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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 216

[Docket No. FDA-2016-N-2462]

### Amendments to the Regulation Regarding the List of Drug Products That Have Been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness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.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to revise the list of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective. Drugs appearing on this list may not be compounded under the exemptions provided by sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Specifically, the proposed rule would add three entries to this list of drug products.

**DATES:** Submit either electronic or written comments on the proposed rule by **[INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**.

**ADDRESSES:** You may submit comments as follows:

#### Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will

be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-N-2462 for "Amendments to the Regulation Regarding the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper 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, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5199, Silver Spring, MD 20993-0002, 301-796-3110.

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## I. Executive Summary

A. Purpose of the Regulatory Action

FDA is proposing to amend its regulations to revise the list of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective (referred to as "the withdrawn or

removed list" or "the list") (§ 216.24 (21 CFR 216.24)). Drugs appearing on the withdrawn or removed list may not be compounded under the exemptions provided by sections 503A and 503B of the FD&C Act (21 U.S.C. 353a and 353b).

The Agency is proposing to add three entries (all drug products containing aprotinin, all drug products containing bromocriptine mesylate, and all intravenous drug products containing greater than a 16 milligram (mg) single dose of ondansetron hydrochloride) as described in this document to the list in § 216.24 of drug products 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.

#### B. Summary of the Major Provisions of the Proposed Regulatory Action

We are proposing that the following drugs that have been withdrawn or removed from the market because such drug products have been found to be unsafe or not effective be added to the list in § 216.24. The specific entries proposed for addition to the list for each of these drugs are provided as follows:

Aprotinin: All drug products containing aprotinin.

Bromocriptine mesylate: All drug products containing bromocriptine mesylate for prevention of physiological lactation.

Ondansetron hydrochloride: All intravenous drug products containing greater than a 16 mg single dose of ondansetron hydrochloride.

#### C. Costs and Benefits

The Agency is not aware of any routine use of the drug products that FDA is proposing to add to the the withdrawn or removed list and, therefore, does not estimate any compliance costs

or loss of sales as a result of the prohibition against compounding these drug products for human use. The Agency has determined that this rulemaking is not a significant regulatory action as defined by Executive Order 12866.

## II. Background

### A. Relevant Provisions of the Statute

Section 503A of the FD&C Act 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)).

In addition, section 503B of the FD&C Act describes the conditions that must be satisfied for a drug compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility to be 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-1) (concerning drug supply chain security).

One of the conditions that must be satisfied to qualify for the exemptions under both sections 503A and 503B of the FD&C Act is that the compounder does not compound a drug product that appears on a list published by the Secretary 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 (withdrawn or removed list) (see sections 503A(b)(1)(C), 503B(a)(4), and 503B(a)(11) of the FD&C Act).

### B. The List of Drug Products in § 216.24

The drug products listed in § 216.24 (the withdrawn or removed list) have been withdrawn or removed from the market because they have been found to be unsafe or not effective and are ineligible for the exemptions set forth in sections 503A and 503B of the FD&C Act. A drug product that is included in the list codified at § 216.24 is not eligible for 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, if compounded. In addition, a drug that is included in the list codified at § 216.24 cannot qualify for the exemptions provided in section 503B(a) of the FD&C Act, and is subject to sections 502(f)(1), 505, and 582 of the FD&C Act, in addition to other applicable provisions, if compounded.

### C. Regulatory History of the List

Following the addition of section 503A to the FD&C Act on November 21, 1997, through the enactment of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), FDA proposed a rule in the Federal Register of October 8, 1998 (63 FR 54082), 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 have been found to be unsafe or not effective (1998 proposed rule) and therefore were not permitted to be compounded for human use under the exemptions provided by section 503A(a).

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).

Following the addition of section 503B to the FD&C Act on November 27, 2013, through the enactment of the Drug Quality and Security Act (Pub. L. 113-54), FDA proposed to amend

the list in § 216.24 on July 2, 2014 (79 FR 37687); FDA published the final rule to amend § 216.24 in the Federal Register of October 7, 2016 (81 FR 69668) (2016 final rule). 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 revised and updated the list at § 216.24 to clarify that it applies for purposes of both sections 503A and 503B.

### III. Description of the Proposed Rule

FDA is proposing to amend § 216.24 to add three drug products, described in the following paragraphs, 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.

As with the 1999 final rule establishing the original list, and the 2016 final rule revising that list, the primary focus of this proposed rule is on drug products that have been withdrawn or removed from the market because they have been 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 have been 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 have been found to be unsafe.

The following drugs proposed for inclusion in § 216.24 are arranged alphabetically by the established names of the active ingredients contained in the 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. For some of the drug products, the proprietary or trade names 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 some 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 the specific drug entry FDA is proposing to add to § 216.24, as well as a brief summary of the reasons why each drug is being proposed for inclusion.

a. Aprotinin: All drug products containing aprotinin.

Bayer suspended marketing of aprotinin (TRASYLOL, NDA 20304) in November 2007 for safety reasons. TRASYLOL, NDA 20304, was approved on December 29, 1993. The indication for TRASYLOL, NDA 20304, was for "prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at increased risk for blood loss and blood transfusion." Prominent known adverse reactions associated with the use of the drug included anaphylactic reactions (with some deaths reported) and impaired renal function. In January 2006, Mangano et al. published a report that described the results from a retrospective analysis of the use of aprotinin compared to two other antifibrinolytic drugs (tranexamic acid and aminocaproic acid) or no antifibrinolytic drugs in 4,374 patients undergoing cardiac surgery (Ref. 1). The conclusions were that there was a statistically greater likelihood of the development of renal dysfunction and the need for hemodialysis, stroke, encephalopathy, myocardial infarction, and congestive heart failure in patients treated with aprotinin than with the other antifibrinolytic drugs or no antifibrinolytic drugs. On February 8, 2006, FDA issued a Public Health Advisory on TRASYLOL, NDA 20304, that called attention to this new information (Ref. 2). On September 21, 2006, FDA convened a meeting of its Cardiovascular and Renal Advisory Committee to evaluate these and other data for the drug (see <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#CardiovascularRenal> for meeting documents from the September 21, 2006, Cardiovascular and Renal Advisory Committee meeting). The

Cardiovascular and Renal Advisory Committee voted that the benefits of TRASYLOL, NDA 20304, compared to its risks warranted continued approvability for the indication (Yes, 18; No, 0; Abstain, 1). Before the advisory committee meeting, the sponsor had funded a study that evaluated a medical database for the outcomes of patients undergoing coronary artery bypass graft surgery (CABG) treated with aprotinin or other antifibrinolytics, which concluded that there was an increased risk of in-hospital death in the aprotinin-treated patients compared to those in patients treated with aminocaproic acid. This information was subsequently published in 2008 by Schneeweiss et al. (Ref. 3). In 2007, Mangano et al. published a report in 3,876 patients undergoing CABG surgery describing a higher mortality after 5 years for those treated with aprotinin compared to those treated with no antifibrinolytic drugs (Ref. 4). In the 2007 Mangano study, patients treated with either tranexamic acid or aminocaproic acid did not experience a higher mortality at 5 years compared to patients treated with no antifibrinolytic drug. These data led to a reconvening of the Cardiovascular and Renal Advisory Committee in a joint meeting with the Drug Safety and Risk Management Advisory Committee on September 12, 2007 (joint meeting), at which these and other data were reviewed (see <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#CardiovascularRenal> for meeting documents from the September 12, 2007, Cardiovascular and Renal Advisory Committee meeting). The Committees at the joint meeting were informed that there was an ongoing prospective randomized trial of aprotinin, tranexamic acid, and aminocaproic acid in patients undergoing CABG surgery with cardiopulmonary bypass in Canada (named the BART study), but that the results would not be available for several years. Some of the Committee members at the joint meeting stated that the issue should be revisited once the data from the BART study were available. The Advisory Committees at the joint meeting voted that TRASYLOL, NDA 20304,

should continue to be authorized to be marketed in the United States. Shortly after the joint meeting, FDA was informed that the Data Monitoring and Safety Committee for the BART study had recommended that the BART trial be terminated early because there appeared to be a greater frequency of death in patients treated with aprotinin (6.0 percent) compared to those treated in the combined tranexamic acid plus aminocaproic acid group (3.9 percent). The study was subsequently published in 2008 by Fergusson (Ref. 5). On October 25, 2007, FDA issued a Safety Alert for Human Medical Products alerting the medical community about the preliminary data from the BART trial (Ref. 6). On November 5, 2007, FDA issued a press release stating that, at the Agency's request, the sponsor had made a decision to suspend the marketing of TRASYLOL, NDA 20304, pending a review of the BART data for safety (Ref. 7). Although some of the data from the BART trial were submitted to FDA and the sponsor submitted its analysis of the data that was made available to the company, FDA was never successful in obtaining the raw data from the trial. Therefore, FDA was not able to conduct its own analyses of the trial data. TRASYLOL, NDA 20304, has not returned to the U.S. market since the sponsor announced its decision to suspend marketing in 2007. Aprotinin was made available by the sponsor for the treatment of certain surgical patients with an established medical need using a treatment protocol under an investigational new drug application (IND) (Ref. 8). Expanded access to aprotinin through this treatment protocol is no longer available (see <https://clinicaltrials.gov/ct2/show/NCT00611845?term=aprotinin&rank=4>). FDA is not aware of any data that would give us reason to believe that the safety issues identified as having been associated with aprotinin should be restricted to a particular formulation, concentration, indication, route of administration, or dosage form. For these reasons, FDA is proposing to include all drug products containing aprotinin on the withdrawn or removed list.

b. Bromocriptine mesylate: All drug products containing bromocriptine mesylate for prevention of physiological lactation.

Bromocriptine mesylate was associated with risks of hypertension, seizures, and cardiovascular accidents, and the unfavorable benefit-risk balance was specific to the use of bromocriptine mesylate for the prevention of physiological lactation. In 1980, PARLODEL (bromocriptine mesylate) was approved for the prevention of physiological lactation as an acceptable alternative to estrogenic therapy. Subsequently, FDA received postmarket reports of serious and life-threatening adverse reactions (hypertension, seizures, and cerebrovascular accidents) associated with the use of bromocriptine mesylate to suppress lactation. According to the approved labeling for PARLODEL, dated July 15, 1988 (Ref. 9), serious adverse reactions reported in postpartum women included 50 cases of hypertension, 38 cases of seizures (including 4 cases of status epilepticus), 15 cases of strokes, and 3 cases of myocardial infarction. These cases were discussed at a 1989 Fertility and Maternal Health Drugs Advisory Committee meeting (Ref. 10). FDA presented reports of its safety findings, which included 28 reports of hypertension, 36 reports of seizures, and 19 reports of cerebrovascular accidents. FDA had received 85 cases of serious adverse events, including 10 deaths, since the approval of bromocriptine mesylate for lactation suppression in 1980 (August 23, 1994 (59 FR 43347)). The Fertility and Maternal Health Drugs Advisory Committee recommended that no drug then labeled for lactation suppression including bromocriptine mesylate be used for this indication. FDA subsequently asked that all manufacturers of these drugs voluntarily remove this indication from drug labeling. All but Sandoz, the manufacturer of PARLODEL, complied with FDA's request. In a document published in the Federal Register of August 23, 1994, FDA concluded that the risks of hypertension, seizures, and cardiovascular accidents outweighed the product's

marginal benefit in preventing postpartum lactation. Accordingly, FDA proposed to withdraw approval of the indication recommending bromocriptine mesylate for preventing physiological lactation in the NDA for PARLODEL, under section 505(e) of the FD&C Act, on the basis that the drug is no longer shown to be safe for this indication. FDA withdrew approval of PARLODEL for the indication of prevention of physiological lactation in a document published in the Federal Register of January 17, 1995 (60 FR 3404). Withdrawal of PARLODEL's indication for the prevention of physiological lactation became effective on February 16, 1995. FDA's review of the withdrawal indicates that the withdrawal of bromocriptine mesylate for prevention of physiological lactation was fundamentally based on an unfavorable benefit-risk balance specific to this indication and not to other approved indications (such as treatment of Parkinson's disease, acromegaly, and prolactin-secreting adenomas). For this reason, FDA is proposing to include all drug products containing bromocriptine mesylate for prevention of physiological lactation on the withdrawn or removed list.

c. Ondansetron hydrochloride: All intravenous drug products containing greater than a 16 mg single dose of ondansetron hydrochloride.

Ondansetron (ondansetron hydrochloride (HCl)) Injection, USP, 32 mg, in 50 milliliters (mL), single intravenous (IV) dose, was associated with a specific type of irregular heart rhythm called QT interval prolongation, and the data suggest that any dose above the maximum recommendation of 16 mg per dose intravenously has the potential for increased risk of QT prolongation. In September 2011, FDA issued a Drug Safety Communication noting concerns that the 32 mg single IV dose of ZOFTRAN (ondansetron HCl) and generic versions of that product could increase the risk of abnormal changes in the electrical activity of the heart, which could result in a potentially fatal abnormal heart rhythm (Ref. 11). Based on data subsequently

collected from a study conducted at FDA's request by ZOFTRAN's sponsor, GlaxoSmithKline (GSK), that identified a significant QT prolongation effect in connection with the 32 mg single IV dose, FDA approved GSK's supplemental application to remove the 32 mg single IV dose information from the labeling for ZOFTRAN and has worked with manufacturers of all 32 mg single IV dose ondansetron HCl products to have them removed from the market. On June 29, 2012, FDA issued a Drug Safety Communication to notify health care professionals that the 32 mg single IV dose of ondansetron HCl, indicated for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy in adult patients, should be avoided due to the risk of QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm (Ref. 12). Subsequently, FDA informed the holders of one NDA and four ANDAs for ondansetron HCl that the Agency believes that, in light of the safety concern associated with ondansetron HCl in the 32 mg single IV dose, these drug products should be removed from the market. The application holders agreed to voluntarily remove their respective 32 mg single IV dose ondansetron HCl products from the market and requested that FDA withdraw approval of their respective applications under 21 CFR 314.150(d). On December 4, 2012, FDA issued an updated Drug Safety Communication alerting health care professionals that these products would be removed from the market because of their potential for serious cardiac risks (Ref. 13). In the Federal Register of June 10, 2015 (80 FR 32966), FDA announced that it was withdrawing the approval of these five applications. On the same day, in a different document in the Federal Register (80 FR 32962), FDA announced its determination under 21 CFR 314.161 and 314.162(a)(2) that the NDA for Ondansetron (ondansetron HCl) Injection, USP, 32 mg/50 mL, single IV dose was withdrawn from sale for reasons of safety. As explained in the review of ondansetron HCl 32 mg single IV dose for the withdrawn or removed

list (see tab 5 of the FDA briefing document for the June 17-18, 2015, Pharmacy Compounding Advisory Committee, available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm431285.htm>), for those approved products for IV ondansetron HCl that remain on the market, the current dosage and administration recommendation for adults and pediatric patients (6 months to 18 years) is three 0.15 mg/kilogram doses, up to a maximum of 16 mg per dose, infused intravenously over 15 minutes, and any dose above the maximum recommended 16 mg per IV dose has the potential for increased risk of QT prolongation. For these reasons, FDA is proposing to include all IV drug products containing greater than a 16 mg single dose of ondansetron HCl on the withdrawn or removed list.

On June 17, 2015, FDA presented these three proposed entries to the Pharmacy Compounding Advisory Committee (see the Federal Register of May 22, 2015 (80 FR 29717)). In addition to these three proposed entries, FDA presented a potential entry for all drug products containing more than 325 mg of acetaminophen per dosage unit to the Pharmacy Compounding Advisory Committee. The addition of all drug products containing more than 325 mg of acetaminophen per dosage unit to the list remains under consideration by the Agency.

The Pharmacy Compounding Advisory Committee voted in favor of including each of FDA's four proposed entries on the list. Although an open public hearing session was scheduled at this meeting to allow members of the public to present their views and opinions on the proposed entries to the committee members and the Agency prior to the vote by the Pharmacy Compounding Advisory Committee, no members of the public signed up to participate. A transcript of the June 2015 Pharmacy Compounding Advisory Committee meeting and briefing information that includes reviews and background on the proposed entries may be found at the

Division of Dockets Management (see **ADDRESSES**) and at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm431285.htm>.

#### IV. Legal Authority

Sections 503A and 503B of the FD&C Act provide the principal legal authority for this proposed rule. As described previously in the Background section of this document, section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505). 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). Section 503A(c)(1) of the FD&C Act also 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.

Section 503B of the FD&C Act describes the conditions that must be satisfied for a drug compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility to be exempt from three sections of the FD&C Act (sections 502(f)(1), 505, and 582). 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)). To be eligible for the exemptions in section 503B, a drug must be compounded in an outsourcing facility in which the compounding of drugs occurs only in accordance with section 503B, including as provided in section 503B(a)(4).

Thus, sections 503A and 503B of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as our principal legal authority for this proposed rule revising FDA's regulations on drug products withdrawn or removed from the market because the drug product or a component of the drug product have been found to be unsafe or not effective in § 216.24.

#### V. Analysis of Environmental Impact

We have 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.

#### VI. Economic Analysis of Impacts

We have 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 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us 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 the proposed 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 us to 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 \$146 million, using the most current (2015) 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 proposed rule would amend § 216.24 concerning human drug 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 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 II of this document). We are proposing to add three entries to the list. We are not aware of any routine compounding for human use of the drug products that are the subject of this proposed rule, and therefore do not estimate any compliance costs or loss of sales if the proposal

is adopted. However, we invite the submission of comments and solicit current compounding usage data for these drug products, if they are compounded for human use.

Unless we certify that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us 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. We are not aware of any routine compounding of these drug products and do not estimate any compliance costs or loss of sales to small businesses as a result of the prohibition against compounding these drug products. Therefore, we propose to certify that this proposed rule will not have a significant economic impact on a substantial number of small entities.

#### VII. Paperwork Reduction Act of 1995

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

#### VIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## IX. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Mangano, D.T., I.C.Tudor, and C. Dietzel, "The Risk Associated With Aprotinin in Cardiac Surgery," New England Journal of Medicine, 354(4):353-365, 2006.
2. FDA News Release, "FDA Issues Public Health Advisory for Trasylol" (February 8, 2006), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108592.htm>.
3. Schneeweiss, S., J.D. Seeger, J. Landon, and A.M. Walker, "Aprotinin During Coronary-Artery Bypass Grafting and Risk of Death," New England Journal of Medicine, 358:771-783, 2008.
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5. Fergusson, D.A., P.C. Hébert, C.D. Mazer, et al., "A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery," New England Journal of Medicine, 358(22):2319-2331, 2008.
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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, it is proposed that 21 CFR part 216 be amended as follows:

**PART 216--HUMAN DRUG COMPOUNDING**

1. The authority citation for part 216 continues to read as follows:

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

2. Amend § 216.24 by adding, in alphabetical order, to the list of drugs "Aprotinin", "Bromocriptine mesylate", and "Ondansetron hydrochloride" to read as follows:

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

\* \* \* \* \*

Aprotinin: All drug products containing aprotinin.

\* \* \* \* \*

Bromocriptine mesylate: All drug products containing bromocriptine mesylate for prevention of physiological lactation.

\* \* \* \* \*

Ondansetron hydrochloride: All intravenous drug products containing greater than a 16 milligram single dose of ondansetron hydrochloride.

\* \* \* \* \*

Dated: October 11, 2016.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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