Proposed Rules

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 98N–0182]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

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

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

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

SUPPLEMENTARY INFORMATION:

I. Background

President Clinton signed the Modernization Act (Pub. L. 105–115) into law on November 21, 1997. Section 127 of the Modernization Act, which added section 503A to the act (21 U.S.C. 353a), clarifies the status of pharmacy compounding under Federal law. Under section 503A of the act, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) The adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351 (a)(2)(B)) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug or abbreviated new drug applications).

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

[1] To identify such FDA-approved drugs, compounders can consult the publication entitled ''Approved Drug Products with Therapeutic Equivalence Evaluation,'' commonly referred to as the ''Orange Book.''

II. Criteria for Bulk Drug Substances

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

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

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

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

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

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

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

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

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

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

III. FDA Development of a Bulk Drugs List

A. Methodology

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

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

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

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

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

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

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

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

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

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

With regard to nominated substances discussed in this proposed rulemaking (substances proposed for inclusion on the proposed list and substances that have been nominated but are still under consideration by the agency), FDA intends to exercise its enforcement discretion regarding regulatory action during the pendency of this proposed rulemaking. For further information on this subject, see the guidance for industry entitled ''Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act'' (see 63 FR 64723, November 23, 1998).

[3] A transcript of the advisory committee meeting may be found at the Dockets Management Branch (address above) under Docket No. 98N–0182.

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

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

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

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

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

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

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

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

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

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

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

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

Guaiacol. Guaiacol is well characterized chemically. It has been used for decades in compounded products as an expectorant. At doses reported in the literature for this indication, guaiacol appears to be relatively nontoxic, and serious adverse reactions associated with its use have not been commonly reported. Limited anecdotal evidence of guaiacol's effectiveness for this indication is also reported in the literature.

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

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

Myrrh gum tincture. Myrrh is a gum resin obtained from the stem of *Commiphora molmol* and other species of camphora. Myrrh is a mixture of many substances and has not been well characterized chemically. Myrrh has been used in its natural form and as a tincture to treat inflammatory disorders of the mouth and pharynx. The preparation reviewed by FDA is the tincture, which, at doses reported in the literature for those indications, appears to be relatively nontoxic. Serious adverse reactions associated with the use of myrrh gum tincture have not been commonly reported. Limited anecdotal evidence of myrrh gum tincture's effectiveness for those indications is also reported in the literature. Because the literature is limited to the topical use of this substance, FDA is proposing to include it on the bulk drugs list for topical use only.

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

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

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

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

[4] Both ferric subsulfate solution and ferric subsulfate powder were nominated for inclusion on the bulk drugs list. FDA combined them under one entry for ferric subsulfate.

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

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

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

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

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

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

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

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

Cyclandelate. Cyclandelate, which is well characterized chemically, is a vasodilator that was formerly approved by FDA for two indications: (1) Treatment for intermittent claudication caused by arteriosclerosis obliterans, and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multi-infarct or Alzheimer's type. Cyclandelate was formerly marketed in Cyclospasmol capsules and tablets, which were removed from the market for lack of effectiveness for these approved indications (see 61 FR 64099, December 3, 1996). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include cyclandelate on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

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

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

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

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

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

Pentylenetetrazole. Pentylenetetrazole, which is well characterized chemically, was approved by FDA for use in the treatment of senile confusion, depression, psychosis, fatigue, and debilitation, as well as for the relief of dizzy spells, mild behaviorial disorders, irritability, and functional memory disorders in elderly patients. Pentylenetetrazole was formerly marketed in numerous drug products, all of which were removed from the market for lack of effectiveness for these approved indications (see 47 FR 19208, May 4, 1982). FDA will consult with the Pharmacy Compounding Advisory Committee at a future meeting about whether to include pentylenetetrazole on the bulk drugs list and will address the effect of its withdrawal from the market at that time.

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

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

IV. Environmental Impact

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

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities if the proposed rule is expected to have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any 1 year by State, local and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

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

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

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

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

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

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

At the October 1998 meeting of the Pharmacy Compounding Advisory Committee, a representative of the International Academy of Compounding Pharmacists (IACP) presented usage and sales data for four of the deferred substances: 3,4-DAP, 4-AP, hydrazine sulfate, and mild silver protein. According to the IACP representative, the drug substances 3,4-DAP and 4-AP are currently being used in compounding to treat patient populations estimated at 1,000 and 10,000 patients, respectively; hydrazine sulfate is currently being used to treat between 5,000 and 10,000 patients annually; and the annual production of mild silver protein is approximately 9 kilograms. FDA does not have a firm estimate of the number of patients being treated with mild silver protein, but estimates it to be several thousand. Similarly, FDA does not have usage or sales data for the six other deferred drug substances, but estimates that their usage is also relatively low. The agency invites comments and data on any projected loss of sales or other compliance costs directly attributable to this proposal.

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

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

VI. Paperwork Reduction Act of 1995

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

VII. Request for Comments

Interested persons may, on or before March 23, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

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

1. Part 216 is added to read as follows:

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

Sec.

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

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

§ 216.23 Bulk drug substances for use in pharmacy compounding.

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

Bismuth citrate.

Caffeine citrate.

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

Choline bitartrate.

Diloxanide furoate.

Dimercapto-1-propanesulfonic acid.

Ferric subsulfate (for topical use only).

Ferric sulfate hydrate (for topical use only).

Glutamine.

Guaiacol.

Iodoform (for topical and intradental use only).

Metronidazole benzoate.

Myrrh gum tincture (for topical use only).

Phenindamine tartrate.

Phenyltoloxamine dihydrogen citrate.

Piracetam.

Sodium butyrate (for rectal enema use only).

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

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

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

§ 216.24 [Reserved]

Dated: December 29, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 52 and 81

[FL–75–1–9806b; FRL 6196]

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

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: On January 28, 1997, the Florida Department of Environmental Protection (DEP) submitted a request for redesignation to attainment for sulfur dioxide (SO_2) in Duval County, Florida. The redesignation request included five years of quality assured monitoring data which showed no exceedances of the National Ambient Air Quality Standards (NAAQS) for SO_2. Duval County was originally designated as an unclassifiable area in 1978 due to lack of adequate monitoring data. Sufficient data have now been collected to make affirmative declaration of attainment status. The EPA is redesignating Duval County from unclassifiable to attainment for SO_2 and approving three permits that provide SO_2 emission reductions.

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

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

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

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

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

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

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

Dated: November 10, 1998.

A. Stanley Meiburg,

Acting Regional Administrator, Region 4.

[FR Doc. 99–230 Filed 1–6–99; 8:45 am]

BILLING CODE 6560–50–M

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 90

[WT Docket No. 96–86; DA 98–2588]

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

AGENCY: Federal Communications Commission.

ACTION: Proposed rule; extension of time for comments.

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

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

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

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

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