UNPUBLISHED
PRELIMINARY DRAFT

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 identifying the bulk drug substances that may be used in pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (FD&C Act) even though they are neither the subject of a current United States Pharmacopoeia (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 (Modernization Act).

DATES: Submit written comments on or before (insert date xxx days after date of publication in the FEDERAL REGISTER).

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 Place, 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 adds section 503A to the FD&C Act (21 U.S.C. 353a), clarifies the status of pharmacy compounding under federal law. According to section 127, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient are potentially exempt from three key provisions of the FD&C Act: the adulteration provision of section 501(a)(2)(B) (concerning the good manufacturing practice requirements); the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and 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, however, a compounded drug product must satisfy several additional

requirements. One of these additional requirements, found in section 503A(b)(1)(A) of the FD&C 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; 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 list being proposed in this rulemaking). For purposes of construing this statutory provision, the term "bulk drug substance" is defined in FDA regulations at 21 CFR 207.3(a)(4) and incorporated by reference in section 503A(b)(1)(A) 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."

II. FDA Development of a Bulk Drugs List

Although the Modernization Act directs FDA to issue a list of bulk drug substances that may be used in pharmacy compounding, it does not specify a process through which candidates for the list are to be identified. On April 7, 1998, FDA published a Federal Register notice (63 FR 17011) inviting all interested persons to nominate bulk drug substances for inclusion on the list. In response to this request, FDA received nominations for 38 different drug substances. The nominations came from Abbott Laboratories, 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 Corporation, Scottsdale Skin & Cancer Center Ltd., Dermatology Associates, and Neil Brody, M.D.

Nine of the nominated substances are the subject of a USP or NF monograph or are components of FDA-approved drugs. As a result, they already qualify for use in pharmacy compounding under section 503A(b)(1)(A)(i) of the FD&C Act (assuming they satisfy all other applicable FD&C Act requirements). The nine are clotrimazole, fluocinonide, hydrocortisone, hydroquinone, pramoxine, quinacrine hydrochloride, salicylic acid, tretinoin,

and triamcinolone. These substances are not addressed further in this proceeding.

The remaining twenty-nine nominated substances have been evaluated by FDA to determine whether they are appropriate for inclusion on the bulk drugs list, and, therefore, appropriate for use in general pharmacy compounding. FDA used three evaluation criteria to assess these nominations: (1) the chemical characterization of the substance; (2) the safety of the substance; and (3) the historical use of the substance in pharmacy compounding.[1] These criteria, as well as the bulk drugs list itself, were developed by FDA in consultation with the United States Pharmacopoeia.

In evaluating the nominated substances under these criteria, the agency employed a balancing test. No single factor was dispositive, nor was each necessarily given equal weight. Rather, the agency considered the totality of the circumstances and balanced all the information at its disposal.

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[1] 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 thnaFD&C Act (see 21 U.S.C. 353a(b)(1)(A)(ii)). This is a separate condition required to qualify for the exemptions provided by section 503A of the FD&C Act. The FD&C Act also provides that all bulk drug substances used in compounding must be accompanied by valid certificates of analysis (see 21 U.S.C. 353a(b)(1)(A)(iii)).

Under the first factor, the chemical characterization of the substance, FDA considered each substance's purity, identity, strength, and quality. This information was used to evaluate whether the substance could be identified consistently based on its chemical characteristics. If a substance could not be well-characterized chemically, this factor weighed against its inclusion on the bulk drugs list because there could 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 factor, FDA addressed the safety issues raised by the use of each substance in general pharmacy compounding. This evaluation proved both difficult and unique because none of the nominated substances has been throughly investigated in well-controlled animal toxicology studies. Additionally, there are no well-controlled clinical studies in humans to substantiate safe use of the substances. The agency, therefore, had at its disposal either none or very little of the type or quality of information about the nominated substances that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the nominated substances, then,

the agency evaluated the limited information available about each substance's acute toxicity and other reported toxicities, including mutagenicity, teratogenicity, and carcinogenicity. The agency also considered reports and abstracts in the literature about adverse reactions the substances have caused in humans. In cases where the toxicity of a substance appeared to be significant, FDA further considered the availability of alternative approved therapies. The existence of alternative approved therapies in those cases weighed against inclusion on the proposed list because the risks of using the substance were more likely to outweigh the benefits.

Under the third factor, the historical use of the substance in pharmacy compounding, FDA considered 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 factor weighed in favor of list inclusion for nominated substances that have enjoyed long-standing and widespread use in pharmacy compounding for a particular indication. Evidence of both widespread and long-standing use for a particular indication was viewed by the agency as indicative of the substance's perceived usefulness and acceptance in the medical community. Fraudulent or "quack" remedies would

likely be excluded from the bulk drugs list by this historical use factor because the practice of compounding such drugs is not expected to have been sufficiently prevalent and long-standing.

The information assessed by FDA under each of the evaluation criteria was obtained from journal reports and abstracts from reliable medical sources, including peer reviewed medical literature. Some of this information was submitted in support of the nominations, as had been requested by FDA. The remainder FDA gathered through independent searches of medical and pharmaceutical databases. The agency did not review any raw data. The materials FDA relied on in evaluating the nominations can be found in the docket identified by the number in brackets in the heading of this document.

The amount of relevant information available about the nominated substances, including their uses and safety, varied considerably. 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, however, the agency reviewed only a limited sample of the available sources.

Based on the foregoing discussion it should be clear, but FDA would like to emphasize, that its assessment of the nominated substances was, out of necessity, far less rigorous and far less extensive than the agency's ordinary evaluation of drugs as part of the new drug approval process. For this reason, the inclusion of a drug substance on the proposed bulk drugs list must 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 FD&C Act (21 U.S.C. 352(a)).

In response to this proposed rule, FDA is specifically seeking comment on whether the substances on this list should remain on the list and whether the substances that have been rejected should remain off the list. After evaluating these comments, FDA will issue the bulk drugs list as a final rule which will be codified in the Code of Federal Regulations. The

final 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 at any time after the final rule is published to amend the list by adding or removing one or more bulk drug substances.

III. Description of the Proposed Rule

A. Nominated Drug Substances Being Proposed For Inclusion in the Bulk Drugs List

Under section 503A(d)(2) of the FD&C Act, FDA is proposing that the following twenty 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 FD&C 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 will qualify for section 503A's compounding exemptions, unless separately listed.

Since passage of the 1962 amendments to the FD&C Act, the

standard for approval of new drugs requires a demonstration of both safety and effectiveness. Drug products that meet this standard have an FDA approval in effect and are generally listed in the publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book. FDA intends for the Orange Book to serve as the reference source for compounders to identify FDA-approved drugs for purposes of complying with section 503A(b)(1)(A)(i)(III) of FD&C Act. Drug products that were discontinued from marketing before the 1984 Amendments to the FD&C Act are not listed in the Orange Book, however, even though they may still have approvals in effect (i.e., approvals not formally withdrawn by FDA). When necessary, compounders will be able to ask the agency whether a particular drug product that does not have a current USP or NF monograph and does not appear in the Orange Book is nevertheless an approved drug for compounding purposes.

This list is being proposed as § 216.23 of Title 21 of the Code of Federal Regulations. This new section will be included in a new part, 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 FD&C Act. During the pendency of this proposed rule, FDA intends

to exercise its enforcement discretion and not take regulatory action against any drug product that is compounded using a bulk drug substance that appears on proposed § 216.23 if all other applicable requirements of the FD&C Act have been satisfied.

NOTE: FDA has identified the following substances as *likely* candidates for inclusion on the bulk drugs list, but questions have been raised about some of the drugs concerning their historical use in pharmacy compounding (i.e., the length of time they have been used in pharmacy compounding, the medical conditions they have been used to treat, and how widespread their use has been). On these substances, FDA is specifically seeking public comment at the Advisory Committee meeting regarding these issues.

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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported.

Caffeine Citrate

Caffeine citrate, which is a mixture of caffeine and citric acid, is well-characterized chemically. Caffeine citrate stimulates the central nervous system and 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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported.

Choline Bitartrate

Choline bitartrate is chemically well-characterized. 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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported. 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). FDA is soliciting public comment on how long choline bitartrate has been used in pharmacy compounding and how widespread that use has been.

Diloxanide Furoate

Diloxanide furoate is chemically well-characterized. 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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA is soliciting public comment on how long diloxanide furoate has been used in pharmacy compounding and how widespread that use has been.

Dimercapto-1-Propanesulfonic Acid

Dimercapto-1-Propanesulfonic (DMPS), a chelating agent, is chemically well-characterized. DMPS has been used to treat heavy metal poisoning. At doses reported in the literature for this indication, DMPS appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA is soliciting public comment on how long DMPS has been used in pharmacy compounding and how widespread that use has been.

Ferric Subsulfate[2]

Ferric subsulfate is well-characterized chemically. It has

[2] 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.

been used topically as a hemostatic agent to control bleeding, including cervical bleeding. At doses reported in the literature for this indication, ferric subsulfate appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. 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. FDA is soliciting public comment on how long ferric subsulfate has been used in pharmacy compounding and how widespread that use has been.

Ferric Sulfate Hydrate

Ferric sulfate hydrate is well-characterized chemically. It has been used topically as a hemostatic agent to control bleeding in dermatological and dental procedures. At doses reported in the literature for these indications, ferric sulfate hydrate appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. 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. FDA is soliciting public comment on how long ferric sulfate hydrate has been used in pharmacy compounding and how widespread that use has been.

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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported.

Guaiacol

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

Iodoform

Iodoform is chemically well-characterized. 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 two-year bioassays

conducted by the National Toxicology Program (NTP), iodoform was found to be noncarcinogenic in rats and mice. At doses reported in the literature for these indications, iodoform appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. However, because the literature is limited to the topical and intra-dental use of this substance, FDA is proposing to include it on the bulk drugs list for topical and intra-dental use only. FDA is soliciting public comment on how long iodoform has been used in pharmacy compounding and how widespread that use has been.

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 non-toxic. Serious adverse reactions associated with the use of myrrh gum tincture have not been commonly reported. FDA is soliciting public comment on how long myrrh gum tincture has been used in pharmacy compounding and how widespread that use has

been.

Phenindamine Tartrate

Phenindamine tartrate is chemically well-characterized. 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 non-toxic, 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). FDA is soliciting public comment on how long phenindamine tartrate has been used in pharmacy compounding and how widespread that use has been.

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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA is soliciting public comment on how long phenyltoloxamine dihydrogen citrate has been used in pharmacy compounding and how widespread that use has been.

Piracetam

Piracetam, a derivative of the amino acid gamma-amino butyric acid, is chemically well-characterized. Believed by some to enhance certain cognitive skills, piracetam has been used to treat children with dyslexia and patients with Alzheimer's disease, among other cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA is soliciting public comment on how long piracetam has been used in pharmacy compounding and how widespread that use has been.

Silver Protein Mild

Mild silver protein is chemically well-characterized. It has been used extensively and for many years to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. At doses reported in the literature for this indication, mild silver protein appears to be relatively

non-toxic, and serious adverse reactions associated with its use have not been commonly reported. When administered internally, however, mild silver protein 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). For this reason, FDA is proposing to include mild silver protein on the bulk drugs list for ophthalmic use only.

Sodium Butyrate

Sodium butyrate is a short chain fatty acid that is chemically well-characterized. It has been used rectally in an enema formulation to treat ulcerative colitis and radiation proctitis. At doses reported in the literature for these indications, sodium butyrate appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported. 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 chemically well-characterized. 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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported.

Thymol Iodide

Thymol iodide is chemically well-characterized. 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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA notes, however, that it was able to identify only two articles in the literature concerning thymol iodide. FDA is soliciting public comment on additional information about this substance generally, including how long it has been used in pharmacy compounding and how widespread that use has been. Additionally, 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.

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 non-toxic, and serious adverse reactions associated with its use have not been commonly reported. FDA is soliciting public comment on how long tinidazole has been used in pharmacy compounding and how widespread that use has been.

NOTE: The following substances have been identified as possible candidates for inclusion on the bulk drugs list, but FDA has specific concerns about the historical use as well as the toxicity of these substances, about which the agency is soliciting Advisory Committee input.

4-Aminopyridine

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 non-depolarising muscle relaxants. The toxicological properties of 4-AP have not been thoroughly investigated in animal studies. 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. Until more information is available about the historical use and safety of 4-AP, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

3,4-Diaminopyridine

3,4-Diaminopyridine (DAP), which is chemically well-characterized, 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 (LEMS), myasthenia gravis, amyotrophic lateral sclerosis, and multiple sclerosis. The toxicological properties of DAP have not been thoroughly investigated in animal studies. 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. Until more information is available about the

historical use and safety of DAP, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Dinitrochlorobenzene

Dinitrochlorobenzene (DNCB) has been used in the treatment of recurrent melanoma and as a skin sensitizer to estimate immune system competency. Chemically, it is well-characterized. DNCB is highly toxic in doses as little as 5 to 50 mg/kg, and 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. Until more information is available about the historical use and safety of DNCB, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Hydrazine Sulfate

Hydrazine sulfate is chemically well-characterized 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. Until more information is available about the historical use and safety

of hydrazine sulfate, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

Metronidazole Benzoate

Metronidazole benzoate is well-characterized chemically. It has been used to treat periodontitis and amoebiasis. FDA assumes that the toxicities for metronidazole benzoate would be the same as the toxicities of metronidazole itself, which is an FDA-approved drug. Serious adverse reactions associated with the use of metronidazole benzoate have not been commonly reported. However, FDA has questions about the effect of the benzoate salt on the dosing and bioavailability of this substance. FDA is soliciting public comment on these issues. FDA is also soliciting public comment on how long metronidazole benzoate has been used in pharmacy compounding and how widespread that use has been. Until more information is available about the historical use, the safety, and the bioavailability of metronidazole benzoate, FDA questions whether the substance is appropriate for inclusion on the bulk drugs list.

B. Nominated Drug Substances That Are Not Being Proposed for Inclusion on the Bulk Drugs List

FDA is proposing that the following five nominated drug

substances be excluded from the list of bulk drug substances that may be used in compounding under the exemptions provided in section 503A of the FD&C Act. After carefully considering the relevant evaluation criteria, FDA does not believe that general compounding with any of these substances is appropriate, either during the pendency of this proposed rule, or after the rule is finalized.

Four of the five substances are being excluded because FDA, in the past, took official action to remove them from the market for reasons of safety or efficacy. In a separate rulemaking FDA intends to include these four substances on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. The other substance was never the subject of such action, but is being excluded from the list for the safety reasons described below. The agency specifically invites comment on whether, and if so, why, these substances should be added to the bulk drugs list, given the information available concerning them.

The exclusion of these substances from the bulk drugs list does not automatically mean that they can never be used in medical or pharmacy practice. Under 21 U.S.C. 505(i) and 21 CFR Part 312, these substances still may be available for use through

an Investigational New Drug exemption, the existence of which would provide important patient safeguards, such as informed consent, that may not exist with general compounding.

Betahistine Dihydrochloride

Betahistine dihydrochloride is a chemically well-characterized histamine analog. It has been used to treat the symptoms of vertigo in patients with Meniere's disease and was formerly marketed as Serc tablets. In 1970, however, FDA withdrew the approval of the NDA for Serc tablets because they were found to lack substantial evidence of effectiveness (see the Federal Register of November 14, 1970 (35 FR 17563)). In a separate rulemaking, FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons, FDA is not proposing to include betahistine dihydrochloride on the list of bulk drugs acceptable for compounding.

Cantharadin

Cantharadin, a substance obtained from the Chinese blister beetle, among other beetle species, has been used topically in the treatment of warts and molluscum contagiosum. Cantharadin is well-characterized chemically. It is, however, an extremely

toxic substance. Not only is cantharadin destructive to eyes, skin, and mucous membranes, it can be fatal if inhaled, swallowed, or absorbed through the skin. As little as 10 milligrams of cantharadin has been reported to cause death.

Topical application of cantharidin has produced acute lymphangitis and persistent lymphedema. Ingestion of cantharadin can produce burning of the mouth, nausea, dysphagia, hematemesis, hematuria, dysuria, erosion and hemorrhage of the upper GI tract, renal dysfunction and failure due to acute tubular necrosis and destruction of the glomeruli. Low grade disseminated intravascular coagulation also has been reported in patients with acute cantharidin poisoning.

For these reasons, FDA believes that the hazards associated with the use of cantharadin outweigh any benefits to be derived from its medicinal use. This is especially true given the availability of safer alternative drugs for the indications that cantharadin has been used to treat.

Cyclandelate

Cyclandelate, which is well-characterized chemically, is a vasodilator that has been used in the treatment of cerebrovascular and peripheral vascular disorders, as well as

diabetic retinopathy. It was formerly marketed in Cyclospasmol capsules and tablets, which were removed from the market for lack of effectiveness (see the Federal Register of December 3, 1996 (61 FR 64099)). In a separate rulemaking, FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons, FDA is not proposing to include cyclandelate on the list of bulk drugs acceptable for compounding.

Pentylenetetrazole

Pentylenetetrazole, which is chemically well-characterized, has been used to enhance the mental and physical activity of elderly patients, to treat schizophrenia, and in the diagnosis of epilepsy. It was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness (see the Federal Register of May 4, 1982 (47 FR 19208)). In a separate rulemaking, FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons, FDA is not proposing to include pentylenetetrazole on the list of bulk drugs acceptable for compounding.

Sulfadimethoxine

Sulfadimethoxine is a chemically well-characterized antibacterial agent that was formerly marketed in Madricidin capsules. Madricidin capsules were removed from the market in 1966 for safety reasons after being associated with Stevens-Johnson syndrome (see the Federal Register of March 19, 1966 (31 FR 4747)). In a separate rulemaking, FDA intends to propose this substance for inclusion on the list of substances withdrawn or removed from the market because they have been found to be unsafe or not effective. For these reasons, FDA is not proposing to include sulfadimethoxine on the list of bulk drugs acceptable for compounding.

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 the 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 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 one year by State, local and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation). [INSERT ECONOMIC ANALYSIS]. In general, FDA seeks public comment on the economic impact associated with any of the nominated bulk drug substances. In particuar, the agency requests public comment and data on the current level of pharmacy compounding of all five of the bulk drugs proposed for exclusion from the bulk drugs list. The agency also requests public comment and data about the

economic impact on small businesses if these five substances are excluded from the bulk drugs list.

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 one year. The publication of FDA's list of bulk drug substances for use in pharmacy compounding is not expected to result in any significant expenditure of funds by State, local and tribal governments or the private sector. Because the expenditures required by the proposed rule are expected to be substantially under $100 million annually, FDA is not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VII. 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 (Pub. L. 104-13) is not required.

VIII. Request for Comments

Interested persons may submit written comments regarding this proposal on or before (insert date xxx days after date of publication in the FEDERAL REGISTER), to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the 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 to read 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, and 371.

Subpart A--General Provisions [Reserved]

Subpart B--Compounded Drug Products

§ 216.23 Bulk drug substances for use in pharmacy compounding.

The following bulk drug substances, which are neither the subject of a current United States Pharmacopoeia or National Formulary monograph nor components of FDA approved drugs, may be used in compounding under 21 U.S.C. 353a(b)(1)(A)(i)(III):

Bismuth Citrate

Caffeine Citrate

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 intra-dental use only)

Metronidazole Benzoate

Myrrh Gum Tincture

Phenindamine Tartrate

Phenyltoloxamine Dihydrogen Citrate

Piracetam

Silver Protein Mild (for ophthalmic use only)

Sodium Butyrate (for rectal enema use only)

Taurine

Thymol Iodide (for topical use only)

Tinidazole

Based on evidence currently available, however, there are inadequate data to establish substantial evidence or general recognition of the safety or effectiveness of any of these drug substances for any indication.

§ 216.24 [Reserved]

Dated: _____

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