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Joan Claybrook, President

Public Citizen's Health Research Group's[1] Comments On:

Food and Drug Administration
List of Bulk Drug Substances That May Be Used in Pharmacy Compounding

[Docket No. 98N-0182]

Submitted - March 23, 1999

Congress, in passing the immodestly titled Food and Drug Administration Modernization Act (FDAMA) of 1997, exempts pharmacists from three provisions of the Federal Food, Drug and Cosmetic Act (FFDCA) that were intended to protect consumers from egregiously poor drug manufacturers: (1) the adulteration provision concerning the Good Manufacturing Practice requirements; (2) the misbranding provision involving the labeling of drugs with adequate directions for use; and (3) the new drug provision pertaining to the approval of new drugs that require proof of safety and effectiveness before marketing. In effect, Congress has created two classes of drugs in the United States: (1) FDA approved drugs that must be shown to be safe and effective before marketing; and (2) pharmacy compounded drugs that can be sold to an unwitting public without evidence of safety or effectiveness and can be produced in facilities that do not meet Good Manufacturing Practice guidelines.

The FDA is soliciting these comments on new regulations that will form the basis to identify bulk drug substances (the powdered form of a drug) that may be used in pharmacy compounding even though some of these substances are not approved in the U.S. or have been withdrawn from the market in this country because of the lack of evidence of effectiveness.

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[1] Since 1972, Public Citizen's Health Research Group has been promoting research-based, system-wide changes in health care policy, as well as advocating for the appropriate prescribing and use of prescription drugs. We testify before Congress and petition the Food and Drug Administration (FDA) on issues such as banning or relabeling of drugs and the misleading advertising of prescription and nonprescription drugs by their manufacturers. Our publications help consumers make informed decisions about the health care they receive and the drugs they are prescribed.

Ralph Nader, Founder

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BACKGROUND

Pharmacists who compound drug products on a doctors prescription for a specific patient and in limited amounts have always been exempt from certain portions of the Good Manufacturing Practice guidelines. Though the FDA had the statutory authority to regulate pharmacy compound drugs as new drugs, with the requirement that these products be shown to be both safe and effective, the Agency deferred to the judgement of the physician and pharmacist in those limited instances when a pharmacy compounded product was considered medically necessary. For example, the preparing of oral liquid forms of FDA approved drugs for children that are only commercially available as tablets or capsules intended for adults was allowed. The controversy began, however, when some compounding pharmacists crossed the line between legitimate compounding and the manufacturing of unapproved new drugs such as large quantities of injectable solutions or solutions intended for use by asthmatics by inhalation.

The FDA by not vigorously enforcing existing law against compounding pharmacists who were engaging in the manufacturing of unapproved new drugs has allowed a second class of drugs to exist. Now, under the weaker FDAMA, many of what were previously violations have been legalized. At issue is when does legitimate compounding stop and the manufacturing of unapproved new drugs begin. FDAMA deals with this issue through a memorandum of understanding between the states and the FDA.[2] In part, the memorandum requires that a state agrees to take action when inordinate amounts of compounded drugs are distributed into interstate commerce. For the purposes of the memorandum interstate distribution of an inordinate amount of compounded drugs occurs under either of the following circumstances:

> The number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician is equal to or greater than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician; or
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> The number of compounded prescriptions dispensed or distributed interstate annually by a pharmacy or physician is less than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by such pharmacy or physician, but prescriptions for one or more individual compounded drug products (including various strengths of the same active ingredient) dispensed or distributed interstate constitute more than 5% on the total number of prescriptions dispensed or distributed.

Under the above two conditions compounding pharmacies would be considered as manufacturers with the requirement of proving that the drugs they produce are both safe and effective.

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[2] http://www.fda.gov/cder/pharmcomp/12199a.txt.

FDA CRITERIA FOR BULK DRUG SUBSTANCES THAT MAY BE COMPOUNDED

FDAMA allows pharmacists to legally compound final finished dosage forms (e.g., tablets, capsules, suppositories, etc.) from bulk drug substances (powdered form of a drug) if: (1) the bulk substance is in a current United States Pharmacopeia (USP) or National Formulary (NF) monograph as well as the current USP chapter on pharmacy compounding; or (2) if a monograph does not exist the bulk drug substance must be a component of an FDA approved drug. 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.

The FDA has proposed four criteria for including other bulk drug substances on the list of substances that may be compounded.[3] These criteria are:

1. **The chemical characterization of the substance**. The FDA will determine whether the substance can be identified consistently based on its chemical characteristics. If a substance cannot be well characterized chemically, this will weigh against its inclusion on the 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.

2. **The safety of the substance**. Based on the FDA's review of the substances nominated to date it is unlikely that the bulk drugs will have thoroughly investigated in well-controlled animal toxicology studies, or that there will be well-controlled clinical studies to substantiate their safety in humans. In applying the toxicity criterion, the 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 drugs 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 treatments are available.

3. **The historical use of the substance in pharmacy compounding**. The FDA will consider evidence of both widespread and long standing use as indicative of the substance's perceived usefulness and acceptance in the medical community. The Agency believes that fraudulent or "quack" remedies, 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 long standing.

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[3] Department of Health and Human Services, Food and Drug Administration. List of Bulk Drug Substances That May Be Used in Pharmacy Compounding. *Federal Register* Vol.64, No.4, January 7, 1999, pages 996-1003.

4. **The available evidence of the substance's effectiveness or lack of effectiveness, if any such evidence exists**. The FDA recognizes that few, if any, of the candidates for the bulk drugs list will have been studied in adequate and well-controlled studies sufficient to demonstrate safety and effectiveness. When evaluating a bulk drug substance used to treat a less serious illness, the Agency will generally be more concerned about the safety of the substance than its effectiveness. The absence of effectiveness data, or the existence of only anecdotal reports will be less likely to preclude inclusion of the substance on the list. For a bulk drug substance used to treat serious or life-threatening conditions, there may be serious consequences associated with ineffective treatment, particularly when there are alternative approved treatments.

Criterion 1 is a reasonable standard in attempting to ensure that only high quality bulk drug substances produced in FDA regulated facilities meeting Good Manufacturing Practice guidelines are used in pharmacy compounded products. However, given the nature of market forces if profits do not meet the expectations of compounding pharmacists, they may seek the lowest cost bulk drug substance available no matter what the quality.

Criterion 2 necessitates that the FDA, using the published toxicology literature and reports of adverse reactions, shows that a nominated bulk drug substance is dangerous to preclude its inclusion on the list of substances that may be compounded. This is similar to the requirements of the Dietary Supplement Health Education Act (DSHEA) of 1994, the law that begat the unregulated dietary supplement industry. Under DSHEA the FDA must show that a dietary supplement is dangerous before regulatory action can be taken. Because there is no requirement that pharmacy compounded products be tested for safety, prescription drug consumers are left with the level of protection that existed before 1938 and the passage of FFDCA.

It must not be forgotten that there is no system that allows an accurate estimate of the numbers of people killed or injured by prescription drugs each year in this country. And that unlike FDA regulated prescription drug manufacturers who are required to report adverse drug reactions, compounding pharmacists have no regulatory requirement to report adverse events associated with the use of their products to the FDA.

Criterion 3 is based on the historical use of a product to gauge the "perceived usefulness and acceptance in the medical community" of pharmacy compounded products. This is known as the Hussey-Stetler Test of Time and was repudiated by Congress when the Kefauver-Harris amendments to the FFDCA were passed in 1962, requiring for the first time that drugs must be shown to be safe and effective before marketing. Dr. Hussey was the dean of the Georgetown University School of Medicine in Washington and Mr. Stetler became executive vice president of the Pharmaceutical Manufacturers Association (PMA) now know as the Pharmaceutical Research Manufacturers of America (PhRMA). In part, the Hussey-Stetler Test of Time

says:

> Medical history and experience clearly demonstrate that the only possible final determination as to the efficacy and ultimate use of a drug is the extensive clinical use of that drug by large numbers of the medical profession over a long period of time.[4]

Harvard Medical School professor Maxwell Finland's view of the Hussey-Stetler Test of Time was:

> With over 200,000 physicians and their patients as potential prey, the result would be untold harm [that] might take long to appreciate and evaluate. The manufacturer would have little difficulty in obtaining and publicizing testimonials as to the value of his products from those who may have gained favorable impressions or from those who were fortunate enough not to see harmful effects or who could not recognize them, while those whose results were indeterminate or unfavorable would hesitate to report them or would not be heard.[5]

Compounding pharmacies could be substituted for manufacturer in Dr. Finland's observations and his words would be just as true today as they were almost 40 years ago.

The FDA assumes, without evidence to support this wishful thinking, in Criterion 3 that "fraudulent or quack remedies" are unlikely to be included on the list of substances that may be compounded. Public Citizen hopes this will be the case. However, after reviewing the drug substances nominated for inclusion on the list (see detailed analyses below) a number are of such questionable value for the treatment of any condition that they closely approach being fraudulent or quack remedies.

Because of FDAMA, the FDA has been placed in the position of developing criteria that set back the level of drug regulatory efficacy and safety standards for compounded drugs that existed pre-1962 and in some aspects pre-1938. The blame for the fact that this regression in U.S. drug regulatory standards was passed must be placed directly on the shoulders of the Congress that created FDAMA in 1997.

DOSAGE FORMS THAT ARE TOO TECHNOLOGICALLY COMPLEX TO BE SAFELY COMPOUNDED

Public Citizen believes that rather than starting with a list of bulk drug substances that may be compounded at this time, the FDA should have first developed the list of drugs that present demonstrable technical difficulties for compounding. The FDA's initial focus should have been on the fact that a drug is not a bulk drug substance but a final finished dosage form, and that a number of dosage forms are too technologically

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[4] Quoted in: Mintz M. By prescription only. Boston: Beacon Press, 1967, page 75.

[5] Quoted in: Mintz M. By prescription only. Boston: Beacon Press, 1967, page 74.

complex to be made safely in unregulated compounding pharmacies not required to adhere to Good Manufacturing Practice guidelines.

By not addressing the drugs that present demonstrable difficulties for compounding initially, the FDA criteria neglect a fundamental fact about the safety and effectiveness of any drug, whether or not it is used to treat a less serious or a serious or life-threatening condition. The safety and effectiveness of drugs not only depends on the inherent pharmacology-toxicology and efficacy of the bulk drug substance but also on the design and quality of manufacture of the final finished dosage form. For example, none of the following dosage forms should be allowed on the list of bulk drug substances that may be compounded:

1. Pharmacy compounded immediate release tablets and capsules have not been shown to consistently disintegrate and dissolve so that the active ingredient(s) is released from inactive fillers and excipients and enter the blood stream rather than passing directly through the body. This may result in a treatment failure.

2. Pharmacy compounded controlled release tablets and capsules have not been shown to consistently release their active ingredient(s). If the active ingredient(s) is released too slowly the patient will receive a sub-therapeutic dose before the tablet or capsule passes through the body. If the active ingredient(s) is released too quickly there may be a potential for toxicity if the active ingredient is a potent drug such as morphine or sub-therapeutic levels of the active ingredient(s) may result at the end of the dosing interval.

3. Inhalation solutions used in nebulizers to treat asthma and other breathing difficulties and respiratory tract infections must be sterile. If they are not the inhalation solution can be a vehicle for infecting the patient. Inhalation solutions must also be designed and tested to ensure that the droplets containing the active ingredient(s) are of the proper size to reach the lungs.

4. Intravenous (IV) injection solutions made from bulk drug substances must be sterile for obvious reasons. These must also be tested to ensure that they do not contain agents called pyrogens that can raise temperature.

In the absence of valid scientific evidence that the final finished dosage forms compounded by pharmacists reliably release their active ingredient(s), pharmacy compounded products must be considered inherently ineffective and perhaps dangerous. Dosage forms that should be sterile and pyrogen free, such as IV injections, made from bulk drug substances must also be considered inherently unsafe unless they are produced in facilities meeting Good Manufacturing Practice guidelines. Because of this lack of evidence that these kinds of pharmacy compounded products are safe and effective, they present a risk to the public when used to treat any illness, serious or not.

NOMINATED DRUG SUBSTANCES BEING PROPOSED FOR INCLUSION ON THE BULK DRUGS LIST

The following are Public Citizen's comments on the bulk drug substances nominated for inclusion on the list of substances that may be compounded by pharmacists. Several of the nominated drugs violate FDAMA in that they have been withdrawn from the market because of a lack of evidence of efficacy, but are being considered for inclusion on the list of substances that may be compounded. Other substances, in our view, can only be considered as fraudulent or quack remedies and should not be included on the list. There are a number of bulk drug substances for which there are FDA approved alternatives available and because of the inherent risks of pharmacy compounded dosage forms these should not be included on the list of substances that may be compounded.

1. **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.

There are two FDA approved regimens available for the treatment of duodenal and gastric ulcers associated with the bacteria *Helicobacter pylori* that contain bismuth compounds. These are bismuth subsalicylate and a product that combines ranitidine (Zantac) with bismuth citrate (162 mg of ranitidine, 128 mg of trivalent bismuth and 110 mg of citrate). One approved regimen does not require a bismuth compound. These treatments are effective in eradicating *H. pylori* in 60 to 95 percent of patients.[6]

Bismuth subsalicylate, available without a prescription, is FDA approved for diarrhea and associated abdominal cramps; heartburn and indigestion; relieving nausea and upset stomach.[7]

The consequences of inadequately treated ulcer disease are the possibilities of gastrointestinal perforation and hemorrhage that can result in death. Because commercially prepared FDA approved treatment regimens for the eradication of *H. pylori* are available, allowing pharmacists to compound bismuth citrate for this purpose would place the public at a needless risk of treatment failure from untested and unproven compounded products.

Public Citizen strongly urges that bismuth citrate not be included on the list of bulk drug substances that may be compounded because of the unproven safety and efficacy of pharmacy compounded dosage forms in treating a serious disease.

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[6] Drugs for Treatment of Peptic Ulcers. *The Medical Letter On Drugs and Therapeutics* 1997;39:1-4.

[7] Labeling for Pepto-Bismol. *Physicians' Desk Reference for Nonprescription Drugs* 19th ed. Montvale, NJ: Medical Economics Company, Inc., 1998.

2. **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 (temporary absence of breathing) in premature infants.

An FDA approved product, Caffeine and Sodium Benzoate injection, is available from Taylor Pharmaceuticals of San Clemente, CA. Based on a laboratory study this preparation has been recommended not to be used because sodium benzoate may displace bilirubin from albumin binding sites harming premature infants.[8] However, we could not locate any clinical reports of elevated bilirubin levels in premature infants who had received Caffeine and Sodium Benzoate injection.

Roxane Laboratories of Columbus, OH has an injectable caffeine citrate product that was deemed approvable by the FDA for the treatment of apnea of prematurity on February 24, 1998 but has not been cleared for marketing at this time.[9]

Public Citizen believes that injectable dosage forms, that should be sterile and pyrogen free, cannot be safely produced from bulk drug substances outside of manufacturing facilities adhering to Good Manufacturing Practice guidelines. We urge that caffeine citrate only be included on the list of drugs that may be compounded as an oral solution.

3. **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 (infectious disease of the skin caused by a virus).

Seres Laboratories of Santa Rosa, CA and Glenwood Inc. of Tenafly, NJ ceased production of their cantharidin preparations in 1992 when the FDA required that New Drug Applications be submitted for review for cantharidin-containing products. Dormer Laboratories of Toronto produce a cantharidin product that is unapproved in the U.S. but apparently imported and used in this country.

A literature search was conducted using the National Library of Medicine's Internet version of MEDLINE. The search terms used were cantharidin, English language, human, and randomized controlled trial. No articles were retrieved.

In a separate search, a report was found of a 39-year-old woman treated with a 0.7% cantharidin preparation for plantar warts. This patient's acute inflammatory

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[8] Schiff D, Chan G, Stern L. Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 1971; 48:139-141.

[9] *F-D-C Reports - Pharmaceutical Approvals Monthly* 1999; 4(2):10.

reaction induced by the cantharidin subsided, but there was gradual obliteration of distal leg lymphatic pathways and ultimately development of refractory lower leg lymphedema.[10] Two cases of lymphangitis (inflammation of the lymph vessels) occurred secondary to single topical applications of cantharidin for resistant plantar (sole of the foot) and periungual (area around the nails) warts. Approximately 30 hours following cantharidin administration (with 40% salicylic acid plaster and occlusion), edema, redness, tenderness, and lymphangitis occurred, as described by red streaks running proximally on legs and forearms. Warm compresses and a broad spectrum of antibiotics were administered, and both patients responded.[11]

Martindale: The Extra Pharmacopoeia, a standard source for drug information, makes the following statement about cantharidin: "Owing to the high toxicity of cantharidin it is recommended that preparations containing it should not be used medicinally.[12]

Several FDA approved drugs are available for the treatment of genital warts such as imiquimod (Aldara) and podofilox (Condylox).[13] There are numerous ways to treat warts, but none is universally effective. The most useful and convenient method is perhaps cryotherapy with liquid nitrogen.[14]

Because there are numerous FDA approved options available for the treatment of various types of warts, and because of its toxicity, Public Citizen strongly urges that cantharidin not be included on the list of bulk drug substances that may be compounded by pharmacists.

4. **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.

A literature search was conducted using the Internet version of the National Library of Medicine's MEDLINE database. The search terms choline bitartrate,

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[10] Stazzone AM, Borgs P, Witte CL, et al. Lymphangitis and refractory lymphedema after treatment with topical cantharidin. *Archives of Dermatology* 1998;134:104-106[letter].

[11] Dilaimy M. Lymphangitis caused by cantharidin. *Archives of Dermatology* 1975; 111:1073[letter].

[12] Reynolds JEF(Ed): Martindale: The Extra Pharmacopoeia (electronic version). MICROMEDEX, Inc., Englewood, CO, 1996.

[13] Imiquimod for genital warts. *The Medical Letter On Drugs and Therapeutics* 1997; 39:118-119.

[14] Swerlick RA, Lawley TJ. Eczema, psoriasis, cutaneous infections, acne, and other common skin disorders. In: Harrison's principles of internal medicine 13th ed. Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL eds. New York: McGraw-Hill, Inc., 1994, pages 274-279.

dementia, English, human, and randomized controlled trial were used. Four articles were retrieved but none dealt specifically with the use of choline bitartrate in the treatment of dementia or Alzheimer's-type dementia. Alzheimer's disease is a serious disease and two drugs are FDA approved for treatment of Alzheimer's-type dementia, tacrine (Cognex) and donepezil (Aricept).

A similar search was conducted using the search terms choline bitartrate and infantile colic. A single article was retrieved that was published in 1968 in the *Journal of the Louisiana State Medical Society.* However, this article was not available at a local medical library for our review.

Choline bitartrate is a constituent of a number of dietary supplement products that are promoted to enhance memory. One product, Bayer's One-A-Day Memory & Concentration advertises on the Internet:

> One-A-Day Memory and Concentration goes beyond just Ginkgo biloba.
>
> Our formula combines natural Ginkgo with B-vitamins, important nutrients for healthy nerve function, and choline [as the bitartrate salt], an important nutrient for brain structure and function.[15]

Choline bitartrate is generally recognized as safe, as a dietary supplement, when produced in accordance with Good Manufacturing Practice (GMP) guidelines. There is nothing in FDAMA that prevents compounding pharmacists from producing and selling dietary supplements using choline bitartrate (as long as no medical claim is made) and therefore no reason to include it on the list of substances that may be compounded to be dispensed following a doctor's prescription.

5. **Diloxanide Furoate**. Diloxanide furoate is well characterized chemically. It has been used to treat parasitic diseases such as intestinal amebiasis.

The Medical Letter On Drugs and Therapeutics list as the drugs of choice for the treatment of asymptomatic amebiasis iodoquinol (Yodoxin) or paromomycin (Humatin), both of which are currently produced in this country by FDA regulated manufacturers. Diloxanide furoate is available as Furomide in the United Kingdom and is listed as an alternative treatment in *The Medical Letter* recommendations.[16]

Diloxanide furoate was available free of charge for treatment of asymptomatic *Entamoeba histolytica* cyst passers from the Centers for Disease Control's (CDC) Drug Service. Diloxanide furoate was dropped by CDC's Drug Service last year when paromomycin (Humatin), a drug currently licensed in the U.S. was found more

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[15] http://www.bayercare.com/oad/oadmem.html#ingredients. (March 22, 1999)

[16] Drugs for Parasitic Infections. *The Medical Letter On Drugs and Therapeutics* 1998; 40:1-12.

effective.[17]

For mild to moderate intestinal parasitic disease *The Medical Letter* recommends either metronidazole (Flagyl), a drug approved in this country, or tinidazole (Fasigyn) that is not available in the U.S. Tinidazole has also been nominated for inclusion on the list of drugs that can be compounded. *The Medical Letter* recommendations also state that treatment with metronidazole or tinidazole should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

In the treatment of severe intestinal disease or hepatic (liver) abscess *The Medical Letter* recommends either metronidazole or tinidazole followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

Amebiasis can result in severe complications, depending on the site of the infection, that includes a chronic form of bowel inflammation, bowel dilatation, and rupture into the lining of the heart from an abscess on the liver.[18] Because of the risk of a treatment failure from untested pharmacy compounded dosage forms and the potential complications of this disease and the fact that equally or more effective products are available from FDA regulated manufacturers, Public Citizen strongly urges that diloxanide furoate not be included on the list of bulk drug substances that may be compounded by pharmacists.

6. **Dimercapto-1-Propanesulfonic Acid**. DMPS, a chelating agent, is well characterized chemically. DMPS has been used to treat heavy metal poisoning.

The apparent intended use of DMPS by compounding pharmacists is suspect. The following statement by Bob Scarborough, a compounding pharmacist from Dallas, TX, was made at the FDA's Pharmacy Compounding Advisory Committee on October 14, 1998:

> I would like to address one of the substances, DMPS, which is dimercapto-1 propane succinate, and a very fine substance. We have to prepare that for a large segment of the population because they have mercury poisoning, essentially. Basically, this is due to amalgams that they have in their teeth. I prepare this for them so they can remove and chelate some of the mercury out of their body. I, too, am a victim of just that thing, so I am very interested, of course, in that particular entity.[19]

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[17] Personal Communication March 5, 1999. John Beecher, Pharm.D. CDC Drug Service, Division of Host Factors, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA. (404) 639-3670.

[18] Reed SL. Amebiasis and infection with free-living amebas. In: Harrison's principles of internal medicine 13th ed. Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL eds., New York:McGraw-Hill, Inc., 1994, pages 883-896.

[19] Transcript of The Pharmacy Compounding Advisory Committee, October 14, 1998, page 120 at http://www.fda.gov/ohrms/dockets/ac/cder98t.htm#Pharmacy Compounding Advisor.

The American Dental Association's Council on Scientific Affairs reviewed recent studies concerning the safety of dental amalgam, with an emphasis on studies that have been published since the 1993 review of dental amalgam by the U.S. Public Health Service Committee to Coordinate Environmental Health and Related Programs. The Council concluded that, based on currently available scientific information, amalgam continues to be a safe and effective restorative material.[20]

Another dubious use of DMPS was reported in the November/December 1998 *International Journal of Pharmaceutical Compounding*.[21] A young couple is described who allegedly have environmental mercury toxicity confirmed with a "quick mercury challenge test." The report includes a formula for preparing an injectable solution of DMPS using a filter for final sterilization (filtering is not intended as a method of final sterilization). The couple was administered one vial of DMPS per day and the treatment continued for two months.

Acute and chronic heavy metal poisoning are serious conditions and a number of chelating agents are available from FDA regulated manufacturers for use in heavy metal poisoning.[22] Because of the risk of treatment failure that may result from untested pharmacy compounded dosage forms or the risk of infection if DMPS is compounded as an injection, Public Citizen strongly urges that DMPS not be included on the list of bulk drug substances that may be compounded.

7. **Ferric Subsulfate and Ferric Sulfate Hydrate**. Both are well characterized chemically and have been used as a topical hemostatic agents to control bleeding associated with minor surgical procedures, biopsies, and minor gynecological surgery involving the cervix. Ferric subsulfate solution is also known as Monsel's solution which is commercially available from at least two sources:

A-A Spectrum	Amend Drug & Chemical
Gardena, CA 90248	Irvington NJ
800-772-8786	973-926-0333

FDAMA permits pharmacists to compound commercially available products and

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[20] ADA Council on Scientific Affairs. Dental amalgam: Update on safety concerns. *Journal of the American Dental Association* 1998;129:494-501, from www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=9573704.

[21] Bader T. Environmental compounding - Case 1: Mercury poisoning. *International Journal of Pharmaceutical Compounding* 1998; 2:417.

[22] Graef JW. Heavy metal poisoning. In: Harrison's principles of internal medicine 13th ed. Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL eds. New York: McGraw-Hill, Inc., pages 2461-2466.

as such ferric subsulfate and ferric sulfate hydrate should not be included on the list of bulk drug substances that may be compounded.

8. **Glutamine**. Glutamine, the most abundant amino acid found in the human body, is well characterized chemically. Glutamine has been used in parenteral nutrition regimes in adults.

With the exception of studies in bone marrow transplant patients,[23] data from human studies that make it possible to target glutamine supplemented nutrition to specific patient groups are lacking.[24]

Glutamine is widely promoted on the Internet for bodybuilding. The follow is an example of one such ad:

> Much raved about in the Bodybuilding and Fitness Industry. . . This supplement is the hottest thing to hit the market since Creatine Monohydrate. Glutamine is in high demand by skeletal muscle tissue following physical exertion, and no wonder since it constitutes a large portion of your muscles.[25]

Public Citizen has been led to believe that Pharmacia & Upjohn, a large FDA regulated drug manufacturer, has held a patent on injectable glutamine since 1988. If this is in fact the case compounding pharmacies may be violating the Pharmacia & Upjohn patent when glutamine containing IV nutrition solutions are sold.

There appears to be nothing in FDAMA that would prevent pharmacists from compounding products using the dietary supplement glutamine and as such it should not be included on the list of substances that may be compounded for treatment purposes.

9. **Guaiacol**. Guaiacol is well characterized chemically. It has been used for decades in compounded products as an expectorant.

Guaifenesin is a constituent of both prescription and non-prescription drugs as an expectorant. Due to the limited evidence in the literature regarding the safety and effectiveness of guaiacol and the availability of guaifenesin (a product of doubtful effectiveness) as an alternative, Public Citizen urges that this substance not be included

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[23] Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. *Annals of Internal Medicine* 1992; 116:821-828.

[24] Smith RJ. Glutamine-supplemented nutrition. *Journal of Parenteral and Enteral Nutrition* 1997; 21:183-184[editorial].

[25] http://www.formulatedsciences.com/glutamin.html. (March 22, 1999)

on the list of bulk drug substances that may be compounded.

10. **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 slowly releases iodine when applied to the tissues and has a mild disinfectant action. Bismuth subnitrate and iodoform paste has been applied to wounds and abscesses. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.[26] However, the 1998 edition of the *American Dental Association Guide to Therapeutics* does not list a dental use for iodoform.

Iodoform gauze has been implicated in a case of post-surgical delirium.[27] Eight weeks after a surgery in which both abdominal and subclavian wounds were packed with iodoform gauze, this patient experienced prolonged delirium with both visual hallucinations and psychomotor excitement, and he was incoherent. His plasma iodine concentration was found to be 471 micrograms per deciliter (normal range is 4 to 9 micrograms per deciliter). His delirium improved in parallel with the fall of his plasma iodine levels.

Encephalopathy has been associated with the use of bismuth iodoform paraffin paste (BIPP) for the packing of wound cavities after surgery to the head and neck, although there is some debate as to whether the bismuth or the iodoform component is responsible.[28, 29] However, encephalopathy has been reported after application of iodoform gauze without bismuth.[30]

Because of the toxicity associated with iodoform and the inherent risks of pharmacy compounded dosage forms, Public Citizen urges that this substance not be included on the list of substances that may be compounded.

11. **Metronidazole Benzoate**. Metronidazole benzoate is well characterized chemically and has been used to treat parasitic diseases such as amebiasis and giardiasis.

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[26] Reynolds JEF(Ed): Martindale: The Extra Pharmacopoeia (electronic version). MICROMEDEX, Inc., Englewood, CO, 1996.

[27] Yamasaki K, Morimoto N, Gion T, et al. Delirium and subclavian abscess. *Lancet* 1997;350:1294.

[28] Wilson APR. The dangers of BIPP. *Lancet* 1994; 344:1313-14.

[29] Farrell RWR. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; 344:1637-8.

[30] Roy P-M, Harry P, Cailleux A, et al. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; 344: 1708.

Metronidazole benzoate is contained in several products available in foreign countries for the treatment of parasitic diseases. Because a number of FDA regulated products are approved for the treatment of amebiasis and giardiasis and the risk of treatment failure from unregulated pharmacy compounded dosage forms, Public Citizen urges that metronidazole benzoate not be included on the list of substances that may be compounded.

12. **Myrrh Gum Tincture**. Myrrh is an astringent to mucous membranes; the tincture is used in mouth-washes and gargles for inflammatory disorders of the mouth and pharynx. It has been used internally as a carminative (for gas). Myrrh is a mixture of many substances and has not been well characterized chemically.

Allergic contact dermatitis has been reported with Chinese topical preparations containing myrrh. In Hong Kong, "allergic contact dermatitis due to herbs used by bonesetters in treating musculoskeletal injury is the commonest cause of contact dermatitis around the joints."[31] In traditional Chinese medicine, myrrh containing preparations are promoted as being effective in "staunching, pain-killing, wound healing, activating blood circulation and relaxing sinews and muscles" and is recommended as an ideal remedy . . . for the treatment of injuries and bruises of all kinds."[32]

Numerous mouth washes, both prescription and non-prescription, are available from FDA regulated manufacturers for various conditions. Nothing could be found to indicate a compelling medical need for myrrh gum tincture that is not met by currently available products. Because this substance is not well characterized chemically 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 FDA. Because myrrh has been associated with contact dermatitis when used topically, Public Citizen strongly urges that this substance not be included on the list of substances that may be compounded by pharmacists.

13. **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).

The 1999 *Physicians' Desk Reference* lists a dye-free phenindamine tartrate 25 milligram tablet (Nolahist) available from Carnick Laboratories of Cedar Knolls, NJ. This product is approved by the FDA for the temporary relief of runny nose, sneezing,

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[31] Lee TY, Lam TH. Myrrh is the putative allergen in bonesetter's herbs dermatitis. *Contact Dermatitis* 1993; 29:279.

[32] Lee TY, Lam TH. Allergic contact dermatitis due to a Chinese orthopaedic solution Tieh Ta Yao Gin. *Contact Dermatitis* 1993; 28:89-90.

itching of the nose or throat, and itchy watery eyes due to hay fever or other upper respiratory allergies or allergic rhinitis.

Because FDAMA allows pharmacists to compound substances that are components of FDA approved drugs there is no need to include phenindamine tartrate on the list of substances that may be compounded.

14. **Phenyltoloxamine Dihydrogen Citrate**. Phenyltoloxamine dihydrogen citrate is an antihistamine that is well characterized chemically. This drug is a structural isomer of diphenhydramine (Benadryl).

Phenyltoloxamine dihydrogen citrate is listed as an active ingredient in at least two FDA approved prescription drugs, Magsal and Norel.[33] Because phenyltoloxamine dihydrogen citrate is a constituent of an FDA approved drug, FDAMA allows pharmacists to compound and sell untested dosage forms of this substance. Phenyltoloxamine dihydrogen citrate should not be included on the list of bulk drug substances that may be compounded.

15. **Piracetam**. Piracetam is a derivative of the amino acid gamma-amino butyric acid and is well characterized chemically. This drug 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.

In some Third World countries, piracetam is described as indicated for the treatment of loss of memory, in others for lack of concentration, and in still others for intellectual deterioration. In India and Thailand, piracetam products are promoted for the treatment of mental retardation or learning problems in children. In Malaysia and Singapore, the Middle East, Mexico, and Colombia, they are recommended for the treatment of alcoholics, or alcohol addiction.[34]

It should come as no surprise that piracetam, a drug never approved in the U.S. and promoted heavily in the Third World, has been nominated by compounding pharmacists for inclusion on the list of drugs that may be compounded. Much of what is advocated by compounding pharmacists, and FDAMA itself, brings the American public in range of Third World drug regulatory standards.

A literature search was conducted using the National Library of Medicine's Internet version of the MEDLINE. The search terms piracetam and Down's syndrome were used. No articles were retrieved.

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[33] *Physicians' Desk Reference* 53rd. Montvale, NJ: Medical Economics Company, Inc., 1999, page 3175.

[34] Silverman M, Lydecker M, Lee PR. Bad Medicine. Stanford, CA: Stanford University Press, 1992, page 33.

A year long double-blind, placebo-controlled, parallel-group study with piracetam given in a dose of 8.0 grams a day to 33 patients with probable Alzheimer's disease was published in *Neurology* in 1993.[35] This drug company sponsored study found no improvement in either the piracetam or placebo groups.

Piracetam is advertised heavily on the Internet. The following promotion for piracetam was found on the web site of the MedQuest Pharmacy in Salt Lake City:

> Piracetam is another intelligence booster. There are more than eight hundred published studies documenting its ability to boost short-term memory and overall cognitive function. This brain booster appears to work by providing more oxygen to and enhancing communication between the left and right brain. Creativity, memory, and ease in certain kinds of learning are supposedly increased. If you're interested in purchasing Piracetam, call our pharmacy.[36]

Public Citizen also remains skeptical about the use of piracetam in the drug treatment of dyslexia. We believe that compounding pharmacists' primary purpose in nominating piracetam is to remain in the "brain booster" business, and thus this substance should not be included on the list of substances that may be compounded.

16. **Sodium Butyrate**. Sodium butyrate is a short chain fatty acid that is well characterized chemically. It has been used rectally in an enema formulation to treat several inflammatory bowel conditions, including ulcerative colitis and diversion colitis.

Using the Internet version of the National Library of Medicine's MEDLINE data base a single randomized, double-blind, placebo controlled trial using sodium butyrate alone in the treatment of colitis was found.

Thirty-eight patients with distal ulcerative colitis were randomly assigned to receive nightly butyrate (n = 19) or saline placebo (n = 19) enemas. Patients were assessed clinically and endoscopically at baseline and at 3 and 6 weeks follow- up. Pre- and post-treatment mucosal biopsies were assessed histologically. Response to therapy was determined by changes in a 12-point clinical disease activity index score based on patient symptoms, endoscopic mucosal appearance and physicians' global assessment. Clinical improvement was noted in seven of 19 (37%) butyrate-treated patients and nine of 19 (47%) placebo-treated patients (P = 0.51). Clinical remission was achieved in three patients in each group (16%). No toxicity was observed in either treatment arm. The results suggest that once nightly 60 ml butyrate enemas (80

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[35] Croisile B, Trillet M, Fondarai J, et al. Long-term and high-dose piracetam treatment of Alzheimer's disease. *Neurology* 1993; 43:301-305.

[36] MedQuest Pharmacy at http://www.medquestpharmacy.com/piracetam.asp.(March 21, 1999)

mmol/L) are not efficacious in the treatment of distal ulcerative colitis.[37]

No matter how small the risks may be with a drug, if the drug has not been shown to be effective, the risk of the drug will always outweigh its benefits. A number of products, including enemas, are FDA approved for the treatment of ulcerative colitis. Public Citizen strongly urges that sodium butyrate not be included on the list of drugs that may be compounded.

17. **Taurine**. Taurine is an amino acid that is well characterized chemically. It has been used as a component in parenteral nutrition solutions (for feeding through the veins) for infants and adult patients.

Taurine is constituent of a least two FDA approved parenteral nutrition solutions. TrophAmine 10% manufactured by McGaw contains 25 milligrams of taurine per 100 milliliters and Abbott's Aminosyn-PF 10% product lists 70 milligrams of taurine per 100 milliliters of solution.[38] A commercially available product of cysteine HCl is available from Abbott Laboratories. Cysteine is metabolized in the body to a precursor for taurine.[39]

There is little direct evidence of benefit of the addition of taurine to infant formulas, including parenteral solutions, and it was not considered to be justified without further study.[40, 41]

Taurine is widely promoted on the Internet for a number of uses including:

> A specialized amino acid which is an ion and pH buffer in the heart, skeletal muscles and central nervous system. Taurine is also a potent antioxidant and antitoxin, and in these roles is particularly important to the liver and immune system. Taurine is also a "semi-essential" nutrient.[42]

Taurine is available in at least two commercially available products produced by FDA regulated manufacturers for use in parenteral nutrition and as such should not be

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[37] Steinhart AH, Hiruki T, Brzezinski A, et al. Treatment of left-sided ulcerative colitis with butyrate enemas: a controlled trial. *Alimentary Pharmacology and Therapeutics* 1996;10(5):729-36 [abstract].

[38] Olin BR (ed). *Drug Facts and Comparisons*. St. Louis, MO: Facts and Comparisons, 1999.

[39] DRUGDEX® System: Thompson GA & Strecker CL: L-cysteine use in pediatric TPN (Drug Consult). In: Gelman CR, Rumack BH & Hess AJ (Eds): DRUGDEX® System. MICROMEDEX, Inc., Englewood, Colorado (Edition expires [3/99]).

[40] Perlman M. Taurine and auditory system maturation. *Pediatrics* 1989; 83:796-798.

[41] Tyson JE, Mize CI. More on taurine. *Pediatrics* 1989; 83: 1072-1073[letter].

[42] http://www1.viaweb.com/vitanet/ltaur.html.(March 23, 1999)

included on the list of bulk drug substances that may be compounded.

18. **Thymol Iodide**. Thymol iodide is well characterized chemically. It has been used as a topical agent for its absorbent, protective, and antimicrobial properties.

Because of the limited evidence of the safety and efficacy of thymol iodide for any medical purpose, Public Citizen urges that it not be included on the list of substances that may be compounded.

19. **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 the proposed list, to treat parasitic diseases such as amebiasis and giardiasis.

The treatment of amebiasis with tinidazole was discussed above with diloxanide furoate. For the treatment of giardiasis, *The Medical Letter* recommends metronidazole (Flagyl) as the drug of choice although the use of metronidazole for this purpose is considered investigational by the FDA.[43] Alternatives, in addition to tinidazole, are furazolidone (Furoxone) a drug approved by the FDA for the treatment of protozoal diarrhea and enteritis caused by susceptible organisms and paromomycin (Humatin) whose use is also considered investigational in the treatment of giardiasis by the FDA.

Several drugs produced by FDA regulated manufacturers are available for the treatment of amebiasis and giardiasis. Because of the inherent risks of unregulated pharmacy compounded dosage forms, including the possibility of treatment failure, Public Citizen urges that tinidazole not be added to the list of substances that may be compounded.

20. **4-Aminopyridine**. 4-Aminopyridine (4-AP) is a potassium channel blocker that is well characterized chemically. It 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. 4-AP is also known as fampridine.

The toxicity of fampridine, particularly seizures, has limited its use for all indications. The use of lower doses (e.g., 0.5 mg/kg) greatly minimizes the risk of seizures, although this may not be clinically effective in some patients. Tolerance has also occurred during oral fampridine therapy, requiring the use of higher doses

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[43] Drugs for Parasitic Infections. *The Medical Letter On Drugs and Therapeutics* 1998;40:1-12.

which can produce seizure activity.[44]

The availability of fampridine is advertised on the Internet by some compounding pharmacies such as the Medicine Shoppe in Arlington, Texas:

> How do I get 4-Aminopyridine?
>
> At this time, 4-Aminopyridine is available only from a compounding pharmacy. It does require a doctor's prescription, so please feel free to have your doctor call us to discuss the medication, or show him this information.[45]

Acorda Therapeutics of Hawthorne, NY is seeking approval of a timed release dosage form of fampridine as an orphan drug for the treatment of spinal cord injury and multiple sclerosis.[46] If Acorda Therapeutics receives approval of its fampridine product, under FDAMA, compounding pharmacists will be free to produce unregulated dosage forms of this drug and there will be no need to include it on the list of substances that may be compounded.

21. **Betahistine Dihydrochloride**. Betahistine dihydrochloride is a chemically well characterized histamine analog. This drug was formerly approved by the FDA to treat the symptoms of vertigo in patients with Meniere's disease. In 1970 its New Drug Application was withdrawn by the FDA because of lack of substantial evidence of effectiveness.

Over 30 years ago *The Medical Letter on Drugs and Therapeutics* reviewed betahistine in the treatment of Meniere's disease and found that the published clinical evidence for the effectiveness of the drug consisted of two studies by the same author and uncontrolled observations. The studies were described as "double-blind cross-over," the controls were seriously inadequate since in each study similar code designations were used for all drug samples, with different code designations for all placebo samples.[47]

The Medical Letter editors concluded their review of betahistine by saying:

> Although the Food and Drug Administration is required by law to base its approval of new drugs on well-controlled trials by qualified investigators, there have been no well-

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[44]DRUGDEX® System: Gelman CR, Rumack BH & Hess AJ (Eds): DRUGDEX® System. MICROMEDEX, Inc., Englewood, Colorado (Edition expires [3/99]).

[45] http://www.rxcompound.com/html/body_multiple_sclerosis.html. (March 23, 1999)

[46] Personal communication with Acorda Therapeutics March 17, 1999.

[47] Betahistine hydrochloride (Serc) for Meniere's Syndrome. *The Medical Letter on Drugs and Therapeutics* 1967;9:29-30,

controlled trials which would permit the conclusion that betahistine is effective prophylactically or therapeutically against any symptom or group of symptoms comprising Meniere's syndrome.

Betahistine was withdrawn from the market because of lack of substantial evidence of effectiveness and therefore should not be included on the list of bulk drug substances that may be compounded. Section 503A (b)(1)(C) of FDAMA provides that a pharmacist or physician may 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." Betahistine must be added to this list.

22. **Cyclandelate**. Cyclandelate is well characterized chemically and was approved by the FDA for treatment for intermittent claudication caused by arteriosclerosis obliterans, and as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multi-infarct or Alzheimer's type. Cyclandelate was removed from the market for lack of effectiveness for these approved indications in 1997.

In their 1964 review of cyclandelate, the editors of *The Medical Letter on Drugs and Therapeutics* stated:

> Because the course and symptoms of cerebrovascular disorders are so variable, proof of the usefulness of a drug in these disorders requires soundly controlled trials; there is little evidence of such controls anywhere in the extensive clinical literature on these drugs.[48]

The Medical Letter editors concluded:

> Many symptoms have been attributed to spasm of arteriosclerotic cerebral vessels. These include episodes of vertigo, tinnitus, hearing loss, headache, disorientation and "little strokes." It has not been shown, however, that such symptoms are in fact due to spasm of cerebral arteries, nor that vasodilator drugs are effective in preventing or relieving these symptoms. They may, on the contrary, decrease blood flow to the brain by causing vasodilatation elsewhere, with a reduction in systemic blood pressure.

Two FDA approved drugs are available for the treatment of Alzheimer's type dementia. These are tacrine (Cognex) and donepezil (Aricept). Both pentoxifylline (Trental) and cilostazol (Pletal) are FDA approved for the treatment of intermittent claudication.

Cyclandelate was withdrawn from the market because of lack of substantial evidence of effectiveness and therefore should not be included on the list of bulk drug

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[48] Cyclospasmol, Vasodilan and Arlidin in cerebrovascular disease. *The Medical Letter on Drugs and Therapeutics* 1964;6:27-28.

substances that can be compounded. Section 503A (b)(1)(C) of FDAMA provides that a pharmacist or physician may not "compound a drug product that appears on a list published by the Secretary in the *Federal Register* on 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." Cyclandelate must be added to this list of drugs which may not be compounded.

23. **3, 4-Diaminopyridine**. This drug substance is well characterized chemically and is a potassium channel blocker that may enhance the release of acetylcholine from nerve terminals. It has been used in the treatment of several neuromuscular disorders, including Lambert-Eaton myasthenic syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis.

The Jacobus Pharmaceutical Company, Inc., of Princeton, NJ produces 3, 4-diaminopyridine bulk powder. This company has also produced a tablet dosage form for approximately the last 1.5 years. Both the bulk powder and the tablets are available without charge. Tablets are shipped under cool conditions to any physician who will complete simple forms required by the FDA for the compassionate use of an experimental drug. Jacobus products are produced by an FDA regulated company and has established that 3, 4-diaminopyridine is stable for four years if kept refrigerated.[49]

The dosage is critical. An overdosage by a factor of two generally will put the patient in the range where convulsions have been noted. An under dosage by a factor of two will lead to failures.

Because of the inherent risks of unregulated pharmacy compounded dosage forms and the fact that 3, 4-diaminopyridine is readily available free of charge from an FDA regulated company this compound should not be included on the list of substances that may be compounded.

24. **Dinitrochlorobenzene.** DNCB is well characterized chemically and 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.

DNCB is a highly toxic substance that may be fatal if inhaled, swallowed, or absorbed through the skin. High concentrations of this substance are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin.

Because of the dangers of DNCB and the fact that there are a number of FDA approved products for the treatment of warts and that skin test antigens produced by FDA regulated manufacturers are available to assess cell-mediated immunity, Public

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[49] Personal communication with Laura R. Jacobus, Jacobus Pharmaceutical Company, Inc., Princeton, NJ March 17, 1999.

Citizen urges that this substance not be included on the list of substances that may be compounded.

25. **Diphenylcyclopropenone**. Diphenylcyclopropenone is well characterized chemically. It has been used for the topical treatment of extensive alopecia areata. Alopecia areata is a condition characterized by circumscribed, inflamed areas of baldness on the scalp, eyebrows, and bearded portion of the face. Its cause is unknown.

Diphenylcyclopropenone has been associated with severe skin reactions when used to treat various forms of alopecia.[50, 51] This substance has also been identified as a causative agent of contact dermatitis among pharmacists and dermatology clinic staff.[52]

The FDA is still reviewing the nomination of diphenylcyclopropenone for the list, and we will withhold further comment until the Agency has completed its review.

26. **Hydrazine Sulfate**. Hydrazine Sulfate is well characterized chemically and has been used to treat cachexia (wasting) in cancer patients. The substance, however, is extremely toxic. Multiple exposures to hydrazine sulfate have caused liver and kidney damage, GI damage, convulsions, and coma. It is also considered by the International Agency for Research on Cancer to be a potential carcinogen (cancer causing agent) to humans.

Hydrazine sulfate is at the center of an alleged conspiracy by the National Cancer Institute (NCI) to deny cancer patients access to this compound. *Penthouse* magazine has maintained for 14 years that the NCI has prevented cancer patients access to hydrazine sulfate as an "effective cancer therapy."[53] Allegations had been made by Dr. Joseph Gold, the developer and leading proponent of hydrazine sulfate, that three NCI sponsored clinical trials of hydrazine sulfate that disapproved any therapeutic role for the substance in cancer patients were methodologically flawed. As a result of Dr Gold's charges the General Accounting Office (GAO) was asked to make a report in 1995 on the allegations to the Chairman and Ranking Minority Member of

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[50] Oh C-W, Han K-D, Kim T-H. Bullous erythema multiforme following topical diphenylcyclopropenone application. *Contact Dermatitis* 1998; 38:220-221.

[51] Alam M, Gross EA, Savin RC. Severe urticarial reaction to diphenylcyclopropenone therapy for alopecia areata. *Journal of the American Academy of Dermatology* 1999;40:110-112.

[52] Adisesh A, Beck M, Cherry NM. Hazards in the use of diphencyprone. *British Journal of Dermatology* 1997;136:470[letter].

[53] Kamen J. Cancer empire strikes back. http://www.kathykeeton-cancer.com/strikesback/.(March 23, 1999)

the Human Resources and Intergovernmental Relations Subcommittee of the House Committee on Government Reform and Oversight.[54]

The GAO report, titled Cancer Drug Research: Contrary to Allegation, NIH Hydrazine Sulfate Studies Were Not Flawed, concluded that:

> The data showed that hydrazine sulfate therapy does not result in any significant benefit. Specifically, in two trials involving over 500 patients with inoperable non-small-cell lung cancer, the addition of hydrazine sulfate to a standard chemotherapy regimen resulted in somewhat worse quality of life, no effect on weight gain or loss, and a suggestion of decreased survival when compared with placebo. In the trial evaluating the use of hydrazine sulfate as the sole therapeutic intervention in 127 patients with metastatic colon cancer, survival time for patients receiving hydrazine sulfate was decreased compared with patients given placebo.[55]

Hydrazine sulfate is a "cult" drug extensively promoted on the Internet not only for cachexia associated with cancer, but also as a treatment for cancer. The following is an example of the type of material that is appearing on the Internet about hydrazine sulfate:

> Hydrazine Sulfate and Effective Cancer Therapy
> Article by
> Julian Whitaker, M.D.
>
> Hydrazine sulfate has helped thousands of people. In spite of this checkered history, hydrazine sulfate has been used by thousands of desperate cancer patients over the past 25 years with remarkable results, like those experienced by Kathy Keeton. Although it has in many cases caused complete remission of cancer, hydrazine sulfate is primarily an anti-cachexia drug. Studies performed in the former U.S.S.R. and UCLA Medical Center demonstrate improvements in appetite, weight gain, albumin maintenance (albumin is a blood protein and low levels of it are an extremely accurate predictor of mortality), energy levels, quality of life and, in terminal patients, survival time. It also appears to have ameliorating effects when taken during chemotherapy, and especially with radiation therapy.[56]

Public Citizen strongly urges that hydrazine sulfate not be included on the list of drugs that can be compounded by pharmacists. This substance has been disproved to have any legitimate role in the treatment of cancer or cachexia. It may lower the quality of life of cancer patients and decrease their survival as well.

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[54] Letter from Bernice Steinhardt, Director, Health Services Quality and Public Health Issues, General Accounting Office to Leonard Weiss, Ph.D., Minority Staff Director, Senate Committee on Governmental Affairs dated January 8, 1998.

[55] U.S. General Accounting Office. Cancer drug research. GAO/HEHS-95-141 hydrazine sulfate. September 13, 1995.

[56] http://www.kathykeeton-cancer.com/index.html.(March 23, 1999)

27. **Pentylenetetrazol**. Pentylenetetrazol is well characterized chemically and was approved by the 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 the elderly. The drug was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness for all of these approved indications in 1982.

Pentylenetetrazol was reviewed in *The Medical Letter on Drugs and Therapeutics* in 1965 and the editors found:

> Uncontrolled studies of the oral preparations have resulted in almost uniformly favorable reports on their effectiveness in elderly persons. But a controlled study showed no difference in effects on mental symptoms between Vita-Metrazol [a mixture of pentylenetetrazol with vitamins] and a placebo (G,G, Haydi et al., Curr. Ther. Res., 3:255, 1961). And in another controlled study of 40 aged patients in a psychiatric unit, no significant differences were found between the Metrazol group and the control group (L. Hollister and W.F. Fitzpatrick Jr., J. Amer. Geriat. Soc., 3:197, 1955).
>
> The improvement reported with Metrazol in uncontrolled trials is undoubtedly due to placebo effects and to the fact that physicians, nurses and other personnel respond to the patient with increased expectation and therapeutic involvement.[57]

A National Institute of Mental Health review of pentylenetetrazol published in 1979 found:

> Although more than 50 clinical trials have been conducted in aged subjects with pentylenetetrazol and the various elixirs and preparations containing the compound, there is virtually no methodologically reasonable evidence to support such indications. None of the 16 controlled studies in the literature clearly indicates that the compound exerts a beneficial effect on cognitive function in the aged.[58]

Pentylenetetrazol in available in the Third-World and has been associated with seizures. The case of a 22-year-old male has been described with uncontrolled, generalized tonic-clonic seizures for one year. The patient was taking a product containing pentylenetetrazol 100 milligrams per milliliter with dihydrocodone 5 milligrams per milliliter. When this drug was discontinued the seizures did not recur.[59]

Pentylenetetrazol's only apparent use is in laboratory animal experiments to

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[57] Metrazol and other drugs in emotional disorders of old age. *The Medical Letter on Drugs and Therapeutics* 1965; 7:19-20.

[58] Crook T. Central-nervous-system stimulants: appraisal of use in geropsychiatric patients. *Journal of the American Geriatrics Society* 1979; 27:476-477.

[59] Mehndiratta MM, Rohatgi A, Husain S, et al. Leptazole-induced seizures. *The Annals of Pharmacotherapy* 1994; 28:285-286[letter].

induce seizure as a screening method for drugs that may be useful in the treatment of certain types of seizure disorders of drugs which may not be compounded.[60]

Pentylenetetrazol was withdrawn from the market because of lack of substantial evidence of effectiveness and therefore should not be included on the list of bulk drug substance that may be compounded. Section 503A (b)(1)(C) of FDAMA provides that a pharmacist or physician may 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." Pentylenetetrazol must be added to this list.

28. **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.

Colloidal silver is a dangerous quack product that is being heavily promoted on the Internet. The following was taken from the web site of Allison's Apothecary, 3628 East Willow Avenue, Phoenix, AZ:

> Without overstating the case, it may be time to recognize colloidal silver as not only the safest medicine on Earth, but also the most powerful.
>
> Since there is not enough room to list all the diseases against which colloidal silver has been used successfully, here is a tiny sample; acne; allergies; appendicitis; acne, allergies, appendicitis, arthritis, athlete's foot, bladder inflammation, blood parasites, blood poisoning, boils, burns, candida, cholera, colitis, conjunctivitis, cystitis, dermatitis, herpes, impetigo, indigestion, keratitis, leprosy, leukemia, lupus, lymphangitis, Lyme disease, malaria, meningitis, neurasthenia, parasitic infections: viral, fungal and bacterial pneumonia, pleurisy, prostate pruritus ani, psoriasis, purulent opthalmia, rhinitis, rheumatism, ringworm, scarlet fever, septic conditions of the eyes, ears, mouth, and throat, seborrhea, septicemia, shingles, staphylococcus and streptococcus infections, stomach flu, syphilis, thyroid, tuberculosis, tonsillitis, toxemia, trachoma, all forms of virus, warts, whooping cough, yeast infection, stomach ulcer, canine parovirus and other veterinary uses, and all fungal and viral attacks on plants. Simply spray diluted silver on the leaves and add to the soil.[61]

Long-term use of silver preparations can lead to argyria, a condition in which silver salts deposit in the skin, eyes, and internal organs, and the skin turns ashen-gray. Many cases of argyria occurred during the pre-antibiotic era when silver was a common ingredient in nose drops. When the cause became apparent, doctors stopped recommending their use, and reputable manufacturers stopped producing them. The

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[60] Franz DN. Central nervous system stimulants. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's the pharmacologic basis of therapeutics. 7th ed. New York: Macmillan, 1985:582-585.

[61] http://apothecary.hypermart.net/ (March 24, 1999)

official drug guidebooks (*United States Pharmacopeia* and *National Formulary*) have not listed colloidal silver products since 1975.[62]

In October 1996, the FDA proposed to establish that all over-the-counter (OTC) drug products containing colloidal silver ingredients or silver salts for internal or external use are not generally recognized as safe and effective and are misbranded. The FDA issued this proposal because many products containing colloidal silver ingredients or silver salts are being marketed for numerous serious disease conditions and the FDA is not aware of any substantial scientific evidence that supports the use of OTC colloidal silver ingredients or silver salts for these disease conditions.[63] Public Citizen strongly urges that the FDA finalize this proposed rule as soon as possible.

Numerous FDA approved ophthalmic products are available for the treatment of conjunctivitis and as antibiotics for use in the eyes and because of its association with argyria mild silver protein should not be included on the list of bulk drug substances that may be compounded.

29. **Squaric Acid Dibutyl Ester**. Squaric acid dibutyl ester (SADBE) is well characterized chemically and is a contact sensitizer that has been used as a topical treatment alopecia areata and warts.

SADBE is a potent topical sensitizer used in the treatment of various cutaneous conditions. Currently, there are no standardized protocols defining safe sensitization methods or treatment regimens following sensitization. SADBE was applied with a cotton swab to the forearm of 14 patients to induce contact dermatitis. Ten of 14 patients (71%) had severe eczematous reactions at the site of sensitization, and 9 of 14 (64%) developed disseminated reactions.[64] There have been other reports of severe skin reactions with the use of SADBE.[65, 66]

The FDA is still reviewing the nomination of diphenylcyclopropenone, and we will

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[62] Barrett S. Colloidal silver: risk without benefit. Quackwatch Web site at http://www.quackwatch.com dated September 13, 1998.

[63] Department of Health and Human Services, Food and Drug Administration. Over-the Counter Drug Products Containing Colloidal Silver Ingredients or Silver Salts. *Federal Register* Vol. 61, No. 200, October 15, 1996, pages 53685-53688.

[64] Foley S, Blattel SA, Martin AG. Clinical sequelae associated with squaric acid dibutylester topical sensitization. *American Journal of Contact Dermatitis* 1996; 7:104-108[abstract].

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withhold further comment until the Agency has completed its review.

PROCEDURES FOR NOMINATING BULK DRUG SUBSTANCES THAT MAY BE COMPOUNDED

It appears all that is required to nominate a bulk drug substance for compounding is the transmittal of the name of the substance to the FDA. This places an inordinate burden on an already overburdened FDA that must now search for a therapeutic justification and the toxicity of every bulk drug substance nominated by compounding pharmacists. Rather than the FDA, the compounding pharmacists who will profit should make the case for a compelling medical need for unproven products, disapproved products, or products that have never been approved in the U.S. that they wish to sell.

At a minimum the following information should accompany the nomination of a bulk drug substance and such information made available to the public:

1. The name and address of the person or organization making the nomination.

2. The intended use for the nominated bulk drug substance.

3. The type of dosage forms that will be prepared from the nominated bulk drug substance.

4. A list of commercially available FDA regulated drugs that are approved for the use intended for the nominated bulk drug substance.

5. Results of a literature search, with citations, documenting the effectiveness and safety of the bulk drug substance for its intended use.

6. Any reports of adverse events associated with the nominated bulk drug substance.

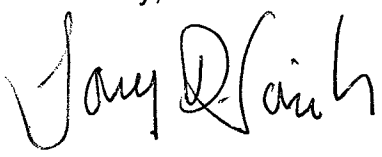
THE PATIENT'S RIGHT OF SELF DETERMINATION

Public Citizen believes that many consumers are not being told either by their doctor or compounding pharmacist that the products they are receiving have not been tested for safety and efficacy and are not required to be produced in facilities meeting good manufacturing guidelines. Because consumers may not have been given sufficient information to make an informed decision about their drug treatment we urge that the FDA require in the Pharmacy Compounding regulations that an auxiliary label be attached to all compounded drugs saying:

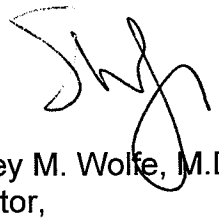
THIS COMPOUNDED DRUG HAS NOT BEEN TESTED OR REVIEWED BY THE FOOD AND DRUG ADMINISTRATION (FDA) FOR SAFETY AND EFFECTIVENESS AND HAS NOT BEEN PRODUCED IN A FACILITY MEETING GOOD MANUFACTURING PRACTICES GUIDELINES.

This simple factual statement will provide consumers with at least some objective information to make an informed decision about accepting or rejecting the risks from pharmacy compounded drugs. Surely, compounding pharmacists must agree with the public's right to objective information about their drugs in order to make informed decisions about their health.

Sincerely,



Larry D. Sasich, Pharm.D., M.P.H., FASHP
Public Citizen's Health Research Group



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