4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-1999-N-0194 (formerly 99N-4490)]

RIN 0910-AH10

Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; withdrawal of previous proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to revise the list of drug products that may not be compounded under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the FD&C Act) because the drug products have been withdrawn or removed from the market after the drug products or components of such drug products were found to be unsafe or not effective. Specifically, the proposed rule would add 25 drug products to this list of drug products and modify the description of one drug product on this list to add an exception. These revisions are necessary because new information has come to the Agency's attention since March 8, 1999, when FDA published the original list as a final rule. FDA is also withdrawing the previous proposed rule regarding additions to this list (see the Federal Register of January 4, 2000).

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The January 4,

2000, proposed rule (65 FR 256) is withdrawn as of [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments, identified by Agency name and Docket No. FDA-1999-N-0194 and/or Regulatory Information Number (RIN) number 0910-AH10, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name, Docket No. FDA-1999-N-0194, and RIN 0910-AH10 for this rulemaking. All comments received may be posted without change to http://www.regulations.gov, including any personal information provided. For additional information on submitting comments, see the "Request for Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Edisa Gozun, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5199, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act: (1) Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that the licensed pharmacist or licensed physician does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (see section 503A(b)(1)(C) of the FD&C Act).

A. Court Decisions Regarding the Pharmacy Compounding Provisions of the FD&C Act

As originally enacted, section 503A of the FD&C Act included prohibitions on the advertising and solicitation of prescriptions for any particular compounded drug, class of drug, or type of drug. Seven compounding pharmacies challenged the advertising and solicitation provisions of section 503A of the FD&C Act as an impermissible regulation of commercial

speech. In February 2001, the U.S. Court of Appeals for the Ninth Circuit held that the prohibition on advertising and promotion in section 503A(c) and the provision of section 503A(a) of the FD&C Act that requires that the prescription be "unsolicited," were unconstitutional restrictions on commercial speech. (See Western States Med. Ctr. v. Shalala, 238 F.3d 1090 (9th Cir. 2001).) Furthermore, the Ninth Circuit held that the advertising and solicitation provisions could not be severed from the rest of section 503A and, as a result, found section 503A of the FD&C Act to be invalid in its entirety. In April 2002, the U.S. Supreme Court affirmed the Ninth Circuit's decision that the advertising and solicitation provisions were unconstitutional; it did not, however, rule on the severability of section 503A of the FD&C Act. (See Thompson v. Western States Med. Ctr., 535 U.S. 357 (2002).)

In light of these decisions, FDA issued a Compliance Policy Guide in 2002 to provide guidance on FDA's approach concerning the regulation of pharmacy compounding. (See the Federal Register of June 7, 2002 (67 FR 39409).)

In September 2004, 10 pharmacies brought suit in the U.S. District Court for the Western District of Texas challenging FDA's authority to regulate compounded drugs. In August 2006, the District Court held, in part, that compounded human drugs are implicitly exempt from the "new drug" definition in section 201(p) of the FD&C Act and, as a result, are not subject to the FD&C Act's new drug approval requirements. (See Medical Ctr. Pharm. v. Gonzales, 451 F. Supp. 2d 854 (W.D. Tex. 2006).) The District Court also held that the advertising and solicitation provisions in section 503A of the FD&C Act that the Supreme Court had found to be unconstitutional were severable from the rest of that section.

The Federal Government appealed the decision of the U.S. District Court for the Western District of Texas. In July 2008, the U.S. Court of Appeals for the Fifth Circuit reversed the

District Court's finding of an implicit exemption for compounded drugs from the new drug approval requirements in the FD&C Act, holding, instead, that compounded drugs fall within the definition of "new drug" in the FD&C Act and, therefore, are subject to regulation by FDA. (See Medical Ctr. Pharm. v. Mukasey, 536 F.3d 383 (5th Cir. 2008).) The Fifth Circuit also held that the advertising and solicitation provisions are severable from the rest of section 503A of the FD&C Act, and as a result, the other provisions of section 503A remain in effect.

The Fifth Circuit's severability ruling conflicted with the earlier Ninth Circuit decision, which held that the advertising and solicitation provisions cannot be severed from section 503A of the FD&C Act, and rendered all of section 503A void. Following a fungal meningitis outbreak in September 2012, FDA sought legislation to, among other things, resolve the split in the Circuits to clarify that section 503A of the FD&C Act was valid nationwide.

B. 2013 Drug Quality and Security Act

On November 27, 2013, President Obama signed the Drug Quality and Security Act (Public Law 113-54) (DQSA) that contains important provisions relating to the oversight of compounding of human drugs. This new law removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the new law clarifies that section 503A of the FD&C Act applies nationwide. In addition, the DQSA adds a new section 503B of the FD&C Act (21 U.S.C. 353b) that creates a new category of "outsourcing facilities." Outsourcing facilities, as defined in section 503B of the FD&C Act, are facilities that meet certain conditions described in section 503B, including registering with FDA as an outsourcing facility. If these conditions are satisfied, a drug compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from three sections of the FD&C Act: (1) Section 502(f)(1), (2)

section 505, and (3) section 582 (21 U.S.C. 360eee); but not section 501(a)(2)(B). One of the conditions in section 503B of the FD&C Act that must be satisfied to qualify for the exemptions is that the drug does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (see section 503B(a)(4)).

Given that nearly identical criteria apply for a drug to be included on the list referred to in section 503A(b)(1)(C) and the list referred to in section 503B(a)(4) of the FD&C Act, FDA is proposing to revise and update the list at § 216.24 (21 CFR 216.24) for purposes of both sections 503A and 503B. Accordingly, the proposed rule that published in the Federal Register of January 4, 2000, which would have amended the list in § 216.24, is withdrawn (see DATES).

C. Regulatory History of the List

1. Original List

In the Federal Register of October 8, 1998 (63 FR 54082), FDA proposed a rule to establish the original list of drug products that have been withdrawn or removed from the market because the drug products or the components of such drug products were found to be unsafe or not effective (1998 proposed rule). The 1998 proposed rule was presented to the Pharmacy Compounding Advisory Committee (Advisory Committee) at a meeting held on October 14 and 15, 1998 (63 FR 47301, September 4, 1998). The Advisory Committee did not have any adverse comments on the 1998 proposed rule and did not suggest any changes. A transcript of the October 1998 Advisory Committee meeting may be found at the Division of Dockets Management (see ADDRESSES) and at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm.

In the Federal Register of March 8, 1999 (64 FR 10944), FDA published a final rule that codified the original list in § 216.24 (1999 final rule).

2. 2000 Proposed Rule and Additional Drug Products for the List in § 216.24

In the Federal Register of January 4, 2000 (65 FR 256), FDA proposed a rule to amend § 216.24 (2000 proposed rule). Specifically, FDA proposed to add all drug products containing aminopyrine and all drug products containing astemizole to the original list of drug products withdrawn or removed from the market because they have been found to be unsafe or not effective. After the 2000 proposed rule published, three additional drug products (cisapride, grepafloxacin, and troglitazone) were identified as candidates for addition to the list. These five drug products were presented to the Advisory Committee at a meeting held on July 13 and 14, 2000 (65 FR 40104, June 29, 2000). The Advisory Committee voted to include aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone to the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective. A transcript of the July 2000 Advisory Committee meeting may be found at the Division of Dockets Management (see ADDRESSES) and at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm290713.htm.

3. New Proposed Rule to Amend the List in § 216.24

This proposed rule would add to § 216.24 the five drug products identified in section I.C.2 and additional drug products that have been withdrawn or removed from the market since the publication of the 1999 final rule because the drug products or components of such drug products were found to be unsafe or not effective. FDA also proposes to modify the description of one drug product contained in the original list to add an exception that would allow the

product to be compounded under certain circumstances. These revisions are necessary to ensure the list of drugs in § 216.24 reflects new information that has come to the Agency's attention since FDA published the original list in the 1999 final rule. As with the original list, the primary focus of this proposed rule is on drug products that have been withdrawn or removed from the market because they were found to be unsafe. FDA may propose at a later date to add other drug products to the list that have been withdrawn or removed from the market because they were found to be not effective, or to update the list as new information becomes available to the Agency regarding products that were removed from the market because they were found to be unsafe.

This proposed rule would replace the 2000 proposed rule. The list set forth in this proposed rule would apply to compounders and outsourcing facilities seeking to qualify for the exemptions under either section 503A or section 503B of the FD&C Act. Accordingly, the 2000 proposed rule to amend § 216.24 is withdrawn. In preparing this proposed rule, FDA has taken into consideration the discussions held by the July 2000 Advisory Committee and that Advisory Committee's vote to include aminopyrine, astemizole, cisapride, grepafloxacin, and troglitazone on the list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective.

Additional nominations for this list can be submitted to FDA for consideration in comments to this proposed rule.

II. Procedural Issue for Comment

Section 503A of the FD&C Act describes the list in section 503A(b)(1)(C) as a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have

been found to be unsafe or not effective. This suggests that FDA can develop the 503A(b)(1)(C) list by publishing it in the Federal Register and does not need to go through notice and comment rulemaking. Section 503A(c)(1) of the FD&C Act, however, states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(C) pertaining to the withdrawn or removed rule, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. In 1998 and 1999, FDA used rulemaking to develop the original list of drug products that had been withdrawn or removed from the market, and consulted the Pharmacy Compounding Advisory Committee about the list. In 2000, FDA also proposed to amend the list through rulemaking after consultation with the Advisory Committee.

Meanwhile, new section 503B of the FD&C Act describes the list in section 503B(a)(4) as a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective. Section 503B(c) of the FD&C Act requires that the Secretary implement through regulations, following consultation with an advisory committee, a list of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs and therefore may not be compounded under section 503B. (See section 503B(a)(6) of the FD&C Act.) Section 503B does not, however, include any similar requirement for rulemaking or consultation with an advisory committee to establish the list of drugs that may not be compounded under section 503B of the FD&C Act because they have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective.

As noted, FDA plans to publish a single list of drug products (referred to as "the withdrawn or removed list" or "the list") that cannot be compounded for human use under the exemptions provided by either section 503A or 503B of the FD&C Act because they have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective. FDA invites comments on the appropriate procedure to update the list in the future. The Agency believes that the timely sharing of information about safety concerns relating to compounding drugs for human use without undue delay is essential to the protection of public health. FDA is concerned that consulting with the advisory committee and completing the rulemaking process are likely to contribute to substantial delay in updating the list to reflect current safety information. FDA therefore is seeking an alternative procedure to update the withdrawn or removed list in the future. Although FDA is publishing a proposed rule today to add 25 drugs to the list, FDA is also soliciting public input through this Federal Register notice on alternative procedures for updating the list and requests that this input be submitted to FDA for consideration in comments to this proposed rule. FDA will specify in the final rule the procedure it will use to update the list in the future.

III. Description of This Proposed Rule

A. Amendments to Introductory Text

FDA is proposing to add the phrase "or section 503B(a)" to the introductory text of § 216.24 to clarify that drug products included in the list in § 216.24 will not qualify for the exemptions under either section 503A(a) or section 503B(a) of the FD&C Act when compounded.

B. Amendments to Add Drug Products to the List

FDA is proposing to amend § 216.24 to include the 25 drug products described in the following paragraphs that have been withdrawn or removed from the market since the 1999 final rule was published (March 1999) because such drug products or components of such drug products have been found to be unsafe or not effective.

A drug product that is included in the list codified at § 216.24 is not entitled to the exemptions provided in section 503A(a) of the FD&C Act, and is subject to sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act, in addition to other applicable provisions. In addition, a drug that is included in the list codified at § 216.24 is not entitled to the exemptions provided in section 503B(a) of the FD&C Act, and is subject to sections 502(f)(1) and 505 of the FD&C Act, in addition to other applicable provisions.

The listed drugs are ineligible for the exemptions set forth in sections 503A and 503B of the FD&C Act because they have been withdrawn or removed from the market because they were found to be unsafe or not effective. Most drugs on the list may not be compounded in any form. There are, however, two categories of exceptions. In the first category, a particular formulation, indication, dosage form, or route of administration of a drug is explicitly excluded from an entry on the list because an approved drug containing the same active ingredient(s) has not been withdrawn or removed from the market. For such drugs, the formulation, indication, dosage form, or route of administration expressly excluded from the list may be eligible for the exemptions provided in sections 503A and 503B of the FD&C Act. In the second category, some drugs are listed only with regard to certain formulations, concentrations, indications, routes of administration, or dosage forms because they have been found to be unsafe or not effective in those particular formulations, concentrations, indications, routes of administration, or dosage

forms. For drugs that are listed with these types of limitations, any compounding of the drug will be closely scrutinized to ensure that the compounding of the drug does not create a product that is unsafe or not effective. If it appears to do so, FDA may determine that the drug is not entitled to the exemptions provided in sections 503A and 503B of the FD&C Act. Those compounding these particular drugs should take note of the reasons FDA has cited for including a drug on this list, and carefully consider these reasons when considering whether or not to compound a drug that is so listed.

The following drug products are arranged alphabetically by the established names of the active ingredients contained in the drug products and are proposed for inclusion in § 216.24. For many of the drugs, the proprietary or trade name of some or all of the drug products that contained the active ingredient are also given in the preamble paragraphs describing the withdrawn or removed drug products. In several cases, the withdrawn or removed drug products are identified according to the established name of the active ingredient, listed as a particular salt or ester of the active moiety. The following list includes a brief summary of the reasons why each drug product is being proposed for inclusion.

Alatrofloxacin mesylate: All drug products containing alatrofloxacin mesylate. Alatrofloxacin mesylate, formerly marketed as TROVAN Injection, was associated with serious liver injury. On June 9, 1999, FDA announced in a Public Health Advisory that the NDA holder agreed to a limited distribution of TROVAN (alatrofloxacin mesylate) Injection and TROVAN (trovafloxacin mesylate) tablets, 100 milligrams (mg) and 200 mg, to in-patient healthcare facilities (Ref. 1). Subsequently, in the Federal Register of June 16, 2006 (71 FR 34940), FDA announced that it was withdrawing the approval of the NDA for TROVAN Injection after the

NDA holder notified the Agency that the drug product was no longer marketed and requested that the approval of the NDA be withdrawn.

Aminopyrine: All drug products containing aminopyrine. Aminopyrine was associated with agranulocytosis, a condition characterized by a decrease in the number of certain blood cells and lesions on the mucous membrane and skin. Some cases of agranulocytosis were fatal. In 1964, FDA declared drug products containing aminopyrine to be new drugs and invited NDAs for these drug products, but only for use as an antipyretic in serious situations where other, safer drugs could not be used. FDA received no NDAs for drug products containing aminopyrine, and those unapproved drug products were removed from the market (see the Federal Register of October 4, 1977 (42 FR 53954), and January 4, 2000 (65 FR 256)). Aminopyrine was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include aminopyrine on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Astemizole: All drug products containing astemizole. Astemizole, formerly marketed as HISMANAL 10-mg tablets, was associated with life-threatening heart arrhythmias. Patients with liver dysfunction or who were taking other drugs that interfered with the metabolism of astemizole were also found to be at risk of serious cardiac adverse events while taking astemizole. On June 18, 1999, the NDA holder withdrew HISMANAL (astemizole) 10-mg tablets from the market. In the Federal Register of August 23, 1999 (64 FR 45973), FDA announced its determination that HISMANAL (astemizole) 10-mg tablets were removed from the market for safety reasons. (See also the Federal Register of January 4, 2000 (65 FR 256).) Astemizole was presented to the Advisory Committee at the July 2000 meeting, and the

Advisory Committee voted to include astemizole on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Cerivastatin sodium: All drug products containing cerivastatin sodium. Cerivastatin sodium, formerly marketed as BAYCOL tablets, was associated with increased risk of rhabdomyolysis. Fatal rhabdomyolysis was reported most frequently when used at higher doses, when used in elderly patients, and particularly, with concomitant use of gemfibrozil (LOPID). In an August 8, 2001, "Dear Healthcare Professional Letter," the NDA holder stated that it discontinued the marketing and distribution of all dosage strengths of BAYCOL (Ref. 2).

Chloramphenicol: All oral drug products containing chloramphenicol. Chloramphenicol was formerly marketed as CHLOROMYCETIN (chloramphenicol) Capsules. In a letter dated October 9, 2007, the application holder requested withdrawal of the ANDA for CHLOROMYCETIN (chloramphenicol) Capsules, 50 mg, 100 mg, and 250 mg. In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the ANDA, effective March 13, 2009. Armenpharm, Ltd., submitted a citizen petition dated February 7, 2011 (Docket No. FDA-2011-P-0081), under § 10.30 (21 CFR 10.30), requesting that the Agency determine whether CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, were withdrawn from sale for reasons of safety or effectiveness. After considering the citizen petition, FDA determined that the drug product was withdrawn for reasons of safety or effectiveness. With the approval of additional therapies with less severe adverse drug effects, FDA determined that the risks associated with CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, as then labeled, outweighed the benefits. Furthermore, CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, may cause a number of adverse reactions, the most serious being bone marrow depression (anemia, thrombocytopenia, and granulocytopenia temporally

associated with treatment). Additionally, prior to the removal of the capsule drug product from the market, a boxed warning in the prescribing information for both chloramphenicol sodium succinate injection and chloramphenicol capsules stated that serious hypoplastic anemia, thrombocytopenia, and granulocytopenia are known to occur after administration of chloramphenicol. The boxed warning also described fatal aplastic anemia associated with administration of the drug and aplastic anemia attributed to chloramphenicol that later terminated in leukemia. There is published literature that suggests that the risk of fatal aplastic anemia associated with the oral formulation of chloramphenicol may be higher than the risk associated with the intravenous formulation (see the Federal Register of July 13, 2012 (77 FR 41412)). FDA is not aware of any oral drug products containing chloramphenicol currently being marketed.

Cisapride: All drug products containing cisapride. Cisapride, formerly marketed as PROPULSID tablets and suspension, was associated with serious cardiac arrhythmias and death. In an April 12, 2000 "Dear Healthcare Professional Letter," the NDA holder stated that it would discontinue marketing the drug as of July 14, 2000, and make the product available only through an investigational limited access program (Ref. 3). Cisapride was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include cisapride on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Esmolol hydrochloride: All parenteral drug products containing esmolol HCl that supply 250 mg/milliliter (mL) of concentrated esmolol per 10-mL ampule. Esmolol hydrochloride (HCl), 250 mg/mL per 10-mL ampule, formerly marketed as BREVIBLOC Injection 250 mg/mL per 10-mL ampule, was associated with increased risk of medication errors resulting in serious adverse events, including deaths. The NDA holder sent a letter to FDA on June 28, 2007,

notifying the Agency that the company had decided to cease the manufacture and distribution of BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule. In a citizen petition dated March 27, 2008 (Docket No. FDA-2008-P-0284), submitted under § 10.30 and in accordance with 21 CFR 314.122 and 314.161, Bedford Laboratories (Bedford) requested that the Agency determine whether BREVIBLOC (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule, was withdrawn from sale for reasons of safety or effectiveness. In the Federal Register of May 5, 2010 (75 FR 24710), FDA announced its determination that BREVIBLOC (esmolol HCl) Injection 250 mg/mL, 10-mL ampule, was withdrawn from the market for safety reasons.

Etretinate: All drug products containing etretinate. Etretinate was formerly marketed as TEGISON Capsules. In a letter dated September 23, 1999, the NDA holder requested that FDA withdraw the approval of the NDA for TEGISON (etretinate) Capsules because it had discontinued marketing the product. The letter also stated that the drug was not withdrawn for safety reasons. However, in an acknowledgement letter dated December 30, 2002, FDA informed the NDA holder that TEGISON (etretinate) Capsules was removed from the market because it posed a greater risk of birth defects than SORIATANE (acitretin), the product that replaced TEGISON (etretinate) Capsules (see the Federal Register of September 10, 2003 (68 FR 53384)). Subsequently, in the Federal Register of September 10, 2003, FDA announced it was withdrawing approval of the NDA.

Gatifloxacin: All drug products containing gatifloxacin (except ophthalmic solutions). Gatifloxacin was formerly marketed as TEQUIN tablets, injection, and oral suspension. In January 2003, FDA received revised product labeling relating to several approved supplements for TEQUIN (gatifloxacin). This revised labeling deleted references to TEQUIN injection, 10 mg/mL (200 mg), indicating that this product was no longer being marketed; therefore, the

product was moved from the prescription drug product list to the "Discontinued Drug Product List" section of the "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book). In response to a citizen petition from Apotex Corp. (Docket No. FDA-2005-P-0369),[1] FDA determined, as set forth in the Federal Register of February 3, 2006 (71 FR 5858), that TEQUIN injection, 10 mg/mL (200 mg), was not withdrawn for reasons of safety and effectiveness. On May 1, 2006, Public Citizen Research Group submitted a citizen petition (Docket No. FDA-2006-P-0081),[2] under § 10.30, requesting that FDA immediately ban TEQUIN because of the increased risk of dysglycemia (hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar) in humans. In June 2006, the NDA holder announced that it would no longer market TEQUIN. In the Federal Register of September 9, 2008 (73 FR 52357), FDA announced its determination that all dosage forms and strengths of TEQUIN (gatifloxacin) were withdrawn from the market for safety reasons. There are currently approved gatifloxacin ophthalmic solutions on the market. Thus, FDA is proposing to include all drug products containing gatifloxacin, except ophthalmic solutions, on the withdrawn or removed list.

Grepafloxacin: All drug products containing grepafloxacin. Grepafloxacin, formerly marketed as RAXAR tablets, was associated with cardiac repolarization, manifested as QTc interval prolongation on the electrocardiogram, which could put patients at risk of Torsade de Pointes. The NDA holder sent a letter to FDA on March 5, 2003, requesting that FDA withdraw the approval of the NDA for RAXAR tablets, stating that the product was no longer being marketed. In an acknowledgment letter dated June 20, 2003, FDA stated that RAXAR

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[1] This citizen petition was originally assigned docket number 2005P-0023/CP1. The number was changed to FDA-2005-P-0369 as a result of FDA's transition to its new docketing system (http://www.regulations.gov) in January 2008.

[2] This citizen petition was originally assigned docket number 2006P-0178. The number was changed to FDA-2006-P-0081 as a result of FDA's transition to its new docketing system (http://www.regulations.gov) in January 2008.

(grepafloxacin) tablets had been removed from the market because of safety concerns. In a followup letter dated January 12, 2007, FDA informed the NDA holder that the RAXAR NDA should be withdrawn because of the cardiovascular risks stated previously. The NDA holder sent a letter to FDA on March 20, 2007, agreeing with FDA's determination to initiate the withdrawal of the RAXAR NDA, and FDA subsequently announced that approval of the NDA was withdrawn (see the Federal Register of June 14, 2007 (72 FR 32852), and July 9, 2007 (72 FR 37244)). Grepafloxacin was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include grepafloxacin on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Methoxyflurane: All drug products containing methoxyflurane. Methoxyflurane, formerly marketed as PENTHRANE Inhalation Liquid, 99.9 percent, was associated with serious, irreversible, and even fatal nephrotoxicity and hepatotoxicity in humans. In the Federal Register of August 16, 2001 (66 FR 43017), FDA announced that it was withdrawing the approval of the NDA after the NDA holder notified the Agency that PENTHRANE (methoxyflurane) Inhalation Liquid was no longer being marketed under the NDA and requested withdrawal of the application. In a citizen petition dated August 25, 2004 (Docket No. FDA-2004-P-0337),[3] submitted under § 10.30, and in accordance with § 314.161, AAC Consulting Group requested that the Agency determine whether PENTHRANE (methoxyflurane) Inhalation Liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. In the Federal Register of September 6, 2005 (70 FR 53019), FDA announced its determination that PENTHRANE Inhalation Liquid, 99.9 percent, was withdrawn from the market for safety reasons.

[3] This citizen petition was originally assigned docket number 2004P-0379. The number was changed to FDA-2004-P-0337 as a result of FDA's transition to its new docketing system (http://www.regulations.gov) in January 2008.

Novobiocin sodium: All drug products containing novobiocin sodium. Novobiocin sodium, formerly marketed as ALBAMYCIN capsule, 250 mg, was associated with adverse reactions that included relatively common skin reactions, jaundice, hepatic failure, and blood dyscrasias (neutropenia, anemia, and thrombocytopenia). Literature also revealed concerns about the development of novobiocin-resistant Staphylococci during treatment and a potential for drug interactions. On June 9, 1999, the NDA holder sent an annual report to FDA that indicated that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was no longer being manufactured, and on June 27, 2007, the NDA holder sent a letter to FDA notifying the Agency that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, had been discontinued. In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of the NDA in response to the NDA holder's withdrawal request. Crixmore LLC submitted a citizen petition dated July 9, 2008 (Docket No. FDA-2008-P-0431), under § 10.30, requesting that the Agency determine whether ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn from sale for reasons of safety or effectiveness. In the Federal Register of January 19, 2011 (76 FR 3143), FDA announced its determination that ALBAMYCIN (novobiocin sodium) capsule, 250 mg, was withdrawn from the market for reasons of safety or effectiveness.

Oxycodone hydrochloride: All extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties. OXYCONTIN (oxycodone hydrochloride) extended-release tablets were approved in multiple strengths under NDA 20-553 in 1995. The formulation was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. This product was voluntarily withdrawn from sale following introduction of a reformulated version, also marketed as OXYCONTIN (oxycodone hydrochloride) extended-

release tablets, which was developed with physicochemical properties intended to make the tablets more difficult to manipulate for purposes of abuse or misuse and was approved in multiple strengths under NDA 22-272 in 2010. Several parties submitted citizen petitions under § 10.30, requesting that the Agency determine whether original OXYCONTIN (oxycodone HCl) extended-release tablets were voluntarily withdrawn from sale for reasons other than safety or effectiveness.[4] In a letter to FDA dated March 19, 2013, the NDA holder requested withdrawal of approval of NDA 20-553 for original OXYCONTIN. In the Federal Register of April 18, 2013 (78 FR 23273), FDA published notice of its determination that original OXYCONTIN, NDA 20-553, was withdrawn from sale for reasons of safety or effectiveness. The notice concluded that "[o]riginal OXYCONTIN…poses an increased potential for abuse by certain routes of administration, when compared to reformulated OXYCONTIN. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OXYCONTIN no longer outweigh its risks." In the Federal Register of August 7, 2013 (78 FR 48177), FDA announced that it was withdrawing the approval of NDA 20-553. In addition, because the drug approval process is the most appropriate way for FDA to evaluate the effect and labeling of products with potentially abuse-deterrent properties, compounding of opioid products with potentially abuse-deterrent properties will be closely scrutinized.

Pemoline: All drug products containing pemoline. Pemoline, formerly marketed as CYLERT tablets and chewable tablets, was associated with liver failure. FDA determined that the overall risk of liver toxicity from CYLERT and generic pemoline outweighed the benefits of

[4] Varam, Inc., Docket No. FDA-2011-P-0473 (June 9, 2011) (10, 15, 20, 30, 40, 50, 80, and 160 mg); Sheppard, Mullin, Richter & Hampton LLP, Docket No. FDA-2010-P-0540 (October 8, 2010) (10, 15, 20, 30, 40, 60, and 80 mg); Lachman Consultant Services, Inc., Docket No. FDA-2010-P-0526 (September 30, 2010) (10, 15, 20, 30, 40, 60, 80, and 160 mg). Lachman also submitted a petition in 2001 concerning just Purdue Pharma LP's 2001 withdrawal of the 160 mg strength, Docket No. FDA-2001-P-0473 (formerly Docket No. 2001P-0426) (September 18, 2001).

the drug. On October 24, 2005, FDA announced in an FDA Alert that the NDA and ANDA holders chose to stop sales and marketing of CYLERT and generic pemoline in May 2005 (Ref. 4).

Pergolide mesylate: All drug products containing pergolide mesylate. Pergolide mesylate, formerly marketed as PERMAX tablets, was associated with increased risk of heart valve damage. On March 29, 2007, FDA announced in a Public Health Advisory that the NDA and ANDA holders agreed to withdraw PERMAX and generic pergolide mesylate from the market (Ref. 5).

Phenylpropanolamine (PPA): All drug products containing PPA. A study demonstrated that PPA was associated with increased risk of hemorrhagic stroke. On November 6, 2000, FDA announced in a Public Health Advisory that it was taking steps to remove PPA from all drug products and requested that all drug companies discontinue marketing products containing PPA (Ref. 6). In response to FDA's request, companies reformulated their products to exclude PPA. In a notice published in the Federal Register on August 14, 2001 (66 FR 42665), FDA offered an opportunity for a hearing on a proposal to issue an order, under section 505(e) of the FD&C Act, withdrawing approval of 13 NDAs and 8 ANDAs for products containing phenylpropanolamine. (Although the August 14, 2001, notice stated that FDA proposed to withdraw approval of 16 NDAs and 8 ANDAs, the notice listed only 13 NDAs and 8 ANDAs.) FDA withdrew approval of ANDA 71-099 for BROMATAPP Extended-Release Tablets in a notice published in the Federal Register of February 20, 2002 (67 FR 7702) after the application holder informed FDA that the product was no longer being marketed and requested withdrawal. In the Federal Register of February 20, 2014 (79 FR 9744), FDA announced that the NDA and ANDA products containing PPA were no longer shown to be safe for use under the conditions that formed the

basis upon which the applications were approved, and thus the Agency was withdrawing approval of 20 products containing PPA.

Polyethylene glycol (PEG) 3350, sodium chloride, sodium bicarbonate, potassium chloride, and bisacodyl: All drug products containing PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and 10 mg or more of bisacodyl delayed-release tablets. PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and four bisacodyl delayed-release tablets, 5 mg (20-mg bisacodyl), formerly marketed as HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl), was associated with ischemic colitis. The NDA holder informed FDA that it ceased to manufacture and market HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl) as of September 25, 2007. On July 15, 2008, FDA received a citizen petition (Docket No. FDA-2008-P-0412), submitted under § 10.30, from Foley & Lardner LLP. The petition requested that the Agency determine whether HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and four bisacodyl delayed release tablets, 5 mg) (HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl)), manufactured by Braintree Laboratories, Inc. (Braintree), was withdrawn from sale for reasons of safety or effectiveness. In the Federal Register of March 19, 2010 (75 FR 13292), FDA announced its determination that HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (20-mg bisacodyl) was withdrawn from the market for reasons of safety or effectiveness. Similarly, PEG 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and two bisacodyl delayed-release tablets, 5 mg (10-mg bisacodyl), formerly marketed as HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl), was associated with ischemic

colitis. The NDA holder informed FDA that it ceased to manufacture and market HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl) as of July 17, 2010. On September 23, 2010, FDA received a citizen petition (Docket No. FDA-2010-P-0507), submitted under § 10.30, from Perrigo Company (Perrigo) requesting that the Agency determine whether HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution and two bisacodyl delayed release tablets, 5 mg) (HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl)), manufactured by Braintree, was withdrawn from sale for reasons of safety or effectiveness. In the Federal Register of August 17, 2011 (76 FR 51037), FDA announced its determination that HALFLYTELY AND BISACODYL TABLETS BOWEL PREP KIT (10-mg bisacodyl) was withdrawn from the market for reasons of safety or effectiveness.

Propoxyphene: All drug products containing propoxyphene. Propoxyphene, formerly marketed under various names such as DARVON and DARVOCET, was associated with serious toxicity to the heart. In a drug safety communication dated November 19, 2010, FDA announced it had requested that companies voluntarily withdraw propoxyphene from the U.S. market and that FDA was recommending against the continued use and prescribing of the pain reliever propoxyphene because new data showed that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA concluded that the safety risks of propoxyphene outweighed its limited benefits for pain relief at recommended doses. The Agency's recommendation was based on all available data including data from a then-new study that evaluated the effects that increasing doses of propoxyphene have on the heart. The results of the study showed that when propoxyphene was taken at therapeutic doses, there were significant

changes to the electrical activity of the heart which can increase the risk for serious abnormal heart rhythms (Ref. 7). In the Federal Register of March 10, 2014 (79 FR 13308), FDA announced that due to this safety risk, the Agency was withdrawing approval of 54 propoxyphene products with agreement from holders of the affected applications. On that date, FDA also published a notice of opportunity for a hearing on its proposal to withdraw approval of three additional propoxyphene products for which FDA had not received correspondence from the application holders requesting that FDA withdraw approval (see the Federal Register of March 10, 2014 (79 FR 13310)).

Rapacuronium bromide: All drug products containing rapacuronium bromide. Rapacuronium bromide, formerly marketed as RAPLON for Injection, was associated with the occurrence of bronchospasm. In a letter dated March 27, 2001, the NDA holder announced that it voluntarily withdrew all batches of RAPLON for Injection from the market (Ref. 8). FDA subsequently announced in the Federal Register of March 19, 2012 (77 FR 16039) that it was withdrawing the approval of the NDA.

Rofecoxib: All drug products containing rofecoxib. Rofecoxib, formerly marketed as VIOXX, was associated with increased risk of serious cardiovascular events, including heart attack and stroke. On September 30, 2004, FDA announced in a Public Health Advisory that the NDA holder voluntarily withdrew VIOXX from the market (Ref. 9).

Sibutramine hydrochloride: All drug products containing sibutramine hydrochloride. Sibutramine hydrochloride (HCl), formerly marketed as MERIDIA oral capsules, was associated with increased risk of heart attack and stroke. In a letter dated October 12, 2010, the NDA holder requested that FDA withdraw the approval of the NDA for MERIDIA. In an acknowledgment letter dated November 1, 2010, FDA stated that the benefits of MERIDIA

(sibutramine HCl) oral capsules no longer outweighed the risks in any identifiable population. FDA subsequently announced in the Federal Register of December 21, 2010 (75 FR 80061) that it was withdrawing approval of the NDA.

Tegaserod maleate: All drug products containing tegaserod maleate. Tegaserod maleate, formerly marketed as ZELNORM, was associated with a higher chance of heart attack, stroke, and worsening heart chest pain that can become a heart attack, compared to a placebo. On March 30, 2007, FDA announced in a Public Health Advisory that the NDA holder agreed to stop selling ZELNORM (Ref. 10). On July 27, 2007, FDA announced that it was permitting the restricted use of ZELNORM (tegaserod maleate) under a treatment investigational new drug (IND) protocol to treat irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women younger than 55 who meet specific guidelines (Ref. 11). On April 2, 2008, FDA announced that the sponsor of ZELNORM notified FDA that it would no longer provide ZELNORM (tegaserod maleate) under a treatment IND protocol to treat IBS-C and CIC in women younger than 55; however, the sponsor agreed to continue to supply ZELNORM for use in emergency situations (Ref. 12).

Troglitazone: All drug products containing troglitazone. Troglitazone, formerly marketed as REZULIN and PRELAY Tablets, a treatment for type 2 diabetes, was shown to be more toxic to the liver than two other more recently approved drugs that offered a similar benefit. In a letter dated May 1, 2002, the holder of the NDA for REZULIN (troglitazone) Tablets requested that FDA withdraw the NDA for REZULIN (troglitazone) Tablets because it had discontinued marketing the product in March 2000. FDA subsequently announced in the Federal Register of January 10, 2003 (68 FR 1469) that it was withdrawing the approval of the NDA for REZULIN. In a letter dated December 31, 2002, the holder of the NDA for PRELAY

(troglitazone) Tablets requested that FDA withdraw the approval of the NDA for PRELAY (troglitazone) Tablets because it never marketed the drug and had no plans to market the drug in the future. In the Federal Register of August 11, 2003 (68 FR 47581), FDA concluded that PRELAY was voluntarily withdrawn after review of safety data showed that REZULIN was more toxic to the liver than two other more recently approved drugs that offered a similar benefit, and FDA announced that it was withdrawing approval of the NDA for PRELAY. Troglitazone was presented to the Advisory Committee at the July 2000 meeting, and the Advisory Committee voted to include troglitazone on the withdrawn or removed list (see the Federal Register of June 29, 2000 (65 FR 40104)).

Trovafloxacin mesylate: All drug products containing trovafloxacin mesylate. Trovafloxacin mesylate, formerly marketed as TROVAN tablets, 100 mg and 200 mg, was associated with serious liver injury. On June 9, 1999, FDA announced in a Public Health Advisory that the NDA holder agreed to a limited distribution of TROVAN (alatrofloxacin mesylate) Injection and TROVAN (trovafloxacin mesylate) tablets, 100 mg and 200 mg, to in-patient healthcare facilities (Ref. 1). The holders of the NDAs for TROVAN (trovafloxacin mesylate) tablets, 100 mg and 200 mg, and TROVAN/ZITHROMAX COMPLIANCE PAK (trovafloxacin mesylate/azithromycin for oral suspension) notified the Agency that the drug products were no longer marketed and requested that the approval of the NDAs be withdrawn (see the Federal Register of September 22, 1999 (64 FR 51325), and June 16, 2006 (71 FR 34940)). FDA announced it was withdrawing approval of the NDAs in the Federal Register of September 22, 1999 (64 FR 51325), and June 16, 2006 (71 FR 34940).

Valdecoxib: All drug products containing valdecoxib. Valdecoxib, formerly marketed as BEXTRA, was associated with increased risk of serious cardiovascular events and an increased

risk of serious skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other nonsteroidal anti-inflammatory drugs. On April 7, 2005, FDA announced in an FDA Alert that it had concluded that the overall risk versus benefit profile of BEXTRA (valdecoxib) was unfavorable and that the NDA holder had voluntarily removed BEXTRA from the market (Ref. 13). In letters dated May 27, 2011, August 8, 2011, and October 31, 2011, the holder of the NDA for BEXTRA (valdexoxib) Tablets requested that FDA withdraw the NDA for BEXTRA (valdexoxib) Tablets. FDA subsequently announced in the Federal Register of August 2, 2013 (78 FR 46984) that it was withdrawing approval of the NDA.

C. Amendment to Modify the Description of a Drug Product on the List

FDA is proposing to amend § 216.24 to modify the description of bromfenac sodium on the list.

Bromfenac sodium: All drug products containing bromfenac sodium (except ophthalmic solutions). The use of bromfenac sodium, formerly marketed as DURACT (bromfenac sodium) Capsules, was associated with fatal hepatic failure. The manufacturer of DURACT Capsules voluntarily withdrew the drug from the market on June 22, 1998 (see the Federal Register of October 8, 1998 (63 FR 54082)). On March 8, 1999, FDA included all drug products containing bromfenac sodium in the list codified at § 216.24 when FDA published the 1999 final rule (64 FR 10944). Since then, FDA has approved bromfenac ophthalmic solutions, and although one of these, XIBROM (bromfenac ophthalmic solution) 0.09%, was discontinued by the NDA holder in 2011, FDA announced its determination in the Federal Register of May 13, 2011 (76 FR 28045) that it was not withdrawn for reasons of safety or effectiveness. (See also Docket No. FDA-2011-P-0128.) Approved bromfenac ophthalmic solutions are currently on the market.

Thus, FDA is proposing to include all drug products containing bromfenac sodium on the list with an exception for ophthalmic solutions.

For the convenience of the reader, the regulatory text of § 216.24 provided with this proposed rule includes the drug products proposed for addition and modification discussed in this document and the drug products codified by the 1999 final rule.

IV. Environmental Impact

FDA 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, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612) and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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 Agency believes that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because small businesses are not expected to incur any compliance costs or loss of sales due to this regulation, we propose to certify that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. We do not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

This rule proposes to amend § 216.24 concerning pharmacy compounding. Specifically, the proposed rule would add to or modify the list of drug products that may not be compounded under the exemptions provided by sections 503A and 503B of the FD&C Act because the drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective (see section III). The Agency is proposing to add 25 drug products to the list and to modify the description of 1 drug product on the list to add an exception. The Agency is not aware of any routine use of these drug products in pharmacy compounding and, therefore, does not estimate any compliance costs or loss of sales as a result of the prohibition against compounding these drugs for human use. However, the Agency invites the submission of comments and solicits current compounding usage data for these drug products, if they are compounded for human use.

Unless an Agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. Most pharmacies meet the Small Business Administration definition of a small entity, which is

defined as having annual sales less than $25.5 million for this industry. The Agency is not aware of any routine compounding of these drug products and does not estimate any compliance costs or loss of sales to small businesses as a result of the prohibition against compounding these drugs. Therefore, the Agency proposes to certify that this proposed rule will not have a significant economic impact on a substantial number of small entities.

VI. Paperwork Reduction Act of 1995

The submission of comments on this proposed rule and the submission of additional nominations for the list that is the subject of this rulemaking would be submissions in response to a Federal Register notice, in the form of comments, which are excluded from the definition of "information" under 5 CFR 1320.3(h)(4) of OMB regulations on the Paperwork Reduction Act (i.e., facts or opinions submitted in response to general solicitations of comments from the public, published in the Federal Register or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency's full consideration of the comment). The proposed rule contains no other collection of information.

VII. Request for Comments

Interested persons may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at http://www.regulations.gov. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. FDA Public Health Advisory Letter from Murray M. Lumpkin, Deputy Center Director (Review Management), Center for Drug Evaluation and Research, FDA, Re: Food and Drug Administration TROVAN (Trovafloxacin/Alatrofloxacin Mesylate) Interim Recommendations (June 9, 1999), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm053103.htm.

2. Letter from E. Paul Mac Carthy, Vice President, Head U.S. Medical Science, Bayer Corporation, to Healthcare Professional, Re: Market withdrawal of Baycol (cerivastatin) (August 8, 2001), http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173692.pdf.

3. Letter from Jan Gheuens, Vice President, Medical Affairs, Janssen Pharmaceutica, to Healthcare Professional (April 12, 2000), PROPULSID (cisapride) Dear Healthcare Professional Letter (April 2000),

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm175000.htm.

4. FDA Alert--Information for Healthcare Professionals: Pemoline Tablets and Chewable Tablets (marketed as CYLERT) (October 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126461.htm.

5. FDA Public Health Advisory--Pergolide (marketed as PERMAX) (March 29, 2007), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051285.htm.

6. FDA Public Health Advisory--Safety of Phenylpropanolamine (November 6, 2000), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm052236.htm.

7. FDA Drug Safety Communication--FDA Recommends Against the Continued Use of Propoxyphene (November 19, 2010), http://www.fda.gov/Drugs/DrugSafety/ucm234338.htm.

8. Letter from Deborah Shapse, Medical Director, Organon, Inc., Re: Voluntary Market Withdrawal of RAPLON (rapacuronium bromide) for Injection, All Batches (March 27, 2001),

http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM173891.pdf.

9. FDA Public Health Advisory--Safety of VIOXX (September 30, 2004), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm.

10. FDA Public Health Advisory--Tegaserod maleate (marketed as ZELNORM) (March 30, 2007), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051284.htm.

11. FDA News Release, "FDA Permits Restricted Use of Zelnorm for Qualifying Patients" (July 27, 2007), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108956.htm.

12. FDA--ZELNORM (tegaserod maleate) Information (April 2, 2008), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm.

13. FDA Alert--Information for Healthcare Professionals: Valdecoxib (marketed as Bextra) (April 7, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124649.htm.

List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, the proposed rule that published on January 4, 2000 (65 FR 256), is withdrawn and it is proposed that 21 CFR part 216 be amended as follows:

PART 216--HUMAN DRUG COMPOUNDING

1. The authority citation for 21 CFR part 216 is revised to read as follows:

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

2. The heading for part 216 is revised to read as set forth above.

3. Section 216.24 is revised to read as follows:

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

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

Adenosine phosphate: All drug products containing adenosine phosphate.

Adrenal cortex: All drug products containing adrenal cortex.

Alatrofloxacin mesylate: All drug products containing alatrofloxacin mesylate.

Aminopyrine: All drug products containing aminopyrine.

Astemizole: All drug products containing astemizole.

Azaribine: All drug products containing azaribine.

Benoxaprofen: All drug products containing benoxaprofen.

Bithionol: All drug products containing bithionol.

Bromfenac sodium: All drug products containing bromfenac sodium (except ophthalmic solutions).

Butamben: All parenteral drug products containing butamben.

Camphorated oil: All drug products containing camphorated oil.

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

Casein, iodinated: All drug products containing iodinated casein.

Cerivastatin sodium: All drug products containing cerivastatin sodium.

Chloramphenicol: All oral drug products containing chloramphenicol.

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

Chlormadinone acetate: All drug products containing chlormadinone acetate.

Chloroform: All drug products containing chloroform.

Cisapride: All drug products containing cisapride.

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

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride.

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.

Dibromsalan: All drug products containing dibromsalan.

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

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate.

Dipyrone: All drug products containing dipyrone.

Encainide hydrochloride: All drug products containing encainide hydrochloride.

Esmolol hydrochloride: All parenteral dosage form drug products containing esmolol hydrochloride that supply 250 milligrams/milliliter of concentrated esmolol per 10-milliliter ampule.

Etretinate: All drug products containing entretinate.

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.

Flosequinan: All drug products containing flosequinan.

Gatifloxacin: All drug products containing gatifloxacin (except ophthalmic solutions).

Gelatin: All intravenous drug products containing gelatin.

Glycerol, iodinated: All drug products containing iodinated glycerol.

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

Grepafloxacin: All drug products containing grepafloxacin.

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

Metabromsalan: All drug products containing metabromsalan.

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride.

Methapyrilene: All drug products containing methapyrilene.

Methopholine: All drug products containing methopholine.

Methoxyflurane: All drug products containing methoxyflurane.

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

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

Nomifensine maleate: All drug products containing nomifensine maleate.

Novobiocin sodium: All drug products containing novobiocin sodium.

Oxycodone hydrochloride: All extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties.

Oxyphenisatin: All drug products containing oxyphenisatin.

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.

Pemoline: All drug products containing pemoline.

Pergolide mesylate: All drug products containing pergolide mesylate.

Phenacetin: All drug products containing phenacetin.

Phenformin hydrochloride: All drug products containing phenformin hydrochloride.

Phenylpropanolamine: All drug products containing phenylpropanolamine.

Pipamazine: All drug products containing pipamazine.

Polyethylene glycol 3350, sodium chloride, sodium bicarbonate, potassium chloride, and bisacodyl: All drug products containing polyethylene glycol 3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution, and 10 milligrams or more of bisacodyl delayed-release tablets.

Potassium arsenite: All drug products containing potassium arsenite.

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

Povidone: All intravenous drug products containing povidone.

Propoxyphene: All drug products containing propoxyphene.

Rapacuronium bromide: All drug products containing rapacuronium bromide.

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

Rofecoxib: All drug products containing rofecoxib.

Sibutramine hydrochloride: All drug products containing sibutramine hydrochloride.

Sparteine sulfate: All drug products containing sparteine sulfate.

Sulfadimethoxine: All drug products containing sulfadimethoxine.

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

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

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

Tegaserod maleate: All drug products containing tegaserod maleate.

Temafloxacin hydrochloride: All drug products containing temafloxacin.

Terfenadine: All drug products containing terfenadine.

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

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

Ticrynafen: All drug products containing ticrynafen.

Tribromsalan: All drug products containing tribromsalan.

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

Troglitazone: All drug products containing troglitazone.

Trovafloxacin mesylate: All drug products containing trovafloxacin mesylate.

Urethane: All drug products containing urethane.

Valdecoxib: All drug products containing valdecoxib.

Vinyl chloride: All aerosol drug products containing vinyl chloride.

Zirconium: All aerosol drug products containing zirconium.

Zomepirac sodium: All drug products containing zomepirac sodium.

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Leslie Kux,

Assistant Commissioner for Policy.

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