrate*: All oral gel drug products containing carbetapentane citrate.

*Casein, iodinated*: All drug products containing iodinated casein.

*Chlorhexidine gluconate*: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.

*Chlormadinone acetate*: All drug products containing chlormadinone acetate.

*Chloroform*: All drug products containing chloroform.

*Cobalt*: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).

*Dexfenfluramine hydrochloride*: All drug products containing dexfenfluramine hydrochloride.

*Diamthazole dihydrochloride*: All drug products containing diamthazole dihydrochloride.

*Dibromsalan*: All drug products containing dibromsalan.

*Diethylstilbestrol*: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.

*Dihydrostreptomycin sulfate*: All drug products containing dihydrostreptomycin sulfate.

*Dipyron*: All drug products containing dipyron.

*Encainide hydrochloride*: All drug products containing encainide hydrochloride.

*Fenfluramine hydrochloride*: All drug products containing fenfluramine hydrochloride.

*Flosequinan*: All drug products containing flosequinan.

*Gelatin*: All intravenous drug products containing gelatin.

*Glycerol, iodinated*: All drug products containing iodinated glycerol.

*Gonadotropin, chorionic*: All drug products containing chorionic gonadotropins of animal origin.

*Mepazine*: All drug products containing mepazine hydrochloride or mepazine acetate.

*Metabromsalan*: All drug products containing metabromsalan.

*Methamphetamine hydrochloride*: All parenteral drug products containing methamphetamine hydrochloride.

*Methapyrilene*: All drug products containing methapyrilene.

*Methopholine*: All drug products containing methopholine.

*Mibefradil dihydrochloride*: All drug products containing mibefradil dihydrochloride.

*Nitrofurazone*: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application).

*Nomifensine maleate*: All drug products containing nomifensine maleate.

*Oxyphenisatin*: All drug products containing oxyphenisatin.

*Oxyphenisatin acetate*: All drug products containing oxyphenisatin acetate.

*Phenacetin*: All drug products containing phenacetin.

*Phenformin hydrochloride*: All drug products containing phenformin hydrochloride.

*Pipamazine*: All drug products containing pipamazine.

*Potassium arsenite*: All drug products containing potassium arsenite.

*Potassium chloride*: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).

*Povidone*: All intravenous drug products containing povidone.

*Reserpine*: All oral dosage form drug products containing more than 1 milligram of reserpine.

*Sparteine sulfate*: All drug products containing sparteine sulfate.

*Sulfadimethoxine*: All drug products containing sulfadimethoxine.

*Sulfathiazole*: All drug products containing sulfathiazole (except those formulated for vaginal use).

*Suprofen*: All drug products containing suprofen (except ophthalmic solutions).

*Sweet spirits of nitre*: All drug products containing sweet spirits of nitre.

*Temafloxacin hydrochloride*: All drug products containing temafloxacin.

*Terfenadine*: All drug products containing terfenadine.

*3,3',4',5-tetrachlorosalicylanilide*: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.

*Tetracycline*: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.

*Ticrynafen*: All drug products containing ticrynafen.

*Tribromsalan*: All drug products containing tribromsalan.

*Trichloroethane*: All aerosol drug products intended for inhalation containing trichloroethane.

*Urethane*: All drug products containing urethane.

*Vinyl chloride*: All aerosol drug products containing vinyl chloride.

*Zirconium*: All aerosol drug products containing zirconium.

*Zomepirac sodium*: All drug products containing zomepirac sodium.

Dated: March 1, 1999.

**William K. Hubbard,**

*Acting Deputy Commissioner for Policy.*

[FR Doc. 99-5517 Filed 3-5-99; 8:45 am]

BILLING CODE 4160-01-F

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 874

[Docket No. 98N-0249]

#### Ear, Nose, and Throat Devices; Classification of the Nasal Dilator, the Intranasal Splint, and the Bone Particle Collector

AGENCY: Food and Drug Administration, HHS.

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# **Guidance for Industry**

## **Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
November 1998**

**Procedural 10**

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# **Guidance for Industry**

## **Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act**

*Additional copies are available from:*

*Office of Training and Communications  
Division of Communications Management  
Drug Information Branch, HFD-210  
5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
November 1998**

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# **DRAFT GUIDANCE FOR INDUSTRY<sup>1</sup>**

## **Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act**

### **I. INTRODUCTION**

This document provides guidance to drug compounders on how the Food and Drug Administration (FDA) intends to enforce section 503A of the Federal Food, Drug, and Cosmetic Act during the transition to full implementation of that provision.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (the Modernization Act). Section 127 of the Modernization Act, which adds section 503A to the Federal Food, Drug, and Cosmetic Act (the act), clarifies the status of pharmacy compounding under Federal law. Under section 503A, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) the adulteration provision of section 501(a)(2)(B) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (concerning the approval of drugs under new drug or abbreviated new drug applications). To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements, some of which are to be the subject of FDA rulemaking or other actions.

Section 503A of the act takes effect on November 21, 1998, one year after the date of the enactment of the Modernization Act. FDA is working on several rules and other documents necessary to implement certain provisions of section 503A. This guidance describes FDA's policy

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<sup>1</sup> This guidance has been prepared by the Pharmacy Compounding Steering Committee, which operates under the direction of the Office of the Center Director in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on enforcement of section 503A of the Federal Food, Drug, and Cosmetic Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) <http://www.fda.gov/cder/guidance.htm>.

on enforcement of section 503A until these preliminary implementation efforts, described below, are completed. The provisions of section 503A that are not discussed in this guidance document may be implemented and subject to enforcement beginning on November 21, 1998. However, in the future, FDA intends to provide general regulations to further clarify some of these provisions.

## **II. THE AGENCY'S ENFORCEMENT PLAN FOR STATUTORY PROVISIONS REQUIRING IMPLEMENTING REGULATIONS OR OTHER AGENCY ACTION**

### **A. Bulk Drug Substances List: Section 503A(b)(1)(A)**

Section 503A(b)(1)(A) restricts the universe of bulk drug substances that a compounder may use. The section provides, in relevant part, that every bulk drug substance used in compounding (1) must comply with an applicable and current United States Pharmacopeia (USP) or National Formulary (NF) monograph, if one exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug; or (3) if a monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug, it must appear on a list of bulk drug substances that may be used in compounding that is developed and issued by FDA through regulation (the bulk drugs list).

To date, 30 bulk drug substances have been nominated and are under consideration for inclusion on the bulk drugs list: bismuth citrate; caffeine citrate; cantharadin; choline bitartrate; diloxanide furoate; dimercapto-1-propanesulfonic acid; ferric subsulfate; ferric sulfate hydrate; glutamine; guaiacol; iodoform; metronidazole benzoate; myrrh gum tincture; phenindamine tartrate; phenyltoloxamine dihydrogen citrate; piracetam; sodium butyrate; taurine; thymol iodide; tinidazole; 4-aminopyridine; betahistine dihydrochloride; cyclandelate; 3,4-diaminopyridine; dinitrochlorobenzene; diphenylcyclopropanone; hydrazine sulfate; pentylenetetrazole; silver protein mild; and squaric acid dibutyl ester. Other bulk drug substances may be nominated in the future for inclusion on the bulk drugs list (see April 7, 1998, call for nominations, 63 FR 17011).

FDA will not have addressed all of the substances nominated for inclusion on the list by the time section 503A of the act becomes effective. In addition, FDA also anticipates that for a period of time after section 503A takes effect, as the compounding community becomes more familiar with the requirements of this provision, additional bulk drug substances will be nominated for inclusion on the list. To make the transition easier for patients and health care practitioners, FDA is adopting the enforcement policy described below.

*1. Substances Nominated On or Before November 21, 1999.*

For bulk drug substances that have already been nominated for inclusion on the list (the 30 bulk drug substances listed above), or for bulk drug substances that are nominated on or before November 21, 1999 (see April 7, 1998, call for nominations, 63 FR 17011), FDA intends to exercise its enforcement discretion. FDA will not normally take regulatory action against a drug product that has been compounded with a bulk drug substance that has been nominated for inclusion on the bulk drugs list while the substance is being evaluated, as long as the compounding complies with the other effective requirements in section 503A and does not appear to present a significant safety risk. FDA will consider a substance to be under evaluation from the time it is nominated until FDA takes final action by either including the substance on the list published as a final regulation or issuing a letter to the nominator indicating that FDA has decided that the substance should not be included on the list. If FDA determines that a nominated substance should not be used in compounding while it is under evaluation because it appears to present a significant safety risk, the Agency will provide notice that the substance cannot be used in compounding prior to a final determination on its acceptability for use in compounding.

*2. Substances Rejected by the Agency and Then Renominated*

This exercise of enforcement discretion will not apply to substances that have been nominated and have been determined by the Agency to be unacceptable for use in compounding. Although the Agency will continue to entertain renominations supported by additional information not previously considered by the Agency, the substance may not be used in compounding during the second and subsequent evaluations of the nomination unless and until the substance is added to the bulk drugs list through a final rule.

*3. Substances Nominated after November 21, 1999*

FDA will continue to entertain nominations for additional bulk drug substances after November 21, 1999. However, drug products compounded using such substances will not qualify for the exemptions described under section 503A of the act unless and until the substance is added to the bulk drugs list through a final rule. FDA believes that this policy strikes an appropriate balance among the needs of patients, the healthcare practitioners, the compounding community, and congressional intent. FDA believes it is appropriate to allow ample time for the compounding community to become aware of the limitations in section 503A(b)(1) concerning the use of bulk drug substances and to nominate those substances that are likely to be included on the bulk drugs list. A one-year period to submit additional nominations, in addition to the year that has already passed, should be sufficient for this purpose. FDA also recognizes that Congress intended that, at some point in time, the requirements for use of bulk drug substances in section 503A(b)(1) would take effect and be enforced. FDA believes that this enforcement policy

appropriately balances these competing considerations.

**B. Withdrawn/Removed List: Section 503A(b)(1)(C)**

Section 503A(b)(1)(C) of the act prohibits a licensed pharmacist or licensed physician from compounding a drug product using drug products or components of drug products that appear on a list, published by the Agency in the *Federal Register*, of drug products that have been withdrawn or removed from the market because the drug products or the components of the drug products have been found to be unsafe or not effective.

In the *Federal Register* of October 8, 1998 (63 FR 54082), the Agency published a proposed rule listing drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective. Until this list is finalized and published in the *Federal Register* as a final rule, section 503A(b)(1)(C) of the act will not be implemented or enforced.

**C. Demonstrable Difficulties in Compounding: Section 503A(b)(3)(A)**

Section 503A(b)(3)(A) of the act provides that a drug product may only be compounded if it is not a drug product identified by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug products. The Agency is presently developing proposed regulations covering difficult-to-compound drug products. Until final regulations identifying demonstrably difficult-to-compound drug products are issued by the Agency, the provision will not be implemented or enforced by the Agency.

**D. Memorandum of Understanding: Section 503A(b)(3)(B)**

Section 503A(b)(3)(B) of the act provides that the compounded drug product must be compounded in accordance with either of the following:

1. It is compounded in a State that has entered into a memorandum of understanding with FDA addressing the interstate distribution of inordinate amounts of compounded drug products and providing for investigation by a State agency of complaints related to compounded drug products distributed outside such state.

*or*

2. It is compounded in a State that has no such memorandum of understanding but the licensed pharmacist, pharmacy, or physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.



The section also directs FDA, in consultation with the National Association of Boards of Pharmacy (NABP), to develop a standard memorandum of understanding (MOU) for use by States in complying with these provisions.

In consultation with the NABP, the Agency is currently developing a draft standard MOU on pharmacy compounding that would establish a cooperative program between FDA and State agencies that choose to enter into the MOU regarding the regulation of interstate distribution of compounded drug products. When this process is completed, the Agency will make the draft standard MOU available to the public for comment through publication in the *Federal Register*. Once the comment period has expired, the Agency will finalize the MOU and make it available to the States for their signature. Until at least 90 days after the standard MOU is finalized and made available to the States for their consideration and signature, the Agency intends to exercise its enforcement discretion and will not normally take regulatory action regarding the requirement in section 503A(b)(3)(B) that a licensed pharmacist, pharmacy, or physician distribute or cause to be distributed out of State no more than 5 percent of the total prescription orders dispensed or distributed.

## Pharmacy Compounding Questions and Answers<sup>1</sup>

### Bulk Drug Substances

#### Testing

**Question:** *Are compounders required under Section 503A of the Federal Food, Drug, and Cosmetic Act (the Act) to perform any tests to assure the quality of the bulk drug substances used to compound drug products?*

**Answer:** There are no tests that a compounding pharmacist is required to perform before using a bulk drug substance. Section 503A requires that if a bulk drug substance appears in the USP/NF, then it must meet the requirements of an applicable monograph. There is no such requirement for drug substances that appear on the FDA list because, by definition, there is no USP/NF monograph for these substances when the substance is added to the list. However, it is possible that the USP will develop monographs for any drug substances that appear on the FDA list.

#### Certificates of Analysis

**Question:** *Under Section 503A of the Act, bulk drug substances used in pharmacy compounding must be accompanied by a valid certificate of analysis. Is there an official regulatory definition of a valid certificate of analysis? If there is an official definition, what are the essential elements of the certificate of analysis? Would it be possible to require that the assay procedure be listed on the certificate of analysis?*

**Answer:** Currently, there is no official regulatory definition of a valid certificate of analysis. The agency is working on a definition, however, as part of the development of the general regulations for pharmacy compounding. Generally, a certificate of analysis is thought of as a piece of paper issued by either the manufacturer or distributor of a bulk drug substance that contains information relating to the manufacture and analysis of the bulk drug substance and may also contain other information. The agency is

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<sup>1</sup>This document has been prepared by the Pharmacy Compounding Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This document represents the Agency's current thinking on various issues related to pharmacy compounding. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

looking at several sources, including the draft Internationally Harmonized Guide for Active Pharmaceutical Ingredients, which address the types of information that should be included on a certificate of analysis.

Generally, acceptance criteria and analytical test results are included on a certificate of analysis. Sometimes, the analytical procedures (e.g., HPLC) are included but detailed descriptions of the procedures are not usually included. FDA is considering whether to require that the analytical procedures be included on a valid certificate of analysis.

### **FDA-Approval**

*Question: Are the drugs that are placed on the bulk drug substances list considered to be FDA-approved drugs?*

**Answer:** No. The drugs are placed on this list only for the purposes of meeting the provisions of Section 503A of the Food, Drug, and Cosmetic Act. Because FDA's assessment of the nominated bulk drug substances was far less extensive than the agency's ordinary evaluation of bulk drug substances as part of the new drug approval process, the inclusion of a drug substance on the bulk drugs list should not, in any way, be equated with an approval, endorsement, or recommendation of the substance by FDA. Nor should it be assumed that substances on the bulk drugs list have been proven to be safe and effective under the standards normally required to receive agency approval.

### **Registration/Good Manufacturing Practices**

*Question: Under Section 503A of the Act, bulk drug substances, the active ingredients used in compounding, must be manufactured in a facility registered with FDA under Section 510 of the Act. Are registered facilities required to follow current good manufacturing practice (CGMP)?*

**Answer:** Yes. Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) requires that all drugs be manufactured, processed, packed, and held in accordance with CGMP, regardless of whether they are manufactured in a registered facility. This applies to bulk drug substances used in compounding but not to finished compounded drug products that qualify for the exemptions in Section 503A of the Act.

Registration of a bulk drug manufacturer does not ensure, however, that the facility will be in compliance with CGMP requirements. FDA may inspect any manufacturer of a bulk drug substance. FDA is required by statute to periodically inspect registered facilities to determine whether

they are in compliance with CGMP.

### **Compounded Drug Products**

**Question:** *Is FDA aware of any data that addresses prescribing trends for compounded drug products over the past five years?*

**Answer:** FDA does not collect or maintain such data. These data may be available from independent sources.

**Question:** *Are there any quality control or testing requirements for finished compounded drug products, especially extended-release and parenteral products?*

**Answer:** Currently, there are no federal requirements that compounded drug products be tested. However, some States may impose such requirements on certain products or classes of products. Quality control and testing requirements may be important for certain difficult to compound products or classes of products. These will be addressed by the Agency in a separate rulemaking, after consultation with the Advisory Committee and opportunity for public comment.

**Question:** *Is there a mechanism for the reporting and monitoring of adverse events for compounded drug products?*

**Answer:** There is a voluntary mechanism in place under the MEDWATCH system, in which health care professionals may voluntarily report drug product defects as well as adverse drug experience information. FDA has promulgated regulations for adverse event reporting under 21 CFR 314.80 and 310.305 for marketed prescription drug products. However, there are no regulations concerning adverse event reporting specifically directed to compounded drug products.

### **Investigational New Drugs**

**Question:** *What are the various options available from the FDA that allow patients with serious and life-threatening illnesses access to experimental or investigational drugs?*

**Answer:** The ideal mechanism for a patient to receive a promising but unproven drug is by participating in a controlled clinical trial. These trials provide many protections and benefits for the patient (e.g., IRB review, informed consent, free product or treatment and FDA review of pre-clinical data)

and maximize the gathering of useful information about the product which benefits the entire patient population. Controlled clinical trials are not always an option for all patients, and FDA believes that it is appropriate to help make certain promising, but unproven, products available to patients with serious and life-threatening illnesses. This should be accomplished in a manner that presents neither an unreasonable risk to the patient nor an unreasonable risk of losing valuable information about the effect of the drug.

The FDA Modernization Act (FDAMA) has codified certain FDA regulations and practices regarding expanded patient access to experimental drugs. The new legislation addresses three expanded access procedures: 1) emergency situations; 2) individual patient access to investigational products intended for serious diseases; and 3) treatment investigational new drug applications. The Agency is in the process of reviewing current regulations and practices to assure consistency with FDAMA. FDA has used a number of mechanisms to provide access to promising investigational therapies. These include: treatment INDs; treatment protocols; single patient INDs; emergency INDs; open label protocols; protocol exemptions; open label extensions; and parallel track.

Attachment 1 is an excerpt from a statement by then Lead Deputy Commissioner Michael A. Friedman, M.D. (before the Committee on Government Reform and Oversight, U.S. House of Representatives) that explains the above mentioned mechanisms in detail. In addition, a copy of 21 CFR 312.34-312.36 (Attachment 2) explains procedures for obtaining a treatment use IND and emergency IND.

FDA undertook these initiatives after careful consideration of suggestions and advice offered by cancer patients and their advocates, pharmaceutical industry representatives, and physicians and researchers about how to speed access to cancer therapies. FDA's goal is to improve significantly patient access to promising cancer treatments without compromising patient safety or the requirement that marketed drugs be proven safe and effective before they are sold.

### III. EXPANDING ACCESS TO INVESTIGATIONAL PRODUCTS

The ideal mechanism for a patient to receive a promising but unproven drug is as a participant in a controlled clinical trial. Such trials provide a range of patient protections and benefits (for example, IRB review, informed consent, free product or treatment, and FDA review of pre-clinical data) and maximize the gathering of useful information about the product thereby benefitting the entire patient population. It is not always possible, however, for all such patients to enroll in controlled clinical trials. In this situation, FDA believes that it is possible, and appropriate, to help make certain promising, but unproven, products available to patients with serious and life-threatening illnesses. This should be done in a way that poses neither an unreasonable risk to the patient nor an unreasonable risk of losing valuable information about the effect of the drug.

While the phrase "compassionate use" is commonly used to describe some of the ways of making unapproved products available, there is no FDA regulation or policy defining a "compassionate use." Compassion, however, should be, and is, an element of all our activities. FDAMA has codified certain FDA regulations and practices regarding expanded patient access to experimental drugs and devices. The new legislation addresses three expanded access procedures with respect to: 1) emergency situations; 2) individual patient access to investigational products intended for serious diseases; and 3) treatment investigational new drug applications and treatment investigational device exemptions. The Agency is in the process of reviewing current regulations and practices to assure coordination with FDAMA. There are a number of mechanisms FDA has used to provide access to promising investigational therapies. These mechanisms fall under a variety of terms, including: treatment INDs; treatment protocols; single patient INDs; emergency INDs; open label protocols; protocol exemptions; continued availability of investigational devices; special exceptions; open label extensions; parallel track; emergency use of unapproved medical devices; and treatment Investigational Device Exemptions (IDE).

#### A. Treatment INDs or Treatment Protocols

As noted, the most useful mechanism for access to unapproved drug or biologics therapies is for patients to be enrolled in a

controlled clinical trial under an IND which may benefit patients' health as well as contribute to the data necessary to determine whether the drug or biologic is sufficiently safe and effective to merit final marketing approval. Some patients who might benefit from access to an investigational new drug, however, might not be enrolled in a controlled clinical trial. If there is sufficient evidence available to provide a reasonable basis for concluding that the drug or biologic may be safe and effective for patients with a serious or immediately life-threatening disease, one mechanism through which patients can have access to the drug or biologic prior to approval is a treatment protocol or treatment IND.

The most explicit expanded access mechanism in the regulations is the treatment IND or treatment protocol. The final rule on treatment protocols or treatment INDs was issued in 1987 and is found at 21 CFR Section 312.34. These regulations were codified in FDAMA. This mechanism is intended explicitly to facilitate the availability of promising new drugs and biologics to desperately ill patients as early as possible in the development process before general marketing begins.

Although a primary purpose of a treatment IND is to allow treatment, this mechanism also is intended to obtain additional data on the drug's safety and effectiveness under certain criteria: the drug must be for a serious or immediately life-threatening disease; the available data must provide a reasonable basis for concluding that the drug or biologic may be effective for its intended use; there must be no comparable treatment alternative; the controlled clinical trials of the drug or biologic must be completed or underway; and the sponsor must actively be pursuing marketing approval.

Since the treatment IND procedures were developed, FDA has designated 40 drug or biologic investigational products for such early availability, and 36 of the products have proceeded to marketing approval or licensure under NDAs or product license applications (PLAs). Of the products approved, 11 have been for cancer, 11 for AIDS or AIDS-related conditions, and the remainder for a wide variety of other severely debilitating and life-threatening diseases, including obsessive compulsive disorder, severe Parkinson's Disease, multiple sclerosis, respiratory distress syndrome in infants, Gaucher's disease, diabetes, amyotrophic lateral sclerosis or ALS (Lou Gehrig's disease), and others.

#### B. Single Patient/Compassionate INDs

As early as 1968, an FDA mechanism, informally known as a "compassionate use" study, provided patients who were not participating in the controlled clinical trials access to investigational drugs. The "compassionate use" study could be

conducted either under a separate or existing IND. Such studies were not formal controlled trials, but they permitted use of an investigational drug under a protocol for an individual patient or patients, or for an early exploration of a novel idea. As noted previously, FDAMA addresses expanded access to unapproved therapies in emergency situations and in the case of individual patients who seek access to investigational products intended for serious diseases. An FDA working group is reviewing existing regulations and practice to assure coordination with FDAMA. Currently, the mechanisms used to provide expanded access include: single patient/single use IND, an emergency use IND, an open label protocol, or an open label extension. The term emergency IND refers to single patient uses for which there is not enough time for the treating doctor to file the required IND paperwork before administering the investigational product. In such cases, FDA can authorize the use of the product over the phone.

Under current practice, single patient/single use (non-emergency) and emergency INDs often are allowed to proceed when a physician determines that a particular unapproved therapy might be of benefit to a particular patient under his or her care for whom other options do not exist. For a treating physician to administer an unapproved product to a patient, the following conditions are necessary: a) the patient must be informed about the relevant circumstances about the drug and consent to take the product; b) the physician must be properly licensed and she/he must agree to administer the product and be responsible for monitoring and reporting data on the patient's use of the product to the sponsor; c) the IRB must approve the proposed single investigation (note that in emergency situations, the physician may notify the IRB promptly but after treating the patient); and d) the manufacturer/sponsor must be willing to provide the product without charge (unless the sponsor has applied for and FDA has allowed charges for cost recovery). Each of these conditions is critical to maintaining the dual goals of providing the patient with a promising product, and protecting the patient from potentially unsafe or ineffective products. There is a minimal amount of paperwork required to process a request for a single patient or emergency use IND.

Emergency INDs are treated as matters of medical urgency and are intended to be handled expeditiously by FDA. In the vast majority of emergency INDs, FDA renders a decision on such requests within a few hours. There are some rare exceptions when the particular therapy is completely unknown and may require additional information. These usually are approved within 48 hours.

For certain unapproved products, FDA has set up internal procedures to facilitate single patient IND requests. One example of this is the process for single patient IND requests



for thalidomide. Physicians are put in touch with a consumer safety officer within the relevant reviewing division; the consumer safety officer helps the physician understand the IND process to facilitate completion of the IND application. Some of the information required includes the name of the drug supplier, the patient's disease history and prior therapies, a detailed protocol of treatment, the patient's informed consent, and the investigator's qualifications.

### C. Open Label Protocol

Patients may be able to gain access to an unapproved product through what is termed an open label protocol. An open label protocol allows patients to receive the drug while some safety information is collected, but these patients have no control group. In effect, these are similar to single patient INDs, but multiple individuals can be processed through one general request by the drug sponsor. When many patients are in need of an unapproved therapy and the above-mentioned conditions pertain [e.g., a physician judges that a particular unapproved therapy might be of benefit to a particular patient for whom other options do not exist; there is sufficient evidence of safety and effectiveness to support the use of the investigational product; and the sponsor of the unapproved new drug or biologic has agreed to provide the drug free of charge (unless the sponsor has applied for, and FDA has allowed charges for cost recovery)] the drug or biologic may be available through the open label protocol.

Many thousands of patients have received unapproved therapies by this means. For example, there have been several large open label protocols for anti-retroviral drugs (e.g., anti-HIV drugs) which have involved tens of thousands of patients.

Open label extensions provided another mechanism for gaining access to unapproved products. These extensions enable those patients who received a therapeutic response during a controlled clinical trial under an IND that has ended to continue the investigational drug treatment.

There are a number of situations in which a patient who wants access to an unapproved drug is unable to receive the drug. In many cases a sponsor is unwilling to provide the product. Patients sometimes are confused by this situation and misinterpret a company's unwillingness to provide the product as an FDA action. Much less frequently, the cause may be FDA's concern about the risk to patients because of the nature of the product. Generally, if a physician makes the request and a sponsor agrees to provide the product, FDA does not object to the study proceeding.

At times, there may be relatively little evidence supporting the usefulness of the drug for the particular indication, but its use may be considered appropriate because there is no alternative for the particular condition. Physicians may always contact FDA to propose such a use for a specific patient when they believe circumstances warrant. Of course, the company still has to make the product available before a patient can gain access.

#### **D. Protocol Exception/Exemptions**

In cases where a patient cannot be enrolled in a protocol because of some factor that makes the patient ineligible to participate in the study, research sponsors or investigators often can make a protocol exception to enroll a patient without including the data on that patient in the report of the results from the controlled study participants. This mechanism is sometimes referred to as a special exception.

#### **E. Parallel Track**

Another mechanism, parallel track, is an FDA policy that was formally announced in the Federal Register in 1992 (53 Federal Register 13250, April 15, 1992). This policy allows promising investigational drugs for AIDS and other HIV-related diseases to be made more widely available under "parallel track" protocols while the controlled clinical trials are carried out. The purpose of the parallel track mechanism is to permit access to unapproved drugs for people with AIDS and HIV who are not able to take standard therapy, or for whom standard therapy is no longer effective, and who are not able to participate in an ongoing controlled clinical trials. Included in this mechanism is the possibility of having a National Institutional Review Board to review the ethical access to these products.

There has been one large parallel track program since the policy was implemented that included 12,000 patients. Other anti-HIV drugs have been made available by the open protocol mechanism, as noted above. Given the accelerated rate of approval for many drugs for people with AIDS and HIV and the availability of open label studies, it has not been necessary to use this process in recent years.

#### **IV. ACCESS TO MEDICAL DEVICES**

Although the Committee has asked that we concentrate on access to drugs and biologics, we feel that a complete picture requires an overview of other FDA mechanisms to permit access to promising investigational products. Similar procedures for access exist in the Center for Devices and Radiological Health (CDRH) which allow access to investigational devices. Under the CDRH "Continued Availability of Investigational Devices" policy, FDA has worked with sponsors and investigators to facilitate treatment use of

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(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under §312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 6862, Feb. 11, 1998]

EFFECTIVE DATE NOTE: At 63 FR 6862, Feb. 11, 1998, §312.33 was amended by revising paragraph (a)(2), effective Aug. 10, 1998. For the convenience of the user, the superseded text is set forth as follows:

## §312.33 Annual reports.

\* \* \* \* \*

(a) \* \* \*

(2) The total number of subjects initially planned for inclusion in the study, the number entered into the study to date, the num-

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ber whose participation in the study was completed as planned, and the number who dropped out of the study for any reason.

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## §312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a treatment protocol under the provisions of this section.

(b) *Criteria.* (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the

ease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) *Serious disease.* For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.

(3) *Immediately life-threatening disease.*  
(1) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:

(A) May be effective for its intended use in its intended patient population; or

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(ii) For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(c) *Safeguards.* Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.

(d) *Clinical hold.* FDA may place on clinical hold a proposed or ongoing

treatment protocol or treatment IND in accordance with §312.42.

[52 FR 19476, May 22, 1987, as amended at 57 FR 13248, Apr. 15, 1992]

#### §312.35 Submissions for treatment use.

(a) *Treatment protocol submitted by IND sponsor.* Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall submit to FDA a treatment protocol under §312.34 if the sponsor believes the criteria of §312.34 are satisfied. If a protocol is not submitted under §312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under §312.34. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

- (i) The intended use of the drug.
- (ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.
- (iii) A brief description of the criteria for patient selection.
- (iv) The method of administration of the drug and the dosages.
- (v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:

- (i) Informational brochure for supplying to each treating physician.
- (ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.
- (iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR part 50.

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(3) A licensed practitioner who receives an investigational drug for treatment use under a treatment protocol is an "investigator" under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR parts 50 and 56.

(b) *Treatment IND submitted by licensed practitioner.* (1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA 1571) meeting §312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with §312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.

(iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.

(v) A statement of the practitioner's qualifications to use the investiga-

tional drug for the intended treatment use.

(vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) Agreement to report to FDA safety information in accordance with §312.32.

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR parts 50 and 56.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 19477, May 22, 1987, as amended at 57 FR 13249, Apr. 15, 1992]

### §312.36 Emergency use of an investigational new drug.

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with §312.23 or §312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. For investigational biological drugs, the request should be directed to the Division of Biological Investigational New Drugs (HFB-230), Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892, 301-443-4864. For all other investigational drugs, the request for authorization should be directed to the Document Management and Reporting Branch (HFD-53), Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4320. After normal working hours, eastern standard time, the request should be directed to the FDA Division of Emergency and Epidemiological Operations, 202-357-3400. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon

as practicable after receiving the authorization.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990]

**§312.38 Withdrawal of an IND.**

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with §312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

**Subpart C—Administrative Actions**

**§312.40 General requirements for use of an investigational new drug in a clinical investigation.**

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in

the IND are subject to a clinical hold under §312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

**§312.41 Comment and advice on an IND.**

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under §312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

**§312.42 Clinical holds and requests for modification.**

(a) *General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to

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# **Pharmacy Compounding Advisory Committee**

## **Public Meeting**

**May 6-7, 1999**

### **Volume 2**

**Dinitrochlorobenzene  
Diphenylcyclopropenone  
Squaric Acid Dibutyl Ester  
4-Aminopyridine and 3,4-Diaminopyridine**

**Advisory Committee Conference Room, 1066  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852**

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# Pharmacy Compounding Advisory Committee

May 6-7, 1999  
Advisory Committee Conference Room, 1066  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852

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## Background Materials

### Table of Contents

#### Volume 2

#### Drug Substances Nominated for the Bulks List

Volume 2 contains documentation regarding the following bulk drug substances nominated for inclusion on the list of bulk drugs acceptable for pharmacy compounding that will be discussed at the meeting. Most of the documentation was compiled by the review divisions responsible for these drugs.

- Dinitrochlorobenzene
- Diphenylcyclopropanone
- Squaric Acid Dibutyl Ester
- 4-Aminopyridine and 3,4-diaminopyridine





**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
Public Health Service  
Food and Drug Administration, Center for Drug Evaluation and Research  
Division of Dermatologic and Dental Drug Products, HFD-540

**Date:** March 16, 1999

**Subject:** Review of Dinitrochlorobenzene, a Candidate for the  
Pharmacy Compounding Bulk List, With Selected References

**To:** Pharmacy Compounding Steering Committee

**From:** Primary Reviewers

James D. Vidra, Ph.D., Chemistry *JDV, 3/17/99*  
Paul C. Brown, Ph.D., Pharmacology *PCB 3/17/99*  
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Director, Office of Drug Evaluation V  
Robert J. DeLap, M.D., Ph.D. *RD 3/29/1999*

**HFD-540 Review of Dinitrochlorobenzene**  
For the FDA Pharmacy Compounding Advisory Committee

**Prepared by:** Paul C. Brown, Ph.D.  
Markham C. Luke, M.D., Ph.D.  
Martin M. Okun, M.D., Ph.D.  
James D. Vidra, Ph.D.

**Date prepared:** January 4, 1999

**Revised:** March 26, 1999

**I. Introduction**

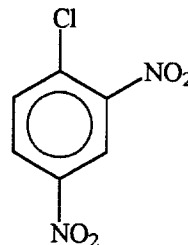
The Division of Dermatologic and Dental Drug Products (HFD-540) has been charged with the review of dinitrochlorobenzene (DNCB) for two indications: alopecia areata and verruca vulgaris (warts). Only published information from the literature was used in the preparation of this review.

**II. Chemical Characterization of DNCB**

**Identity**

*2,4-Dinitro-1-Chlorobenzene*  
*1-Chloro-2,4-Dinitrobenzene*  
**DNCB**

<i>CAS #</i>	<i>97-00-7</i>
<i>Molecular Weight</i>	<i>202.55</i>
<i>Molecular Formula</i>	<i>C<sub>6</sub>H<sub>3</sub>ClN<sub>2</sub>O<sub>4</sub></i>
<i>Melting Point</i>	<i>53°C</i>
<i>Boiling Point</i>	<i>315°C</i>
<i>Solubilities</i>	<i>Insoluble in Water</i> <i>Slightly Soluble in Ethanol</i> <i>Soluble in Ether &amp; Benzene</i>



The available chemistry information on 2,4-dinitro-1-chlorobenzene, or DNCB, confirms the Federal Register's conclusion (Federal Register, January 7, 1999) that DNCB is a well-characterized molecule.

**Stability**

Dinitrochlorobenzene is considered stable under normal temperature and pressure conditions. However, when heated, it decomposes into toxic fumes of hydrogen chloride, chlorine gas, nitric oxides, carbon monoxide and carbon dioxide. DNCB is incompatible with strong

oxidizing agents and alkaline bases and reacts violently with hydrazine hydrate or hydrazine sulfate.

### **Synthesis and Purity**

There are at least four synthetic routes for DNCB, using various starting materials (1-chloro-4-nitrobenzene, 1-chloro-2-nitrobenzene, chlorobenzene or 1,3-dinitrobenzene). Multiple impurities (see safety section) have been identified in bulk DNCB from various sources (Wilkerson, 1983).

**Assessment 1: Although the chemical DNCB is well characterized, its impurity profile in the bulk substance may differ depending upon the route of synthesis. The acceptability of any lot of bulk for compounding should be based on knowledge of the level of the 1-chloro-4-nitrobenzene and 1-chloro-2-nitrobenzene impurities. DNCB used in compounding could vary significantly from DNCB used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.**

## **III. Safety of DNCB**

### **A. Animal Toxicology**

DNCB and some impurities frequently found in commercial DNCB are mutagenic in the Ames assay (Kratka et al., 1979; Strobel & Röhrborn, 1980; Summer & Göggemann, 1980; Black et al., 1985; Wilkerson et al., 1988; Gupta et al., 1997). This mutagenicity appears to be due to the direct interaction of the compounds with DNA and does not require metabolic activation. In fact, metabolism appears to decrease the mutagenicity of DNCB. DNCB is genotoxic by sister chromatid exchange in human skin fibroblasts *in vitro* at the lowest dose tested of 2.5  $\mu\text{M}$  or 0.00005% (DeLeve, 1996). DNCB is also effective at causing the transformation of Syrian hamster kidney cells *in vitro* (Strobel & Röhrborn, 1980).

1-Chloro-2-nitrobenzene and 1-chloro-4-nitrobenzene, which are impurities of DNCB, caused significant increases in multiple tumor types when fed to mice (Weisburger et al., 1978). DNCB did not cause tumors in mice or rats in an 18-month feeding study (Weisburger et al., 1978). This study is difficult to interpret because the initial levels of DNCB fed to the animals were toxic and had to be reduced after only two months for the rats and four months for the mice. A further limitation of this study is that it was not conducted by the clinical route of exposure. As stated by DeLeve, "since the proposed clinical use is topical, it would perhaps be more pertinent to study the carcinogenicity of topically applied drug. Particularly in a drug that is less mutagenic in the presence of a metabolic activating system, the first pass effect of an orally administered drug may lead to a quite different outcome than topical application." DNCB is rapidly conjugated to glutathione and might be largely metabolized by first-pass metabolism when administered in the diet.

In addition to inducing contact hypersensitivity, DNCB is also an acute skin irritant in animal models. For example, DNCB in acetone at concentrations of 1 to 10% causes mild to

moderate irritation in mouse skin (Helman et al., 1986). DNCB also causes a rapid decline in the glutathione concentration of the skin after topical application (Summer & Göggemann, 1980).

Topical DNCB has been shown to activate the LTR promoter of the human immunodeficiency virus (HIV) in transgenic mice (Morrey et al., 1993). Although this suggests that HIV positive individuals may face additional risks from DNCB treatment, plasma HIV RNA levels declined one-half to greater than one log in HIV-positive patients treated with topical DNCB (Stricker et al., 1997).

**Assessment 2: DNCB is genotoxic and two of its impurities are carcinogenic in mice. Reproductive toxicity and chronic toxicity studies of DNCB have not been conducted. Thus, it is not known what the potential toxicities of DNCB are in humans or whether it is likely to be teratogenic in humans.**

## **B. Human Safety**

There are no published reports of studies designed to systematically evaluate the safety of DNCB. In a comprehensive review of immunomodulatory therapy, Naldi et al. (1990) determined that the discussion of side effects was adequate in only four of thirteen trials involving dinitrochlorobenzene.

Although not always adequately characterized, the adverse events described in clinical studies reporting the use of DNCB for treatment of alopecia areata and warts have included: burning sensation at application site, dermatitis (localized to the application site or generalized), pruritus, painful/tender cervical lymphadenopathy, urticaria, vitiligo, shivering, insomnia, arthralgias, psoriatic flares, headaches. Burning sensation and dermatitis are commonly described, but it is difficult to assess the frequency of the other adverse events because that information is not included in most clinical study reports.

It is difficult to draw conclusions about the long-term adverse event profile of DNCB because so few of the clinical studies had long-term follow-up of patients after treatment was discontinued: only 135 patients (mostly adults) received follow-up for longer than 6 months. One indirect measure of the frequency of severe adverse events is the fraction of patients who withdrew from clinical studies because of adverse reactions to DNCB: in the study reports that discussed withdrawals, 52 of 454 patients (11%) withdrew. The majority of reported adverse events appear to have resolved upon discontinuation of therapy. The absence of long-term adverse event information is even more unsettling for the pediatric age population, as warts and alopecia areata are diseases that afflict patients in this age group. *The likelihood of detecting an increased cancer incidence in the DNCB-treated population is lower if a relatively small number of patients receive long-term follow-up.*

DNCB is significantly absorbed through the skin. In one study four human subjects were treated topically with C<sup>14</sup>-labeled DNCB dissolved in acetone. An average of 53% of the applied C<sup>14</sup> was detected in the urine over the 5 days after application (Feldmann & Maibach, 1970).

Because DNCB and other cross-reacting nitrobenzene compounds are used in the chemical and agricultural industries, there is a risk that workers in these industries who are sensitized to DNCB will develop occupational disease. Physicians and other health care workers including compounding pharmacists are at risk for DNCB sensitization. Persons handling the drug should exercise contact precautions and be careful not to inhale these potent sensitizers, as even trace amounts can cause severe allergic reactions. Unwitting exposure and re-exposure can lead to an unwanted adverse reaction that is similar to exposure to poison ivy (the mechanism of action for poison ivy sensitization and sensitization with DNCB are thought to be similar).

**Assessment 3: There is limited characterization of the human safety profile. In addition, since there is significant transcutaneous absorption, systemic safety cannot be assured.**

Available alternative approved therapies for alopecia areata include intralesional, topical, and systemic corticosteroids.

Available alternative approved therapies for verruca vulgaris include podophyllin, imiquimod, and salicylic acid. Other well-accepted modalities with excellent safety include ablation using cryotherapy or laser treatment.

**Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.**

#### **IV. Historical Use of DNCB in Pharmacy Compounding**

Although the use of DNCB was originally embraced by the dermatologic community, the use of this compound has significantly decreased during the past decade. The first report of the use of DNCB for the treatment of a dermatosis (parapsoriasis en plaques) was reported in 1971. Dr. Henry Lewis is credited with first suggesting the use of DNCB for treatment of plantar warts at the American Academy of Dermatology meeting in December, 1972 (Greenberg). Rosenberg and Drake are credited with first suggesting the use of DNCB for treatment of alopecia areata: they reported in 1976 the results from a case study that was conducted in 1974 (Rosenberg and Drake). Happle, who was among the first to recommend DNCB for the treatment of alopecia areata, subsequently regarded it as unacceptably hazardous (as a mutagen) in its present impure form (de Prost et al.). No studies describing the use of DNCB for treatment of warts have been published since 1993 (Choi et al.). The most recent study of the use of DNCB for treatment of alopecia areata was published in 1991 (Kalam et al.).

Numerous animal and human studies have demonstrated that dinitrochlorobenzene (DNCB) is a potent contact sensitizer. The ability of the vehicle to influence the strength of the sensitization reaction could have clinical relevance. If different vehicles were used from one treatment to the next, significant differences in the strength of the hypersensitivity reaction, and consequently the efficacy and adverse effects, could result. It has been investigated for topical immunotherapy of conditions such as warts and alopecia areata. The mechanism by which topical immunotherapy can improve these conditions is not known.

DNCB has been compounded into solution, cream, and ointment forms for topical use. In most published studies, DNCB is applied topically by a physician, podiatrist, or a trained staff member, in two phases. First, in the sensitization phase, DNCB allergy is induced in patients by sensitizing them to a comparatively high concentration of DNCB (usually a 2% acetone solution) applied to a 10 to 16 cm<sup>2</sup> area on one side of the scalp (for alopecia areata patients), or forearm, or back (reviewed by Rokhsar et al., 1998). Once patients are sensitized, in the elicitation phase they are exposed to a much lower concentration of DNCB applied to lesional skin. Caution must be exercised to avoid a severe blistering response, but the therapeutic desideratum is to induce a brisk allergic dermatitis, with erythema, edema, and weeping.

In 1998, Rokhsar et al. examined the use of contact sensitizers in alopecia areata in a summary review of the literature. With regard to DNCB, the authors of the review state that, "The presence of high degrees of other mutagenic contaminants, along with a 65% absorption rate through the skin and ultimate excretion in the urine, has convinced most clinicians to abandon the use of the chemical in humans."

**Assessment 5: Evidence of widespread and long-standing use of DNCB for the treatment of alopecia areata and verruca vulgaris is not apparent. Reports of the use of DNCB have declined in recent years, even in reviews of immunomodulatory treatments.**

## **V. Available Evidence of Effectiveness or Lack of Effectiveness**

Alopecia areata and warts frequently resolve without any therapeutic intervention. For example, in a study of the natural history of alopecia areata, of 63 alopecia areata patients followed for one year without treatment, hair had regrown in all but 4 patients in one year, and in all but 1 patient after two years. The great majority had regrown hair by 3 months after their only office visit (Arnold, 1952). Alopecia areata with less than 25% involvement has a high incidence of spontaneous recovery, whereas more severe involvement has a lesser rate of recovery (Moschella and Hurley, 1992). Regarding the natural history of warts, a two-year study showed that two-thirds of warts regressed without treatment (Massing and Epstein, 1963).

Warts, caused by cutaneous infection with the human papillomavirus, are another very common dermatological ailment. Aside from the cosmetic disfigurement caused by warts, patients seek treatment for these lesions because plantar (foot) warts may cause pain on walking or interfere with gait, and warts on the fingers may interfere with manual dexterity. As with alopecia areata, therapy is not always effective.

Several problems exist with published clinical studies. Due to the high incidence of spontaneous recovery, a control arm is necessary to accurately evaluate experimental therapies such as DNCB. However, all but two of the reviewed clinical efficacy studies were either uncontrolled or internally controlled. Studies that demonstrate a "positive" result, such as enhanced resolution of disease, are more likely to be submitted for publication or published than are studies with "negative" results. Therefore, the published literature may overstate the efficacy

of novel therapies. Additionally, most clinical studies lack long-term follow-up, so the lasting treatment benefits cannot be evaluated.

### Warts (Verruca)

Thirteen published clinical studies on the use of DNCB for treatment of verruca in the English language literature have been reviewed (see Table 1). Ten were uncontrolled studies, while three (Goihman-Yahr et al., Dunagin and Millikan, and Shah et al.) were internally controlled. Among the internally controlled studies, one did not specify the clearance rate of untreated warts. In the other two studies, the untreated wart clearance rate was not significantly different from the treated wart clearance rate. One explanation for the lack of difference in the response rate may be that patients become sensitized to wart hapten as a consequence of topical immunotherapy, and therefore mount an immune responses against all verruca. The absence of a control arm precludes any definitive comparisons with other modalities.

**Table 1 - Use of DNCB in Human Papillomavirus Infection**

Author	Journal	Year	N	Treatment Length	Percentage of Patients with Complete Resolution of Treated Lesions/ITT
Greenberg et al.	Arch. Dermatol.	1973	5	One or two applications	80%
Lewis	Cutis	1973	85	2 months to 17 months	79%
Goihman-Yahr et al.	Lancet	1978	10	Up to 1 year	100% (80% of untreated side)
Bekhor et al.	Aust. J. Dermatol.	1978	13	Up to 1 year	69%
Buckner and Price	Br. J. Dermatol.	1978	51	Up to 42 weeks	45%
Eriksen	Dermatologica	1980	63	Not specified	80%
Sanders and Smith	Cutis	1981	84	Not specified	82%
Dunagin and Millikan	J. Am. Acad. Dermatol.	1982	30	Up to 6 months	70% (clearance rate of untreated warts not specified)
Grayson et al.	J. Am. Pod. Assoc.	1982	10	2 to 10 weeks	60%
Lee et al.	Int. J. Dermatol.	1984	59	Not specified	78%
Georgala et al.	Australas. J. Dermatol.	1989	15	6 to 8 weeks	87%
Shah et al.	J. Dermatol.	1991	50	1 to 24 weeks	54% of treated lesions, 38% of control lesions (not statistically significant)
Choi et al.	J. Dermatol.	1993		Up to 20 weeks	67%

### Alopecia areata

Alopecia areata is a nonscarring loss of hair, that, depending upon its severity, can affect patches of scalp, the entire scalp (alopecia totalis), or the entire body (alopecia universalis). The etiology of this illness is unknown. Alopecia areata is a relatively common dermatologic disease that is associated with functional impairment, especially if eyebrows or eyelashes are lost, and with cosmetic disfigurement.

Eleven published clinical studies on the use of DNCB for treatment of alopecia areata in the English language literature have been reviewed. The treatment outcomes for the different categories of alopecia areata [i.e., alopecia areata (AA), alopecia totalis (AT), and alopecia universalis (AU)] have been listed when such information was available from the publication:

**Table 2 – Use of DNCB in Alopecia Areata, Alopecia Totalis, Alopecia Universalis**

Author	Journal	Year	N	Treatment Length	Response/ITT	Cosmetically Acceptable Response/ITT	Permanent, Cosmetically Acceptable Response/ITT
Happle and Echternacht	Lancet	1977	43	Not specified	AA: 95% AT: 61%	Not specified	0%
Frentz and Eriksen	Acta Dermatovener	1977	10	Twelve weeks	AT: 30%	Not specified	Not specified
Breullard and Szapiro	Lancet	1978	30	Not specified	67%	Not specified	0%
Happle et al.	Arch. Dermatol.	1978	90	4-23 months	Not specified	AA: 90% AT: 71%	Not specified
Daman et al.	Arch. Dermatol.	1978	26	Not specified	AA: 61% AU/AT: 63%	AU: 67%	Not specified
Friedmann	Lancet	1979	24	3 to 6 months	AA: 91% AT/AU: Not specified	AA: 55% AT/AU: 0%	AA: 36%
Warin	Lancet	1979	8	Up to 40 weeks	38%	13%	0%
Friedmann	Br. J. Dermatol	1981	51	3 to 9 months	53%	AA: 23% AT: 0%	AA: 23%
de Prost et al	Arch Dermatol	1982	42	3 to 30 months	62%	AA: 10% AT: 22% AU: 23%	AA: 10% AT: 22% AU: 23%
Temmerman et al	Acta Derm Venereol	1984	30	3 months to 2 years	67%	AA: 21% AT: 8% AU: 0%	AA: 7% AT: 8%
Valsecchi et al.	Acta Derm Venereol	1986	51	Not specified	AA: 82% AT: 50% AU: 15%	Not specified	AA: 46% AT: 30% AU: 8%
Kalam et al	J. Indian Med. Assoc	1991	50	3-6 months	72%	Not specified	Not specified

Examination of these publications suggests: (1) outcomes are better among patients with limited disease (who have a higher rate of spontaneous regrowth) than for patients with alopecia universalis/totalis; and (2) a very small fraction of patients have permanent, cosmetically acceptable regrowth.

Naldi et al. (1990) reviewed the clinical trials on dinitrochlorobenzene published between January 1977 and January 1988. The authors of the paper stated, "According to our evaluation,



the published literature is of limited use in defining the role of topical immunotherapy in alopecia areata. Half the studies examined used informal methods (uncontrolled or historically controlled trials)... In general, the studies that we examined had serious drawbacks in reporting critical procedures such as assessing treatment and selecting and following up patients... In conclusion, a definite role of topical immunotherapy for alopecia areata has yet to be established and this treatment should be offered only as an experimental modality..."

A tabular summary of the suggested role of immunomodulators (as gleaned from some of the leading dermatology textbooks) for the treatment of these disorders is presented below in Table 3. There exist many therapeutic alternatives for alopecia areata and warts. The general consensus is that DNCB may be too hazardous because of the positive Ames (bacterial mutagenicity) test.

**Assessment 6: There is little evidence that DNCB is effective in the treatment of alopecia areata or verruca. Treatment of alopecia areata with DNCB may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.**

**Table 3 - Perspectives on use of DNCB for Treatment of Alopecia Areata and for Warts**

Reference	Disease	Treatment of Choice	Other Suggested Treatments	Immunomodulator's Role in Therapeutic Armamentarium
<i>Andrews' Diseases of the Skin: Clinical Dermatology</i> , ed. by Arnold et al., Eighth edition (1990)	Alopecia Areata—patchy involvement	Intralesional injections of corticosteroids	“None of the other various therapeutic approaches are clearly superior to corticosteroids”	DNCB: “unacceptably hazardous (as a mutagen) in its present impure form”;
	Alopecia Areata—totalis/universalis	Systemic (IM) steroids should be “seriously considered”.		
	Common/Plantar Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M	SADBE is preferable to DNCB, to avoid carcinogenicity risk. “It (SADBE) may be worth trying in very large and resistant warts.”
<i>Dermatology in General Medicine</i> , ed. by Fitzpatrick et al., Fifth edition (1999)	Alopecia Areata	Treatment of choice not identified	N (little efficacy), P, Q, R	DPCP or SADBE can be very effective, but their use runs the risk of intolerable irritation if the dose titration is inappropriate
	Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K, T, U, V	DNCB: found effective in uncontrolled studies;
<i>Textbook of Dermatology</i> , ed. by Rook et al., Fifth Edition (1992)	Alopecia Areata	Treatment of choice not identified	O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z	Topical immunotherapy is considered a treatment option; authors do not discuss the relative merits of the topical immunomodulators
	Warts	Treatment of choice not identified	B, C, D, L, L', E, H, I, J, T, A', B', ; avoid A,U (risk of scarring)	DNCB: “impressive...on resistant warts but there is a risk of generalized sensitization reactions.”
Pediatric Dermatology, ed. by Schachner and Hansen, Second edition (1995)	Alopecia Areata	Topical corticosteroids, alone or under occlusion; Intralesional corticosteroids	O (for severe involvement, unresponsive to topical or intralesional treatment)	DNCB: risks include possible mutagenesis, chronic scalp irritation, generalized sensitization. “This form of therapy is currently not recommended.”
	Warts	Treatment of choice not identified	A, B, C, G, K	DNCB: use is discouraged

A: Electrodesiccation and curettage; B: Cryotherapy; C: Salicylic Acid; D: Lactic Acid; E: Trichloroacetic/ other caustic acids; F: Podophyllin; G: laser; H: 5-Fluoro-uracil; I: Retinoids; J: Interferon; K: Cantharin; L: Formalin; L': Glutaraldehyde; M: Bleomycin; N: Topical corticosteroids; O: Systemic corticosteroids; P: Intralesional corticosteroids; Q: Anthralin; R: PUVA (Psoralen and UV-A); S: Inosiplex; T: Bleomycin; U: Surgical excision; V: Vaccination with autogenous-wart extracts; W: Ultraviolet radiation; X: Minoxidil; Y: Dithranol; Z: Zinc sulfate; A': Levamisole; B': Photodynamic inactivation; C': Psychological methods (hypnosis)

similar to exposure to poison ivy (the mechanism of action for poison ivy sensitization and sensitization with SADBE are thought to be similar).

**Assessment 3: There is limited characterization of the human safety profile. Adverse side effects from exposure to SADBE include severe eczematous dermatitis, blistering, lymphoplasia and skin pigmentation changes.**

Available alternative approved therapies for alopecia areata include intralesional, topical, and systemic corticosteroids .

Available alternative approved therapies for verruca vulgaris include podophyllin, imiquimod, and salicylic acid. Other well-accepted modalities with excellent safety include ablation using cryotherapy or laser treatment.

**Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.**

#### **IV. Historical Use of SADBE in Pharmacy Compounding**

This agent is a strong topical sensitizer that is rarely used industrially, for example, in photographic emulsions as a stabilizer and antifog agent (Noster et al., 1976). SADBE was developed clinically largely due to the discovery of DNCB's potential mutagenicity. Clinical use of SADBE for the treatment of alopecia areata was first reported in 1980 (Happle et al., 1980).

Numerous animal and human studies have demonstrated that squaric acid dibutyl ester (SADBE) is a potent contact sensitizer. It has been investigated for topical immunotherapy of conditions such as warts and alopecia areata. The mechanism by which topical immunotherapy can improve these conditions is not known, however exposure to this agent in patients results in a clinical picture similar to that of exposure to poison ivy. Since abnormal cytokine patterns have been measured in the skin of patients with alopecia areata, it has been theorized that topical immunotherapy may restore the cytokine pattern to a more normal pattern or it may produce additional cytokines that antagonize the abnormal pattern. In the treatment of warts, topical immunotherapy has been theorized to stimulate an immune reaction to the human papilloma virus responsible for the warts. Other mechanisms may also exist.

SADBE is usually applied cutaneously in a health care provider's office by a physician (usually a dermatologist), podiatrist, or trained staff member. First, patients are sensitized with a 2% solution in acetone, applied to a 10 to 16 cm<sup>2</sup> area on one side of the scalp, or forearm, or back (Rokhsar et al., 1998). If a severe eczematous response does not occur at the initial sensitization site, a 0.0001 to 0.1% solution is applied to one side of the scalp (if the initial reaction is too severe, two weeks are allowed to elapse between the sensitization and elicitation phases and/or a lower concentration of the treatment solution is used). Caution must be exercised to avoid a severe blistering response.

## **VI. Conclusions**

**Assessment 1:** Although the chemical DNCB is well characterized, its impurity profile in the bulk substance may differ depending upon the route of synthesis. The acceptability of any lot of bulk for compounding should be based on knowledge of the level of the 1-chloro-4-nitrobenzene and 1-chloro-2-nitrobenzene impurities. DNCB used in compounding could vary significantly from DNCB used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

**Assessment 2:** DNCB is genotoxic and two of its impurities are carcinogenic in mice. Reproductive toxicity and chronic toxicity studies of DNCB have not been conducted. Thus, it is not known what the potential toxicities of DNCB are in humans or whether it is likely to be teratogenic in humans.

**Assessment 3:** There is limited characterization of the human safety profile. In addition, since there is significant transcutaneous absorption, systemic safety cannot be assured.

**Assessment 4:** Many approved products are available for the treatment of verruca and alopecia areata.

**Assessment 5:** Evidence of widespread and long-standing use of DNCB for the treatment of alopecia areata and verruca vulgaris is not apparent. Reports of the use of DNCB have declined in recent years, even in reviews of immunomodulatory treatments.

**Assessment 6:** There is little evidence that DNCB is effective in the treatment of alopecia areata or verruca. Treatment of alopecia areata with DNCB may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

## **VII. Recommendation:**

It is recommended that DNCB not be placed on the list of bulk drug substances for compounding. Placing DNCB on the list would increase the availability of a drug substance that is readily absorbed transcutaneously, that is genotoxic, and that contains variable amounts of impurities known to be carcinogenic in mice. Published clinical studies do not describe a sufficient number of patients (especially within the pediatric age group) who have long term follow-up without adverse events to quell the safety concerns raised by these nonclinical toxicology studies. There are other approved products that have been demonstrated to be safe and effective for the treatment of verruca and alopecia areata. Among clinicians who use immunomodulatory agents to treat these diseases, DNCB appears to have been eclipsed in recent years by other immunomodulatory agents, presumably because of safety concerns. In addition, there is minimal evidence that DNCB is effective in the treatment of these diseases.

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 3/23/99

To: Mary Jean Kozma-Fornaro, HFD-540  
Martin Okun, HFD-540

From: Katherine Laessig, M.D.  
CDER/ODE IV  
Division of Antiviral Drug Products

RE: dinitrochlorobenzene (DNCB) nomination for compounding

Background

DNCB has been nominated for inclusion on a list of bulk drug substances for use in pharmacy compounding and is therefore being evaluated by the Food and Drug Administration based on specific criteria of chemical characterization, safety, historical use, and evidence of effectiveness. The purpose of this consult is to document the historical use of DNCB in the treatment of HIV disease, and to evaluate the availability and quality of evidence of the effectiveness of DNCB in the treatment of HIV disease.

Summary of published data

The use of DNCB in the treatment of HIV disease has been neither widespread nor longstanding, and available evidence in the literature regarding its effectiveness is sparse. The theoretical benefit of DNCB is based on its ability to stimulate cellular immunity, thereby potentially counteracting some of the deleterious effects of HIV infection on the immune system. Proposed mechanisms of action include correction of the dysregulation between antigen-presenting cells and T cells, and amplification of the Th1 CD4 T-cell subset that regulates cell-mediated immunity. These immunologic changes could result in mobilization of cytotoxic CD8 T-cells and NK cells and control of HIV replication via elimination of virally infected cells, therefore slowing disease progression. Unfortunately, the limited available data do not support these suppositions.

The majority of the published data has been generated by one investigator, Dr. R.B. Stricker, and his associates. In 1994, he published a study of a cohort of 24 homosexual, predominantly white males who were treated with weekly applications of 2% DNCB and followed for a mean of 28 weeks. The 24 patients were divided into 2 groups based on compliance with therapy, resulting in a group of 13 compliant patients and 11 noncompliant patients, though the reasons for noncompliance were not reported. The mean CD4 count at initiation of therapy was 396 in the compliant patients and 315 in the noncompliant patients. This difference was reported as not significant. Prior history of opportunistic infection or other medical illness was not discussed. Eleven of the patients were on antiretroviral therapy simultaneously, primarily with AZT monotherapy. Eight of those 11 patients were in the noncompliant group. Patients were monitored clinically for progression of HIV disease and development of AIDS-

defining illness. Analyses of lymphocyte subsets were also performed. Two of the 13 compliant patients developed localized cutaneous Kaposi's sarcoma (KS), while 5 of the 11 noncompliant patients developed AIDS (3 patients had PCP and 2 had progressive KS), and 4 of those died. The actual cause of death was not reported. Lymphocyte subset analyses revealed a significant decrease in CD4 cells in both groups, with a reportedly significantly greater decrease in the noncompliant group. There were no significant changes in CD8 cell count during the course of the study, or differences between the two groups. The compliant patients had a statistically significant increase in the number of NK cells compared to patients in the noncompliant group, but functional assays were not performed. Thirteen percent of patients developed adverse reactions, including severe local reactions, generalized rash, and weight gain. The fact that the mean pretreatment CD4 count in the noncompliant group was less than that in the compliant group (although apparently not significant), and that the majority of patients in the noncompliant group were on at least one antiretroviral medication, suggests that the noncompliant group had more progressed HIV disease at onset of treatment, which would bias the results in favor of the DNCB treatment.

Another study done in Brazil by A. Traub, S.B. Margulis, and R.B. Stricker evaluated a cohort of 35 HIV+ patients, who were divided into 2 groups. The first group was composed of 29 patients who received weekly applications of 2% DNCB and the second group included 6 patients who refused further DNCB therapy after an initial application. The treated patients were followed for a mean of 17.8 months and the untreated patients for 19.7 months. The treated and untreated groups were matched in terms of age and initial clinical status. None of the patients received antiretroviral therapy. One of 6 patients in the untreated group and 4 of 29 patients in the DNCB treated group had AIDS at onset of treatment. The patients were monitored every 3 months with clinical evaluation, weight, fecal parasitology, complete blood count, Venereal Disease Research Laboratory test, and lymphocyte subset analysis. The DNCB treated group was reported to have fewer adverse clinical events including fungal, bacterial, parasitic, and herpetic infections, and were less likely to progress to AIDS. In actuality, only 1 of 25 patients in the treatment group and 2 of 5 patients in the untreated group developed an AIDS defining illness during the course of the study. These numbers are too small for any meaningful interpretation. The treatment group had a statistically significant increase in mean CD4 cells of 46, compared to a mean decrease of 170 in untreated patients. There was a trend toward increased CD8 cell count which was not significant. No functional assays were performed. None of the treated patients discontinued topical therapy due to adverse reactions. Whether there is any benefit of an increase in CD4 count without knowing the effect on viral load is not clear. If, in fact, the DNCB treatment resulted in an increase in HIV viral load, then the prognosis could actually be worse.

A third study by RB Stricker et al evaluated the effect of DNCB therapy on HIV viral load. A cohort of 14 patients divided into a treatment group of 8 patients and a control group of 6 patients was followed for 3-4 months. The treatment group received weekly topical applications of 2% DNCB. The control group consisted of patients who refused DNCB therapy. The clinical status of the 8 patients in the treatment group included 5 with asymptomatic HIV+, 1 with AIDS-related complex (ARC), and 2 with AIDS. The clinical status of the 6 patients in the control arm of the study included 3 with AIDS, 1 with ARC, and 1 with asymptomatic HIV+. However, review of the CD4 counts of all patients presented in the study revealed that actually 5 of the 6 control patients had AIDS by CD4 count criteria alone. None of the treatment patients were on antiretroviral therapy, but 2 of the control patients were on zidovudine. Analysis was performed only on the surrogate markers of CD4 count and HIV viral load by quantitative RNA PCR. No analysis of development of opportunistic infections or progression to AIDS was done. There was no difference in mean CD4 count or HIV viral load between the two groups at initiation of the study. As a result of DNCB treatment, there was no statistically significant change in CD4 count.

However, the investigators reported a statistically significant decrease in mean HIV viral load of one log in the DNCB treatment group while the control group had a 0.7 log increase in mean viral load. The exact timing and frequency of specimen collection for CD4 count and HIV viral load was not described.

Although this study suggests that DNCB treatment may decrease HIV viral load, there are several reasons not to use this as evidence for the effectiveness of DNCB in treatment of HIV disease and therefore include it on the list of bulk drug substances for compounding. First, this is the only documented trial of the effect of DNCB on HIV viral load, and it evaluated only 8 patients. Second, there were some concerning inconsistencies in the study including the fact that the control group had further advanced HIV disease at the initiation of the study, which would bias the results in favor of the treatment group. Intercurrent illnesses and/or opportunistic infections, alcohol and drug use during the course of the study was not discussed. These are potential confounding factors that are known to increase HIV viral load. Nor was initiation of currently available antiretroviral therapy during the course of the study specifically prohibited, or even addressed. Finally, the one log drop in HIV viral load in the DNCB treatment group without a significant change in CD4 count is confusing because generally there is some increase in CD4 count in response to decrease in viral load. Thus, although this study hints at some effect of DNCB on HIV viral load, it certainly does not constitute convincing or weighty evidence for its use in HIV disease.

### Conclusions

In summary, the data from the few studies evaluating the effect of DNCB treatment on HIV disease do not demonstrate any consistent or convincing beneficial effect of DNCB treatment on HIV viral load, CD4, CD8, or NK cell count, or on progression to AIDS. Although the possibility of a marginal effect of DNCB treatment on the course of HIV disease remains, the absence of any convincing supportive published data, or other widespread use and anecdotal evidence, should preclude DNCB from inclusion on the list of bulk drug substances approved for pharmacy compounding, at least not based on a role in the treatment of HIV disease. As treatment for HIV disease continues to evolve and become more complex, the inclusion of DNCB in the armamentarium of therapeutic modalities without knowing the potential interactions of DNCB with currently available therapies, would be ill-advised.

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Concurrence:

HFD-530/M.O. Team Leader/Murray *JSM 3/23/99*  
HFD-530/ D.D. Acting Director/Birnkrant *DB 3/24/99*

cc:

HFD-530/M.O. Consultant/Laessig  
HFD-530/M.O. Team Leader/Murray  
HFD-530/D.D. Acting Director/Birnkrant  
HFD-530/Director/Jolson  
HFD-530/S.C.S.O./Decicco  
HFD-540/M.O./Okun  
HFD-540/C.S.O./Kozma-Fornaro

# Bulk Drug Substance to be Used in Pharmacy Compounding

Docket No. 98N-0182

## Bulk Drug Substance

Ingredient Name: Chlorodinitrobenzene; CDNB; Dinitrochlorobenzene; DNCB  
Chemical Name: 1-Chloro-2,4-Dinitrobenzene CAS: 97-00-7  
Chemical Grade or Strength: Minimum 98%  
How Supplied: Loose powder and/or chunks  
International Pharmacopeial Recognition: Martindale The Extra Pharmacopoeia p.1698  
Bibliography: 1) MSDS attached  
2) Medline search identified 356 articles since 1966. A bibliography of 175 articles appearing since 1990 is attached.

## Compounded Product

Formulations: Topical liquid. DNCB dissolved in acetone.  
Strength(s): Bulk stock solution compounded at 2 mg/0.1 mL.  
Dilutions in acetone prepared at concentrations of:  
100 µg/0.1 mL  
50 µg/0.1 mL  
25 µg/0.1 mL  
12.5 µg/0.1 mL  
6.25 µg/0.1 mL  
Route of Administration: Topically on skin.  
Past/Proposed Use: DNCB is used as a skin sensitizer to estimate immune system competency. See attached articles. No commercial product of DNCB exists.  
Stability Data: None available  
Additional Information: None  
Nominated by: University of Texas M. D. Anderson Cancer Center  
Division of Pharmacy (Box 90)  
1515 Holcombe Blvd.  
Houston, Texas 77030  
tel: (713) 792-2870



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MATERIAL SAFETY DATA SHEET PAGE 1

SECTION 1. - - - - - CHEMICAL IDENTIFICATION - - - - -

CATALOG #: C6396  
NAME: 1-CHLORO-2,4-DINITROBENZENE

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS #: 97-00-7  
MF: C5H3CLN2O4  
EC NO: 202-551-4

SYNONYMS

CONR \* 1-CHLOR-2,4-DINITROBENZENE (DUTCH) \* 1-CHLOR-2,4-DINITROBENZENE \* 1-CHLORO-2,4-DINITROBENZENE \* 4-CHLORO-1,3-DINITROBENZENE \* 6-CHLORO-1,3-DINITROBENZENE \* 1-CHLORO-2,4-DINITROBENZOL (GERMAN) \* 1-CHLORO-2,4-DINITROBENZENE (ITALIAN) \* 1,3-DINITRO-4-CHLOROBENZENE \* 2,4-DINITROCHLOROBENZENE \* 2,4-DINITRO-1-CHLOROBENZENE \* DINITROCHLOROBENZOL \* DNCS \*

SECTION 3. - - - - - HAZARDS IDENTIFICATION - - - - -

LABEL PRECAUTIONARY STATEMENTS

HIGHLY TOXIC (USA)  
TOXIC (EU)  
TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.  
MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.  
DANGER OF CUMULATIVE EFFECTS.  
CAUSES SEVERE IRRITATION.  
TARGET ORGAN(S):  
NERVES  
BLOOD  
IN CASE OF ACCIDENT OR IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE IMMEDIATELY (SHOW THE LABEL WHERE POSSIBLE).  
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.  
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.  
DO NOT BREATHE DUST.

SECTION 4. - - - - - FIRST-AID MEASURES - - - - -

CONTINUED ON NEXT PAGE

MATERIAL SAFETY DATA SHEET PAGE :

-----

CATALOG #: CS396  
 NAME: 1-CHLORO-2,4-DINITROBENZENE

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH CUPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES WHILE REMOVING CONTAMINATED CLOTHING AND SHOES.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS. CALL A PHYSICIAN IMMEDIATELY.

DISCARD CONTAMINATED CLOTHING AND SHOES.

SECTION 5. ----- FIRE FIGHTING MEASURES -----

EXTINGUISHING MEDIA  
 WATER SPRAY.  
 CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES  
 WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS  
 EMITS TOXIC FUMES UNDER FIRE CONDITIONS.  
 CONTAINER EXPLOSION CAN OCCUR UNDER FIRE CONDITIONS. IN ADVANCED OR MASSIVE FIRES THE AREA SHOULD BE EVACUATED AND THE FIRE SHOULD BE FOUGHT FROM A REMOTE EXPLOSION-RESISTANT LOCATION.

SECTION 6. ----- ACCIDENTAL RELEASE MEASURES-----

EVACUATE AREA.  
 WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY RUBBER GLOVES.  
 SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.  
 VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

SECTION 7. ----- HANDLING AND STORAGE-----

REFER TO SECTION 8.

SECTION 8. ----- EXPOSURE CONTROLS/PERSONAL PROTECTION-----

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.  
 SAFETY SHOWER AND EYE BATH.

CONTINUED ON NEXT PAGE



MATERIAL SAFETY DATA SHEET PAGE 3

-----

CATALOG #: C6396  
 NAME: 1-CHLORO-2,4-DINITROBENZENE  
 USE ONLY IN A CHEMICAL FUME HOOD.  
 DO NOT BREATHE DUST.  
 DO NOT GET IN EYES, ON SKIN, ON CLOTHING.  
 AVOID PROLONGED OR REPEATED EXPOSURE.  
 READILY ABSORBED THROUGH SKIN.  
 WASH THOROUGHLY AFTER HANDLING.  
 HIGHLY TOXIC.  
 SEVERE IRRITANT.  
 STRONG SENSITIZER.  
 KEEP TIGHTLY CLOSED.  
 STORE IN A COOL DRY PLACE.

SECTION 9. ----- PHYSICAL AND CHEMICAL PROPERTIES -----

APPEARANCE AND COLOR  
LIGHT-YELLOW TO BROWN CRYSTALS

PHYSICAL PROPERTIES

BOILING POINT: 316 C  
 MELTING POINT: 49 C TO 52 C  
 FLASHPOINT 36/F  
 186.11C

EXPLOSION LIMITS IN AIR:

UPPER	22%
LOWER	2%

SECTION 10. ----- STABILITY AND REACTIVITY -----

INCOMPATIBILITIES

STRONG BASES  
STRONG OXIDIZING AGENTS

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:  
CARBON MONOXIDE, CARBON DIOXIDE  
NITROGEN OXIDES  
HYDROGEN CHLORIDE GAS

SECTION 11. ----- TOXICOLOGICAL INFORMATION -----

ACUTE EFFECTS

MAY BE FATAL IF INHALED, SWALLOWED, OR ABSORBED THROUGH SKIN.  
CAUSES SEVERE IRRITATION.

CONTINUED ON NEXT PAGE

M A T E R I A L   S A F E T Y   D A T A   S H E E T                      P A G E   4

-----

CATALOG #:                      C5396  
NAME:                              1-CHLORO-2,4-DINITROBENZENE  
HIGH CONCENTRATIONS ARE EXTREMELY DESTRUCTIVE TO TISSUES OF THE MUCOUS  
MEMBRANES AND UPPER RESPIRATORY TRACT, EYES AND SKIN.  
SYMPTOMS OF EXPOSURE MAY INCLUDE BURNING SENSATION, COUGHING,  
WHEEZING, LARYNGITIS, SHORTNESS OF BREATH, HEADACHE, NAUSEA AND  
VOMITING.  
ABSORPTION INTO THE BODY LEADS TO THE FORMATION OF METHEMOGLOBIN  
WHICH IN SUFFICIENT CONCENTRATION CAUSES CYANOSIS. ONSET MAY BE  
DELAYED 2 TO 4 HOURS OR LONGER.  
MAY CAUSE ALLERGIC RESPIRATORY AND SKIN REACTIONS.  
TARGET ORGAN(S):  
PERIPHERAL NERVOUS SYSTEM  
CENTRAL NERVOUS SYSTEM  
BLOOD  
LIVER, KIDNEYS

RTECS #: CZ0525000  
BENZENE, 1-CHLORO-2,4-DINITRO-

IRRITATION DATA

SKN-HMN 30 UG	CODEDG 2,217,1976
SKN-RBI 100 UG/24H UPEN	AIHAAP 23,95,1962
SKN-RBT 2 MG/24H SEV	85JCAE -,600,1986
EYE-RBT 50 UG/24H SEV	85JCAE -,600,1986

TOXICITY DATA

ORL-RAT LD50:780 MG/KG	GTPZAB 32(2),48,1988
IPR-RAT LD50:280 MG/KG	AGGHAR 17,217,1959
SKN RDT LD50:130 MG/KG	AIHAAP 23,95,1962

TARGET ORGAN DATA

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)  
GASTROINTESTINAL (PERITONITIS)  
BLOOD (METHEMOGLOBINEMIA-CARBOXYHEMOGLOBINEMIA)  
SKIN AND APPENDAGES (PRIMARY IRRITATION)  
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES  
(RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR  
COMPLETE INFORMATION.

SECTION 12. ----- ECOLOGICAL INFORMATION -----

DATA NOT YET AVAILABLE.

SECTION 13. ----- DISPOSAL CONSIDERATIONS -----

CONTINUED ON NEXT PAGE

MATERIAL SAFETY DATA SHEET PAGE 5

CATALOG #: C6396  
NAME: 1-CHLORO-2,4-DINITROBENZENE  
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER. OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

SECTION 14. - - - - - TRANSPORT INFORMATION - - - - -

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SECTION 15. - - - - - REGULATORY INFORMATION - - - - -

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TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

R 42/43

MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.

R 33

DANGER OF CUMULATIVE EFFECTS.

S 45

IN CASE OF ACCIDENT OR IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE IMMEDIATELY (SHOW THE LABEL WHERE POSSIBLE).

S 26

IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.

S 36/37/39

WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

S 22

DO NOT BREATHE DUST.

REVIEWS, STANDARDS, AND REGULATIONS

OEL=MAK

NOHS 1974: HZD 83616; NIS 1; TNF 174; NOS 1; TNE 1221

NOHS 1983: H7D 83616; NTS 2; TNF 82; NOS 2; TNF 170; TFF 14

EPA TSCA SECTION 8(B) CHEMICAL INVENTORY

EPA TSCA SECTION 8(D) UNPUBLISHED HEALTH/SAFETY STUDIES

EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, SEPTEMBER 1997

SECTION 16. - - - - - OTHER INFORMATION - - - - -

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO

CONTINUED ON NEXT PAGE

CUST#: 1-085-83857

M A T E R I A L S A F E T Y D A T A S H E E T      P A G E   6

-----  
CATALOG #:                    C6396  
NAME:                         1-CHLORO-2,4-DINITROBENZENE  
BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA SHALL NOT BE  
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH  
THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR  
ADDITIONAL TERMS AND CONDITIONS OF SALE.

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# DIPHENYLCYCLOPROPENONE

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
Public Health Service  
Food and Drug Administration, Center for Drug Evaluation and Research  
Division of Dermatologic and Dental Drug Products, HFD-540

**Date:** March 16, 1999

**Subject:** Review of Diphenacyclopropenone, a Candidate for the  
Pharmacy Compounding Bulk List, With Selected References

**To:** Pharmacy Compounding Steering Committee

**From:** Primary Reviewers

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**HFD-540 Review on Diphenylcyclopropenone**  
For the FDA Pharmacy Compounding Advisory Committee

**Prepared by:** Paul C. Brown, Ph.D.  
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Markham C. Luke, M.D., Ph.D.  
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**Date prepared:** January 4, 1999  
**Revised:** March 26, 1999

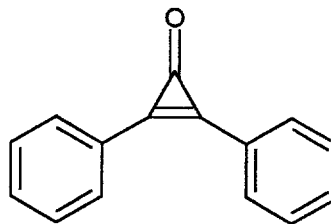
**I. Introduction**

The Division of Dermatologic and Dental Drug Products (HFD-540) has been charged with the review of diphenylcyclopropenone (DPCP) for two indications: alopecia areata and verruca vulgaris (warts). Only published literature was used in the preparation of this review.

**II. Chemical Characterization of DPCP**

**Identity:**

*Diphenylcyclopropenone*  
*Diphencyprone*  
*2,3-Diphenyl-2-cyclopropen-1-one*  
*DPCP*



*CAS #:* 886-38-4  
*Molecular Weight:* 206.24  
*Molecular Formula:* C<sub>15</sub>H<sub>10</sub>O  
*Melting Point:* 119-121° C (anhydrate); 87-90° C (monohydrate)

The physical and spectroscopic properties of DPCP are well-characterized. DPCP is insoluble in water, soluble in alcohols and other organic solvents, and is rapidly hydrolyzed in dilute alcoholic base. DPCP reacts with nucleophiles, such as pyridine and hydroxylamine, to form a variety of unidentified products. Thermal instability has been reported. Heating this material above its melting point results in decomposition to diphenylacetylene and carbon monoxide. DPCP reacts photochemically to ultraviolet (UV-A and UV-B), fluorescent and incandescent lights, as well as natural sunlight. There are no published quantitative methods for analysis of this material. The adequacy of the methods for determination of purity and levels of contaminants cannot be assessed.

### Quality and Stability

DPCP is an off-white to beige crystalline powder and has a melting point of 119-121° C. It is thermally unstable above its melting point, decomposing primarily into diphenylacetylene and a possible dimeric product; this degradant has not been definitively identified. It is insoluble in water, readily hydrolyzed in dilute alkali base ( $t_{1/2} < 5$  min. in 0.1N NaOH in ethanol) to cis-1,2-diphenylacrylic acid, and relatively stable to acidic conditions. DPCP reacts readily with strong electrophiles, as well as with nucleophiles such as pyridine and hydroxylamine. The addition products of these reactions have not been fully identified.

DPCP is photochemically reactive. It decomposes during irradiation with both short- and long-wavelength UV (UVB and UVA), fluorescent, incandescent and solar light. The predominant decomposition products appear to be diphenylacetylene and a product which has tentatively been identified as a dimer.

### Synthesis and Purity

DPCP was first prepared in 1959 by Breslow (Breslow et al., 1959) and Vol'pin (Vol'pin et al., 1959). Several methods of preparation have been reported in the chemical literature (Breslow et al., 1959, 1963, 1965, 1973; Vol'pin et al., 1959, 1960), only one of which appears amenable to large-scale production (Breslow et al., 1973).

Several domestic commercial sources of DPCP have been identified, including Fisher Scientific (Acros Organics), Spectrum Chemical Co., and Sigma-Aldrich Co. Each has confirmed their knowledge of the identity or identities of the actual manufacturing site(s) for DPCP, but all of them have declined to make this information public.

Literature on the syntheses of DPCP predates modern analytical methodology. These reports cite IR spectroscopy, UV spectroscopy, elemental analysis, and melting point as the determinants of purity. While these methods are common analytical techniques, they are not established quantitative methods for analysis of this material. The adequacy of these methods for determination of the purity and level of contaminants in DPCP can not be assessed.

A monohydrate form of DPCP (melting point 87°-90°C) results from recrystallization in cyclohexane and is probably due to incomplete drying. The reported yield of this synthesis is 44%. The description of the purification indicates the presence of significant amounts of unidentified byproducts (e.g., a "reddish oily impurity"); thus, the impurity profile of this material is unknown.

**Assessment 1: Although DPCP is well characterized, it degrades readily by basic hydrolysis or exposure to light. The degradation products have not been identified. DPCP used in compounding could vary significantly from DPCP used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.**



### III. Safety of DPCP

#### A. Animal Toxicology

DPCP is not mutagenic in the Ames assay except in the presence of light (Wilkerson et al., 1987). In the presence of light (350 nm) and rat microsomes, DPCP caused a doubling of the mutation rate in one strain of *Salmonella*. Since the photo-conversion products of DPCP were not mutagenic, some short-lived intermediate(s) must cause the mutations. The synthetic precursor to DPCP,  $\alpha,\alpha$ -dibromodibenzylketone, is mutagenic in the Ames assay with and without metabolic activation (Wilkerson et al., 1987).

**Assessment 2: DPCP is photo-genotoxic. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with DPCP. Thus, it is not known what the potential toxicities of DPCP are in humans or whether it is likely to be teratogenic in humans.**

#### B. Human Safety

There are no published reports of studies designed to systematically evaluate the safety of DPCP. The reported side effects are similar to those of other contact sensitizers. Numerous case reports of adverse events are associated with the use of DPCP. Especially notable are reports of vitiligo and pigmentary changes, some of which are permanent. There have been three reports of erythema multiforme (which is characterized by the appearance of purpuric [bruise-like], often blistering, ring-shaped lesions scattered over the body surface, with systemic signs and symptoms including fever and malaise).

DPCP has been shown to elicit eczematous reactions with or without blistering. These reactions may occur at the site of application and other areas of the body. Other reactions include itching and resulting insomnia, urticaria, edema of the scalp, eyelids, and face, lymphadenopathy, and high fever (Rokhsar et al., 1998).

**Table 1 - Side Effects of DPCP**

Author	Journal	Year	Side Effect
Alam et al.	J. Am. Acad. Dermatol.	1999	Severe urticarial reaction, eczematous dermatitis, and dermographism
Oh et al.	Contact Derm.	1998	Bullous erythema multiforme
Henderson et al.	Br. J. Dermatol.	1995	Vitiligo
Puig et al.	Int. J. Dermatol.	1994	Erythema multiforme-like reaction
Van der Steen et al.	Arch. Dermatol.	1992	Pigmentation changes (4/243 pts) – ‘dyschromia in confetti’
Duhra et al.	Br. J. Dermatol.	1990	Persistent vitiligo
Perret et al.	Dermatologica	1990	Erythema multiforme (3 patients)
Tosti et al.	Contact Derm.	1989	Contact urticaria

In human skin absorption studies, DPCP was not detected in the serum or urine of human subjects treated with 0.5 ml of 1% DPCP in a mixture of denatured alcohol and propylene glycol in a 9:1 ratio for a total dose of 5 mg (Berth-Jones et al., 1994). The limit of detection in this study was 60 ng/ml for serum and 20 ng/ml for urine. The authors note that their results do not eliminate the possibility that DPCP is absorbed and rapidly metabolized.

Topical sensitizers such as DPCP present a particular hazard to those who work with the compounds since, by definition, repeated exposure is likely to elicit an allergic response. There are several published accounts of workers, including pharmacists and nurses, becoming sensitized to DPCP (Sansom et al., 1995; Shah et al., 1996; Adishes et al., 1997).

**Assessment 3: There is limited characterization of the human safety profile. With human exposure to DPCP, adverse side effects have been reported in the literature, including erythema multiforme, eczematous dermatitis, urticaria, persistent vitiligo and post-inflammatory pigmentation changes.**

Available alternative approved therapies for alopecia areata include intralesional, topical, and systemic corticosteroids.

Available alternative approved therapies for verruca vulgaris (warts) include podophyllin, imiquimod, and salicylic acid. Other well-accepted modalities with excellent safety include ablation using cryotherapy or laser treatment.

**Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.**

#### **IV. Historical Use of DPCP in Pharmacy Compounding**

DPCP's ability to induce strong allergic reactions was first reported in 1972 (Whittaker, 1972). Clinical use of DPCP for the treatment of alopecia areata was first reported in 1983 (Happle et al., 1983).

Numerous animal and human studies have demonstrated that DPCP is a potent contact sensitizer. It has been investigated for topical immunotherapy of conditions such as warts and alopecia areata. The mechanism by which topical immunotherapy can improve these conditions is not known, however exposure of patients to this agent results in a clinical picture similar to that of exposure to poison ivy.

DPCP is usually applied in a health care provider's office by a physician (usually a dermatologist), podiatrist, or trained staff member. First, patients are sensitized with a 2% DPCP solution in acetone applied to a 10 to 16 cm<sup>2</sup> area on one side of the scalp, forearm, or back (Rokhsar et al., 1998). If a severe eczematous response does not occur at the initial sensitization site, a 0.0001% solution is applied to one side of the scalp (if the initial reaction is too severe, two

weeks are allowed to elapse between the sensitization and elicitation phases). Caution must be exercised to avoid a severe blistering response.

**Assessment 5: Since its first clinical report in 1983, DPCP has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence of its widespread use is not apparent.**

## **V. Available Evidence of Effectiveness**

Alopecia areata and warts frequently resolve without any therapeutic intervention. For example, in a study of the natural history of alopecia areata, of 63 alopecia areata patients followed for one year without treatment, hair had regrown in all but 4 patients in one year, and in all but 1 patient after two years. The great majority had regrown hair by 3 months after their only office visit (Arnold, 1952). Alopecia areata with less than 25% involvement has a high incidence of spontaneous recovery, whereas more severe involvement has a lesser rate of recovery (Moschella and Hurley, 1992). Regarding the natural history of warts, a two-year study showed that two-thirds of warts regressed without treatment (Massing and Epstein, 1963).

Despite the necessity for a placebo arm in evaluating experimental therapies such as DPCP, much of the putative success of topical immunomodulators stems from studies that were either uncontrolled or internally controlled. Describing therapy for alopecia areata, Rook et al. states, "The widely conflicting claims for the success of many different measures merely reflect the very great variations in the spontaneous course of the disease."

Studies that demonstrate a "positive" result, such as regrowth of hair, are more likely to be submitted for publication or published than are studies with "negative" results. Therefore, the published literature may overstate the efficacy of novel therapies. Additionally, most clinical studies lack long-term follow-up, so the lasting treatment benefits cannot be evaluated.

To date, in the peer-reviewed English-language literature, there have been at least 18 reports of studies using DPCP in alopecia areata and 5 studies on the treatment of warts.

### **Warts**

Warts, caused by cutaneous infection with the human papillomavirus, are a very common dermatological ailment. Aside from cosmetic disfigurement, patients seek treatment because plantar (foot) warts may cause pain on walking or interfere with gait, and warts on the fingers may interfere with manual dexterity. As with alopecia areata, therapy is not always effective.

The largest trial with DPCP on warts was an open study on 134 subjects with palmoplantar and periungual verruca done by Rampen and Steijlen in 1996. After 8 weeks of treatment, 36.6% of subjects exhibited a complete response. The low rate of response is worse than that of other therapeutic modalities for warts, although the absence of a control arm precludes any definitive comparisons with other modalities.

### Alopecia areata

Alopecia areata is a nonscarring loss of hair, that, depending upon its severity, can affect patches of scalp, the entire scalp (alopecia totalis), or the entire body (alopecia universalis). The etiology of this illness is unknown. Alopecia areata is a relatively common dermatologic disease that is associated with cosmetic disfigurement and functional impairment, especially if eyebrows or eyelashes are lost.

**Table 2 - Use of DPCP in Alopecia Areata**

Author	Journal	Year	Disease	N	Treatment	Response/ITT	Ctrl
Schuttelaar et al.	Br. J. Dermatol.	1996	Alopecia areata Children	26	3 mo – 1 yr	30.8% acceptable regrowth	Yes
Gordon et al.	Br. J. Dermatol.	1996	Alopecia areata	48	30.8 months follow-up	38 % “good” regrowth	Yes
Shapiro et al.	J. Am. Acad. Dermatol.	1993	Alopecia areata > 50 % hair loss	15	24 weeks + 5% minoxidil	33.3% marked regrowth	Yes
van der Steen et al	Dermatology	1991	Alopecia areata	139	> 7 months	30.2% complete 20.1% partial	Yes
Berth-Jones et al	Clin. Exp. Dermatol.	1991	Alopecia totalis	22	6 months	9.1% response	Yes

Naldi et al., 1990, assessed the efficacy of topical sensitizers for the treatment of alopecia areata in a review of 26 papers on “published clinical trials on dinitrochlorobenzene, squaric acid dibutylester, and diphenylprone [DPCP] each published between January 1977 and January 1988.” The authors of the paper stated, “According to our evaluation, the published literature is of limited use in defining the role of topical immunotherapy in alopecia areata. Half the studies examined used informal methods (uncontrolled or historically controlled trials)... In general, the studies that we examined had serious drawbacks in reporting critical procedures such as assessing treatment and selecting and following up patients... In conclusion, a definite role of topical immunotherapy for alopecia areata has yet to be established and this treatment should be offered only as an experimental modality...”

In 1998, Rokhsar et al. examined the efficacy of contact sensitizers in alopecia areata in a summary review of the literature. They reported a response rate range from 9% to 85%. This range included the sum of both complete and partial responders. The weighted average response rate was 58%, similar to the response rate seen in the largest study by van der Steen et al. (1998). A relapse rate of about 50% was seen in the patients, even with continuation of treatment, suggesting that in many patients the response is temporary at best.

A tabular summary of the suggested role of immunomodulators (as gleaned from leading dermatological textbooks) for the treatment of alopecia areata and warts is presented in Table 3. Many therapeutic alternatives exist for these conditions.. The consensus is that DPCP is an experimental therapy, with a modicum of short-term efficacy. Additional well-controlled, long-term studies are needed to evaluate efficacy.

**Assessment 6: There is little evidence that DPCP is effective in the long-term treatment of alopecia areata or verruca. Treatment of alopecia areata with DPCP may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.**

**Table 3 - Perspectives on Treatment for Alopecia Areata and for Warts**

Reference	Disease	Treatment of Choice	Other Suggested Treatments	Role of DPCP in Therapeutic Armamentarium
<i>Andrews' Diseases of the Skin: Clinical Dermatology</i> , ed. by Arnold et al., Eighth edition (1990) (textbook)	Alopecia Areata—patchy involvement	Intralesional injections of corticosteroid	“None of the other various therapeutic approaches are clearly superior to corticosteroids”	DPCP: not discussed
	Alopecia Areata—totalis/universalis	Systemic (IM) steroids should be “seriously considered”.		
	Common/Plantar Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M	DPCP: not discussed
<i>Dermatology in General Medicine</i> , ed. by Fitzpatrick et al., Third edition (1987) (textbook)	Alopecia Areata	Treatment of choice not identified	N (little efficacy), P, Q, R	DPCP: not discussed
	Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K, T, U, V	DPCP: not discussed
<i>Textbook of Dermatology</i> , ed. by Rook et al., Fourth Edition (1986) (textbook)	Alopecia Areata	Treatment of choice not identified	O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z	DPCP: not discussed
	Warts	Treatment of choice not identified	B, C, D, L, L', E, H, I, J, T, A', B', ; avoid A,U (risk of scarring)	DPCP: not discussed
<i>Pediatric Dermatology</i> , ed. by Schachner and Hansen, (1988) (textbook)	Alopecia Areata	Topical corticosteroids, alone or under occlusion; Intralesional corticosteroids	O (for severe involvement, unresponsive to topical or intralesional treatment)	DPCP: as effective as DNCB (another topical sensitizer). “Here again these chemicals [DPCP] cannot be regarded as completely safe until extensive toxicologic evaluation has been completed.”
	Warts	Treatment of choice not identified	A, B, C, G, K	DPCP: not discussed

A: Electrodesiccation and curettage; B: Cryotherapy; C: Salicylic Acid; D: Lactic Acid; E: Trichloroacetic/ other caustic acids; F: Podophyllin; G: laser; H: 5-Fluoro-uracil; I: Retinoids; J: Interferon; K: Cantharin; L: Formalin; L': Glutaraldehyde; M: Bleomycin; N: Topical corticosteroids; O: Systemic corticosteroids; P: Intralesional corticosteroids; Q: Anthralin; R: PUVA (Psoralen and UV-A); S: Inosiplex; T: Bleomycin; U: Surgical excision; V: Vaccination with autogenous-wart extracts; W: Ultraviolet radiation; X: Minoxidil; Y: Dithranol; Z: Zinc sulfate; A': Levamisole; B': Photodynamic inactivation; C': Psychological methods (hypnosis)

## **VI. Conclusions**

**Assessment 1:** Although DPCP is well characterized, it degrades readily by basic hydrolysis or exposure to light. The degradation products have not been identified. DPCP used in compounding could vary significantly from DPCP used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

**Assessment 2:** DPCP is photo-genotoxic. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with DPCP. Thus, it is not known what the potential toxicities of DPCP are in humans or whether it is likely to be teratogenic in humans.

**Assessment 3:** There is limited characterization of the human safety profile. With human exposure to DPCP, adverse side effects have been reported in the literature, including erythema multiforme, eczematous dermatitis, urticaria, persistent vitiligo and post-inflammatory pigmentation changes.

**Assessment 4:** Many approved products are available for the treatment of verruca and alopecia areata.

**Assessment 5:** Since its first clinical report in 1983, DPCP has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence of its widespread use is not apparent.

**Assessment 6:** There is little evidence that DPCP is effective in the long-term treatment of alopecia areata or verruca. Treatment of alopecia areata with DPCP may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

## **VII. Recommendation:**

Four criteria have been used to evaluate DPCP for inclusion on the bulk drug compounding list: (1) the chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness. Our evaluation of DPCP, based on a balanced assessment of each criterion in the context of the others, leads to our recommendation that it is not appropriate for DPCP to be included on the list.

The nonclinical studies conducted to date minimally evaluate the safety of diphenylcyclopropanone. The studies do not characterize the potential toxicity to internal tissues nor do they characterize the dermal toxicity from long term topical application. Conclusions about the safety of DPCP cannot be made before such studies are done.

The evidence from historical use suggests that DPCP may be useful as second or third line therapy for warts and possibly as a therapy for alopecia areata. It is our impression that DPCP has become more commonly used as a topical sensitizer than dinitrochlorobenzene (DNCB), largely because the latter compound, available for toxicologic evaluation for more than 20 years, has well-established toxicities. The notion seems to be that the known toxicities of DNCB make it less attractive than the unknown toxicities of DPCP.

If DPCP is not placed on the list of bulk drug substances for compounding, a physician/investigator could still file an investigational new drug application (IND) for use of DPCP in humans. Pursuing this route would provide important and clinically relevant information about: (1) the chemistry of DPCP (i.e., its stability, its comparative solubility in different vehicles), (2) the safety profile – pharmacology/toxicology of DPCP (i.e., safety information about long-term dermal usage), and (3) the clinical side effect profile (i.e., risk of pigmentary and eczematous reactions).

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June 5, 1998

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
U.S. Department of Health and Human Services  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

*Re: Bulk Drug Substances To Be Used in Pharmacy  
Compounding; Request for Nominations  
Docket No. 98N-0182*

Dear Sirs:

I am responding on behalf of the American Academy of Dermatology to the Food and Drug Administration's (FDA) Notice and Request for Nominations entitled, "Bulk Drug Substances To Be Used in Pharmacy Compounding." This notice was published in the April 7 issue of the *Federal Register* [63 Fed. Reg. 17011]. The FDA is seeking candidates for a list of bulk drug substances that can be used in pharmacy compounding that do not have a United States Pharmacopeia (USP) or National Formulary (NF) monograph and are not components of approved drugs.

The Academy would like to nominate the following drug substances:

1. *Cantharidin* This drug is compounded and used for the treatment of warts and molluscum contagiosum.
2. *Diphencyprone (diphenylcyclopropanone)*. This powder is dissolved in Acetone 2%, 1%, .05%, .01%, and .001% strengths for the topical treatment of extensive alopecia areata.

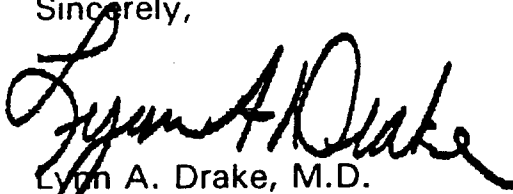
Dockets Management Branch  
HFA-305  
Food and Drug Administration  
June 5, 1998  
Page 2

3. *Merchlorethamine*. This drug is a nitrogen mustard used in compounded topical preparations for the treatment of cutaneous T-cell lymphoma.
4. *Squaric acid dibutyl ester*. This drug substance is a contact sensitizer used as a topical treatment for alopecia areata and warts.

I hope this information is helpful, and I ask that you give these nominations every favorable consideration. The Academy may submit additional nominations in the future. In the meantime, I thank you in advance for your time and attention to this matter. If you have any questions, please do not hesitate to contact me or the Academy's Washington Office at the above address and telephone numbers.

With best wishes.

Sincerely,



Lynn A. Drake, M.D.  
President

LAD/br

Ingredient name: diphencyprone  
Chemical name: diphenylcyclopropenone  
Common name: DPCP

Ingredient name: squaric acid dibutyl ester  
Common name: SADBE

For additional information, see enclosed.

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# SQUARIC ACID DIBUTYL ESTER

## Table of Contents

### FDA Review/Recommendation

### Background Information

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- Tab 2      Wilkerson M et al: Squaric acid and esters: Analysis for contaminants and stability in solvents: J Am Acad Dermatol, Vol 13, No 5, (Aug)1985 pp 229-234
- Tab 3      Foley S et al: Clinical sequelae associated with squaric acid dibutylester topical sensitization: American Journal of Contact Dermatitis, Vol 7, No 2, (June)1996: pp 104-108
- Tab 4      Additional background information provided by the American Academy of Dermatology



**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
Public Health Service  
Food and Drug Administration, Center for Drug Evaluation and Research  
Division of Dermatologic and Dental Drug Products, HFD-540

**Date:** March 16, 1999

**Subject:** Review of Squaric Acid Dibutyl Ester, a Candidate for the  
Pharmacy Compounding Bulk List, With Selected References

**To:** Pharmacy Compounding Steering Committee

**From:** Primary Reviewers

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*RJD 3/29/1999*

**HFD-540 Review on Squaric Acid Dibutyl Ester**  
For the FDA Pharmacy Compounding Advisory Committee

**Prepared by:** Paul C. Brown, Ph.D.  
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Martin M. Okun, M.D., Ph.D.

**Date prepared:** January 4, 1999  
**Revised:** March 26, 1999

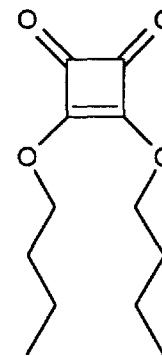
**I. Introduction**

The Division of Dermatologic and Dental Drug Products (HFD-540) has been charged with the review of squaric acid dibutyl ester (SADBE) for two indications: alopecia areata and verruca vulgaris (warts). Only published literature was used in the preparation of this review.

**II. Chemical Characterization of SADBE**

**Identity**

*3,4-Dibutoxy-3-cyclobutene-1,2-dione*  
*Dibutyl Squarate*  
*Squaric Acid Dibutyl Ester*  
*SADBE*



<i>CAS #</i>	2892-62-8
<i>Molecular Weight</i>	226.27
<i>Molecular Formula</i>	$C_{12}H_{18}O_4$
<i>Appearance</i>	<i>Colorless to slightly yellow oily liquid</i>
<i>Density</i>	0.9650 g/mL
<i>Refr. Index</i>	1.4943
<i>Boiling Point</i>	148-150° C @ 0.6 torr; 121-122° C @ 0.2 torr
<i>Flash Point</i>	>110 C
<i>Storage Precautions:</i>	<i>Keep cold and away from moisture, protect from light</i>

The physical and spectroscopic properties of squaric acid dibutyl ester (SADBE) have been well characterized.

**Stability**

Squaric acid esters have been shown to be readily hydrolyzed in aqueous solutions, and are hydrolyzed in basic solution at a much higher rate than at acidic or neutral pH. No thermal



instability has been reported. The photochemical reactivity and stability traits of SADBE have not been reported in the literature; however, it is likely to be photochemically reactive based on the molecular structure.

### **Synthesis and Purity**

Squaric acid was first prepared in 1959 by Cohen et al., and its first derivatives, dimethyl squarate and diethyl squarate, were reported in 1966 (Cohen and Cohen, 1966). SADBE is a neutral compound, which contains the unusual unsaturated, dicarbonyl-containing 4-carbon ring, which shows aromatic character. The alkoxy substituents are analogous to carboxylic acid esters, showing similar chemical behavior. Several methods of preparation have been reported in the chemical literature (Cohen and Cohen, 1966), and this material is available from several commercial suppliers, though the methods of production currently are not known. An investigation into the hydrolysis, contaminants, and degradants of this material has been published (Wilkerson et al., 1985).

Several domestic commercial sources of SADBE have been identified: Fisher Scientific (Acros Organics), Frinton Laboratories, Inc., and Sigma-Aldrich Co. Each has confirmed their knowledge of the identity or identities of the actual manufacturing site(s) for SADBE: all but one has declined to make this information public.

Literature on the syntheses of SADBE, refers in general to modern analytical methodology but provide few details as to the actual practices. These reports cite IR spectroscopy, UV spectroscopy, elemental analysis, gas chromatography and GC-mass spectrometry as the determinants of purity. While these are common techniques, they are not established quantitative methods for analysis of this material. The adequacy of these methods for determination of purity and levels of contaminants in SADBE cannot be assessed.

**Assessment 1: Although squaric acid dibutyl ester is well characterized, it hydrolyzes readily in the presence of water. Since it is exquisitely sensitive to water, it should only be compounded in media in which there is no water. The impurity profile of SADBE may differ depending on the route of synthesis. SADBE used in compounding could vary significantly from SADBE used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.**

## **III. Safety of SADBE**

### **A. Animal Toxicology**

Squaric acid dibutylester is not mutagenic in the Ames assay nor does it cause the transformation of hamster kidney cells *in vitro* (Happle et al., 1980; Strobel & Röhrborn, 1980). The synthetic precursors of squaric acid, hexachlorobutadiene and tetrachlorocyclobutenedione show some carcinogenic activity (van Duuren et al., 1971; Kociba et al., 1977).

The ability of the dibutyl and diethyl esters to penetrate human or mouse skin *in vitro* has been investigated (Sherertz & Sloan, 1988). Diffusion of the diethyl ester was 4.5 fold higher than squaric acid and the dibutyl ester was 24-fold higher than squaric acid.

Guinea pigs have been sensitized to the dibutyl and diethyl ester derivatives of squaric acid by the application of 0.1 to 10% solutions (Noster et al., 1976; Happle et al., 1980; Avalos et al., 1989). The dibutyl ester appears to be more effective at sensitizing than the diethyl ester. The sensitization to the diethyl ester is specific in that animals sensitized to this ester are not sensitized to the other esters as well. In addition, these studies have shown that the dimethoxy (dimethyl), diethoxy (diethyl), diisopropoxy (diisopropyl), dihydroxy and phenylethoxy derivatives of squaric acid are strong irritants.

**Assessment 2: SADBE is not mutagenic in the Ames assay. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with SADBE. Thus, it is not known what the potential toxicities of SADBE are in humans or whether it is likely to be teratogenic in humans.**

## B. Human Safety

There are no published reports of studies designed to systematically evaluate the safety of SADBE. In a comprehensive review of immunomodulatory therapy, Naldi et al. (1990) determined that the discussion of side effects was adequate in only half (5 out of 10) trials involving SADBE.

Although not always adequately characterized, the adverse events described in clinical studies reporting the use of SADBE for treatment of alopecia areata and warts have included: burning sensation immediately after application, dermatitis (localized to the application site or generalized), transient perioral burning after application, autoeczematization, persistent contact dermatitis on the primary site of sensitization (rare), severe generalized dermatitis, generalized pruritus without dermatitis, leukoderma, xerosis, scaling, edema of treated skin, scalp folliculitis, and systemic reactions with fever and arthralgias (see review by Rokhsar et al., 1998). Please see Table 1 regarding some of the published reports on side effects.

**Table 1 - Side Effects of SADBE**

Author	Journal	Year	Side Effect
Foley et al.	Am. J. Contact Derm.	1996	Severe eczematous reaction in 10/14 pts and disseminated reactions in 9/14
Nishioka et al.	Contact Derm.	1993	Benign lymphoplasia
Valsecchi et al.	Contact Derm.	1984	Depigmentation

Physicians and other health care workers, including compounding pharmacists, are at risk for SADBE sensitization. Persons handling the drug should exercise contact precautions and be careful not to inhale these potent sensitizers, as even trace amounts can cause severe allergic reactions. Unwitting exposure and re-exposure can lead to an unwanted adverse reaction that is