



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-AH08

Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness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

SUMMARY: The Food and Drug Administration (FDA or the Agency) is amending its regulations to revise the list of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective.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 rule adds 24 entries to this list of drug products, modifies the description of one entry on this list, and revises the list's title and introductory language. These revisions are necessary because information has come to the Agency's attention since March 8, 1999, when FDA published the original list as a final rule.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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:

Table of Contents

Executive Summary

 Purpose of the Regulatory Action

 Summary of the Major Provisions of the Regulatory Action in Question

 Costs and Benefits

I. Background: The Provisions of 503A and 503B Pertaining to the Withdrawn or Removed List

II. Proposed Rule and Final Rule

 A. The Proposed Rule

 B. Presentation to the Advisory Committee

 C. The Final Rule

III. Comments on the Proposed Rule and FDA's Responses

 A. Comments on Proposed Entries for Inclusion on the List

 B. Comments on Other Issues

 C. Comments on Updating the List

 D. Miscellaneous Comments

IV. Legal Authority

V. Analysis of Environmental Impact

VI. Economic Analysis of Impacts

VII. Paperwork Reduction Act of 1995

VIII. Federalism

IX. References

Executive Summary

Purpose of the Regulatory Action

FDA is amending its regulations to revise the list of drug products that have been withdrawn or removed from the market because the drug products or components of such drug products have been found to be unsafe or not effective (referred to as “the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. In this final rulemaking, the Agency is finalizing in part the proposed amendments to § 216.24 set forth in the proposed rule published in the Federal Register of July 2, 2014 (79 FR 37687).

Section 503A of the FD&C Act (21 U.S.C. 353a) refers to a list published by the Secretary of Health and Human Services 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. Furthermore, section 503A(c)(1) of the FD&C Act 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 list, 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 addition, section 503B of the FD&C Act (21 U.S.C. 353b) refers to 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.

After soliciting public comments and consulting with the Pharmacy Compounding Advisory Committee (Advisory Committee), FDA is issuing this final rule revising and updating the list in § 216.24 for purposes of both sections 503A and 503B of the FD&C Act. FDA may update this list in the future as necessary when information comes to the Agency's attention indicating that changes to the list are needed.

Summary of the Major Provisions of the Regulatory Action in Question

The final rule: (1) Adds 24 entries to the list of drug products in § 216.24 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, (2) modifies one entry already on the list to add an exception that allows a drug product to be compounded under certain circumstances, and (3) modifies the title of part 216 and the introductory text of § 216.24.

Costs and Benefits

The Agency is not aware of any routine compounding for human use of the drug products that are the subject of this rule, and therefore does not estimate any compliance costs or loss of sales as a result of finalizing regulations making these drugs ineligible for exemptions under sections 503A and 503B of the FD&C Act. The Agency has determined that this rule is not a significant regulatory action as defined by Executive Order 12866.

I. Background: The Provisions of 503A and 503B Pertaining to the Withdrawn or Removed
List

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)).

Section 503B of the FD&C Act created 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-1) (concerning drug supply chain security), but not from section 501(a)(2)(B).

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) and 503B(a)(4) of the FD&C Act).

II. Proposed Rule and Final Rule

A. The Proposed Rule

In the Federal Register of July 2, 2014, FDA proposed 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 (the July 2014 proposed rule). Drugs appearing on this list may not be compounded under the exemptions provided by sections 503A and 503B of the FD&C Act. Specifically, FDA proposed to add 25 entries to this list of drug products and to modify the description of one entry on this list to add an exception for products compounded under certain circumstances. The preamble of the proposed rule explained that these revisions are necessary to ensure the list of drug products in § 216.24 reflects information that has come to the Agency's attention since FDA published the original list in the 1999 final rule. Given that nearly identical criteria apply for a drug product 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 proposed revising and updating the list at § 216.24 for purposes of both sections 503A and 503B.

As with the original list, the primary focus of the July 2014 proposed rule and this final 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 information becomes available to the Agency regarding products that were withdrawn or removed from the market because they have been found to be unsafe.

In the preamble of the July 2014 proposed rule, FDA also invited comments on the appropriate procedure to update the list in the future. FDA described the provisions of sections 503A and 503B of the FD&C Act regarding how the Agency is to create and update the list, and noted the differences between the procedures set forth in sections 503A and 503B. The Agency explained that it believes that the timely sharing of information about safety concerns relating to compounding drugs for human use is essential to the protection of public health. FDA also explained that it 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 announced that the Agency was seeking an alternative procedure to update the withdrawn or removed list in the future and solicited public comment. FDA also stated that it would specify in the final rule the procedure it will use to update the list in the future.

B. Presentation to the Advisory Committee

At a meeting held on February 23 and 24, 2015 (see the Federal Register of January 26, 2015 (80 FR 3967)), FDA presented to the Advisory Committee the 25 entries it proposed to include on the list and the proposed modification to the listing for one entry. The Advisory Committee voted in favor of including each drug product entry on the list as proposed by FDA. In addition, because FDA had received a comment on the July 2014 proposed rule requesting that FDA clarify the entry for adenosine phosphate, FDA presented a potential modification to the Advisory Committee and the Committee voted in favor of the modification.

C. The Final Rule

1. List of Drug Products

The Agency has considered the record of the February 2015 Advisory Committee deliberations, that Advisory Committee's votes, and the comments submitted on the July 2014 proposed rule (see section III). Based on the information before FDA and its own knowledge and expertise, FDA is:

- Adding 24 entries to the withdrawn or removed list in § 216.24 as written in the proposed rule; and
- Modifying the description of one drug product entry already on this list, bromfenac sodium, to add an exception when the product is compounded under certain circumstances as written in the proposed rule.

At this time, FDA is not finalizing the entry in the proposed rule for all extended-release drug products containing oxycodone hydrochloride that have not been determined by FDA to have abuse-deterrent properties. The addition of an entry to the withdrawn or removed list for oxycodone hydrochloride remains under consideration by FDA.

2. A Single Withdrawn or Removed List Will Apply for the Purposes of Both Sections 503A and 503B

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 revising and updating the list at § 216.24 for purposes of both sections 503A and 503B. The list in § 216.24 applies to compounders seeking to qualify for the exemptions under section 503A and outsourcing facilities seeking to qualify for the exemptions under section 503B. Drug products that appear on this list have been withdrawn or removed from the market because they

have been found to be unsafe or not effective and may not be compounded for human use under the exemptions provided by either section 503A or 503B of the FD&C Act.

3. Procedure for Updating the List Going Forward

After consideration of the comments submitted on the July 2014 proposed rule (see section III of this document), at this time FDA intends to continue updating the list through notice and comment rulemaking, and we are therefore not proposing or adopting an alternative process with the publication of this final rule. We recognize that adding drug products to the list may limit their availability, and the notice and comment process informs interested members of the public of how the Agency proposes to revise the list and gives them an opportunity to contribute to the process. Additionally, we intend to create a Web page, described in more detail in the paragraphs that follow, that contains information about any drugs that we are considering proposing or that we have proposed for addition to the withdrawn or removed list. We believe that the Web page will be a valuable source of timely information for patients, prescribers, and compounders.

In the following paragraphs, FDA discusses its current thinking about the procedures we intend to use to revise the withdrawn or removed list as needed. This discussion does not create rights or impose binding obligations on the Agency. In section III, we respond further to specific comments about whether the Agency should adopt alternative procedures.

We intend to propose regulations to revise the withdrawn or removed list periodically, as appropriate, as we identify drugs that we tentatively determine should be listed. We would also propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing, for example, if some version of a drug on the list has been approved for marketing. As FDA identifies drugs that it is considering

for a future rule proposal, we intend to collect and post together on a single page of the Agency's Web site relevant information about those drugs. The information may include, for example, Federal Register notices announcing withdrawal of approval of a drug application and accompanying safety communications or information, Federal Register notices announcing an Agency determination that a drug product was removed from sale for reasons of safety or effectiveness, or other relevant FDA Alerts, FDA Drug Safety Communications, FDA News Releases, Public Health Advisories, Dear Healthcare Practitioner Letters, Citizen Petitions, and Sponsor Letters.

If FDA determines that issuing proposed and then final regulations to add a drug product to the withdrawn or removed list before consulting the Advisory Committee is necessary to protect the public health, then it will do so as permitted under section 503A(c)(1) of the FD&C Act. Based on the Agency's experience to date, we expect that this will rarely be necessary, and that we will instead generally consult the Advisory Committee before adding a drug product to the withdrawn or removed list.

When FDA consults the Advisory Committee in the ordinary course, FDA may issue a proposed rule announcing proposed updates to the list prior to convening the Advisory Committee, or it may convene the Advisory Committee first to discuss potential updates and then publish a proposed rule. The order will depend on the timing of the Advisory Committee meetings, the priority of matters that may be brought before the Advisory Committee, and the status of other compounding-related rulemakings. There are numerous steps that must be completed before holding an FDA advisory committee meeting, which make it difficult to schedule a meeting on short notice. For instance: (1) Meeting participants must be contacted to determine their availability, and travel and lodging arrangements must be made; (2) conflict of

interest screening and review must be completed before an advisory committee member can participate in a particular matter; (3) a Federal Register notice must be published for each meeting to announce to the public that a meeting will be held, and it must generally be published no later than 15 days prior to the meeting; (4) a meeting location must be secured; (5) meeting materials for the committee must be compiled for committee members, and a redacted version must be created for posting on the FDA Web site; numerous other logistical steps must be completed.

Regardless of the order in which FDA holds the Advisory Committee meeting and issues a proposed rule, and with the exception noted previously of the likely to be rare instances where FDA determines that it is necessary to revise the list in § 216.24 prior to consultation with the Advisory Committee to protect the public health, FDA will only finalize any additions or modifications to the list after consulting the Advisory Committee about the relevant drug or drugs, and after FDA has provided an opportunity for public comments to be submitted on the proposed rule. In addition to having an opportunity to submit comments on any specific proposals to the docket of the proposed rule, members of the public will also have an opportunity to comment on any potential updates to the list at the Advisory Committee meetings as well. An open public hearing session will be scheduled at each of these meetings, during which interested persons will have an opportunity to submit their views.

In instances where FDA first consults the Advisory Committee about a drug product and subsequently proposes regulations to update the list with a new or modified entry for the drug product, FDA generally does not expect to convene the Advisory Committee a second time before deciding whether to finalize the entry. The Agency may bring the entry back to the Advisory Committee if that is warranted. We do not expect this will occur very often given the

opportunity to submit views to the Advisory Committee before the rule is proposed and as evidenced by the fact that we received no comments on 25 of the 26 entries that were proposed for addition or modification to the list in the July 2014 proposed rule.

III. Comments on the Proposed Rule and FDA's Responses

Seven comments were submitted on the July 2014 proposed rule. Comments were received from two pharmacists; two health professionals; an organization representing health care practitioners, as well as food and dietary supplement companies and consumer advocates; and two organizations representing pharmacists. FDA has summarized and responded to these comments in the following paragraphs.

To make it easier to identify the comments and FDA's responses, the word "Comment," in parentheses, appears before the comment's description, and the word "Response," in parentheses, appears before the Agency's response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number, and, in some cases, different subjects discussed in the same comment are separated and designated as distinct comments for purposes of FDA's response. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which the comments were received.

A. Comments on Proposed Entries for Inclusion on the List

1. General

(Comment 1) One comment supported the list in the proposed rule and recommended that FDA finalize the list as soon as possible.

(Response) FDA agrees with the comment.

2. Specific Drug Entries for Inclusion on the List

a. Oral Chloramphenicol (Comment 2). FDA received one comment on the proposal to include all oral drug products containing chloramphenicol on the withdrawn or removed list. The comment requested that FDA “reconsider and reclassify Chloramphenicol 250 mg tablets labeling for tropical [sic] medical use and packaging changes; rather than withdraw from the marketplace for developing nations [World Health Organization,] WHO list of drug use.” The comment stated that chloramphenicol 250 milligrams (mg) is used to control hemorrhagic fever-like illnesses (e.g., Lassa Fever, Ebola) and also stated that control and survival benefits outweigh the risks of thrombocytopenia and aplastic anemia in the already anemic patient when used in the short term appropriately.

(Response) FDA disagrees with the suggested revisions. For the reasons that follow, FDA will add all oral drug products containing chloramphenicol to the list in § 216.24.

In the Federal Register of February 11, 2009 (74 FR 6896), FDA announced that it was withdrawing approval of ANDA 60-591 for Chloromycetin (chloramphenicol) Capsules 50 mg, 100 mg, and 250 mg, 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)).

In December 2015, FDA initiated the process to suspend chloramphenicol ANDA 60-851, which was held by Armenpharm. FDA sent a letter to Armenpharm notifying the company of the Agency's initial determination that Chloromycetin (chloramphenicol) Capsules, 250 mg were withdrawn for reasons of safety or effectiveness and of the Agency's initial decision to suspend approval of ANDA 60-851 (See Docket No. FDA-2011-P-0081). Under § 314.153(b)(2) (21 CFR 314.153(b)(2)), Armenpharm had 30 days from that notification in which to present written comments or information bearing on the initial decision. On December 17, 2016, Armenpharm submitted comments requesting an oral hearing under § 314.153(b)(4). On March 17, 2016, however, Armenpharm withdrew its oral hearing request.

FDA issued a notice in the Federal Register announcing the suspension of ANDA 60-851 (see 81 FR 64914, September 21, 2016). In the same notice, FDA announced the following drug products were withdrawn from sale for reasons of safety or effectiveness: Chloromycetin (chloramphenicol) Capsules, 50 mg and 100 mg; Amphicol (chloramphenicol) Capsules, 100 mg;

and Chloromycetin Palmitate (chloramphenicol palmitate), oral suspension 150 mg/5 mL as currently labeled.

After reviewing the comment regarding the proposed oral chloramphenicol entry, FDA reassessed whether to include oral chloramphenicol on the list, and if so, how to describe the entry. FDA's January 2015 review on oral chloramphenicol (available as Tab 8 of Ref. 1 of the briefing document for the February 2015 Advisory Committee meeting) determined that oral chloramphenicol formulations, regardless of the specific oral forms and strengths, are expected to have a safety profile similar to that of chloramphenicol capsules, 250 mg. Furthermore, FDA's January 2015 review on oral chloramphenicol noted that the Agency was not aware of any evidence that chloramphenicol has antiviral activity against causative agents of viral hemorrhagic fever, including Ebola. Chloramphenicol's mechanism of antibacterial action is by binding to the 50S subunit of the bacterial ribosome, a structure not found in viruses. Therefore, there is no putative mechanism to expect antiviral activity.

This FDA review on oral chloramphenicol was presented to the Advisory Committee on February 23, 2015, and the Advisory Committee voted in favor of the Agency's proposal to include all oral drug products containing chloramphenicol on the list.

b. Adenosine Phosphate (Comment 3). FDA received one comment asking that FDA clarify whether the entry for adenosine phosphate that was part of the original list finalized in 1999 is intended to include all three forms of adenosine phosphate (mono-, di-, and triphosphate).

(Response) For the reasons that follow, FDA declines to modify the entry for adenosine phosphate on the list in § 216.24 at this time.

The preamble of the 1998 proposed rule to establish the original list (see 63 FR 54082, October 8, 1998) stated that adenosine phosphate, formerly marketed as a component of Adeno for injection, Adco for injection, and other drug products, was determined to be neither safe nor effective for its intended uses as a vasodilator and an anti-inflammatory. FDA directed the removal of these drug products from the market in 1973.

After reviewing the comment to the docket of the July 2014 proposed rule regarding the adenosine phosphate entry, FDA began to assess whether to modify the adenosine phosphate entry and, if so, how.

FDA prepared a review on adenosine phosphate (available as Tab 7 of Ref. 1 of the briefing document for the February 2015 Advisory Committee meeting) and consulted with the Advisory Committee on February 23, 2015 on the comment, as discussed in section II.B.

Ultimately, FDA determined that it is unnecessary to modify the entry for adenosine phosphate on the list in § 216.24 at this time. None of the substances raised in the comment (adenosine 5'-monophosphate (AMP), adenosine 5'-diphosphate (ADP), and adenosine 5'-triphosphate (ATP)) satisfy the requirements for a bulk drug substance that may be used in compounding under either section 503A or section 503B.¹ Consequently, at this time, a drug product compounded with AMP, ADP, or ATP would be ineligible for the exemptions provided under either section 503A or section 503B.

c. Propoxyphene. No comments were submitted regarding propoxyphene. Since the time the proposed rule was published, however, FDA announced in the Federal Register of

¹ These substances are not the subject of an applicable United States Pharmacopeia or National Formulary monograph, a component of an FDA-approved drug, on a list of bulk drug substances established by FDA that may be used in compounding, or on a drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e). See section 503A(b)(A)(i) and section 503B(a)(2)(A) of the FD&C Act.

September 12, 2014 (79 FR 54729) that it was withdrawing approval of three propoxyphene products. The holders of the applications for the three products had been given notice of opportunity for a hearing in the Federal Register of March 10, 2014 (79 FR 13308) (the March 10, 2014, notice), and no timely request for a hearing on the matter was received. In addition, FDA announced in the Federal Register of April 15, 2016 (81 FR 22283), that it was correcting a notice that appeared in the Federal Register of March 10, 2014 (79 FR 13308). The March 10, 2014, notice announced the withdrawal of approval of 54 propoxyphene products with agreement from holders of the affected applications. The April 15, 2016, notice added one additional propoxyphene product, NDA 017507, held by Xanodyne Pharmaceuticals, to the table of products for which approval was withdrawn with agreement from the holders of the affected applications.

B. Comments on Other Issues

1. Ripeness of Proposed Rule

(Comment 4) FDA received two comments suggesting that the issuance of the July 2014 proposed rule was premature. The comments expressed concern that FDA had proposed adding drug products to the previously existing list of drug products withdrawn from the market for safety and efficacy reasons without first obtaining input from the Advisory Committee. One of the comments further suggested that the proposed rule be withdrawn until such time as the drug products, proposed to be added, could be reviewed by the Advisory Committee.

(Response) FDA notes that the July 2014 Federal Register notice was a notice of proposed rulemaking, not a final rule. Section 503A(c)(1) of the FD&C Act states 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. The changes in a proposed rule are not effective or implemented unless and until a proposed rule is finalized. Because the Agency convened and consulted the Advisory Committee on February 23, 2015, regarding each of the amendments to the list we are finalizing in the present rule, the Agency has satisfied the statutory requirements of section 503A(c)(1) of the FD&C Act.

2. Single List

(Comment 5) One comment suggested that the Agency should finalize its proposal to publish one list for both section 503A and section 503B of the FD&C Act.

(Response) FDA agrees with this comment.

C. Comments on Updating the List

FDA received comments from five different submitters on the procedure for updating the list.

(Comment 6) FDA received two comments regarding a specific alternative approach to the current process of issuing first a proposed rule followed by a final rule before adopting any additions or modifications to the list. One comment recommended use of an interim final rule or final rule with comment to allow for the flexibility to review public input, yet incorporate the latest safety information into the practice of compounding. Another comment recommended that in instances where public health may be of significant concern, the Agency convene an emergency meeting of the Advisory Committee within 5 business days to obtain specific input and recommendations to the Secretary for immediate inclusion of a drug product on the list.

(Response) As noted previously in section II.C.3, there are numerous steps that must be completed before holding an FDA advisory committee meeting, which make it difficult to

schedule a meeting on short notice. In the likely to be rare instances where FDA determines that it is necessary to revise the list in § 216.24 prior to consultation with the Advisory Committee to protect the public health, FDA will add the drug to the list prior to consultation with the Advisory Committee under section 503A(c)(1) of the FD&C Act.

With respect to issuing interim final rules or final rules with comment, the Agency's current thinking is that the process described in section II.C.3 will allow the Agency to provide timely public notice of emerging safety information and appropriate opportunity for interested persons to comment before FDA revises the withdrawn or removed list.

(Comment 7) FDA received a comment suggesting that upon receipt of a notice to withdraw a product from the market for safety and efficacy reasons by the NDA or ANDA holder, FDA inform the Advisory Committee and include a review of that request on the Committee's next scheduled meeting agenda.

(Response) FDA does not agree that it should inform the Advisory Committee when it is advised by an NDA or ANDA holder that the NDA or ANDA holder has removed a drug from the market for safety or efficacy reasons, or that such a drug should necessarily be included on the Advisory Committee's next scheduled meeting agenda. FDA considers but does not rely solely on an NDA or ANDA holder's assertions or representations to determine whether a drug has been withdrawn or removed from the market because it has been found to be unsafe or not effective. Rather, the Agency considers a range of information before the Agency, such as information provided by the NDA or ANDA holder, information contained in the Agency's files, and the Agency's independent evaluation of relevant literature and data on possible postmarketing adverse events. When the Agency decides to propose a change, it will proceed as described previously in section II.C. The timing of any consultation with the Advisory

Committee will also depend on, among other things, the timing of the Advisory Committee meetings and the relative priority of matters that may be brought before the Advisory Committee.

(Comment 8) Another comment recommended soliciting public input specifically on how to incorporate the “do not compound” list when publishing intent to withdraw a drug.

(Response) FDA does not believe it is necessary or that it would be efficient to separately solicit public input every time the Agency publishes a notice in the Federal Register of its intent to withdraw approval of a drug.

When the Agency publishes a notice in the Federal Register of its intent to withdraw approval of a drug, it does so to give a particular party or parties notice and an opportunity for a hearing on the proposed withdrawal. This process may or may not result in a withdrawal of approval of the application, and even if the application is withdrawn the reasons may not relate to the safety or efficacy of the drug. Whether or how a drug should be included on the withdrawn or removed list under sections 503A and 503B of the FD&C Act is a separate question. In general, as discussed previously in this document in section II.C.3, interested members of the public will have the opportunity to review and comment on any proposals to add a drug to or revise an entry for a drug already on the withdrawn or removed list.

(Comment 9) FDA received several comments opposing any approach to updating the withdrawn or removed list that would eliminate public review from the process. One comment stated that FDA already has the ability to remove from the market any drug that is dangerous and claimed that this does not justify completely eliminating public involvement in the process of making additions to the withdrawn or removed list. Another suggested that additions and changes to the withdrawn or removed list be made through notice and comment rulemaking, observing that such a notice and comment period will allow stakeholders to review FDA’s safety

and efficacy concerns for a particular drug product prior to addition to the withdrawn or removed list. One comment recommended incorporating public discussion about how to address a drug on the list when convening a drug advisory committee. One suggested all additions to the list go through an advisory committee that is open to public comment. One suggested that no revisions to the list occur without the input and review of the Advisory Committee.

(Response) We appreciate these comments, and as explained in section II.C.3., at this time we have decided not to adopt or propose an alternative process to notice and comment rulemaking for revising the withdrawn or removed list. Additionally, FDA intends to consult the Advisory Committee prior to placing a drug on the withdrawn or removed list unless we determine that the issuance of such regulations before consultation is necessary to protect the public health. These procedures provide ample opportunity for public input regarding additions or modifications to the list, including: (1) An opportunity to present relevant information at an open public hearing held when the Advisory Committee meets to consider proposed revisions to the list and (2) an opportunity to submit comments on each proposed rule before it is finalized.

(Comment 10) One comment recommended that all drug products currently on the list be reviewed by the Advisory Committee on an annual basis to determine whether any change in therapy or use of those drugs necessitates either removal or the clarification of certain salts, dosage forms, or other clinical application to assure accessibility of medications for patients.

(Response) FDA has considered this comment and does not believe it is necessary to require an annual review by the Advisory Committee of all drug products on the list. Such a review is not necessary, practical, or feasible. Once a drug has been added to the list, FDA does not expect that there will frequently be a need to revise the entry for that drug. FDA intends to monitor future approvals, withdrawals, or removals of listed drugs, to consult other relevant

information that may suggest a need for revisions to the list, and to propose modifications as appropriate. In addition, members of the public can submit a citizen petition at any time under § 10.30 requesting that FDA modify or remove an entry on the list (with adequate data to support their request), and FDA will consider and respond to the petition.

(Comment 11) One comment recommended that FDA issue an annual request in the Federal Register for submissions by the public of drug products to be reviewed and considered for inclusion on the list, inform the Advisory Committee of any submitted drug products, and include a review of those submissions on the Advisory Committee's next scheduled meeting agenda.

(Response) FDA disagrees with the suggestion to issue an annual request in the Federal Register for submissions by the public of drug products to be reviewed and considered for inclusion on the list. We welcome suggestions by the public of drug products to consider and review for inclusion on the list, or of a modification to an entry in the list, at any time through the citizen petition process (see response to comment 10). We do not wish to restrict the submissions of such suggestions to just once a year. FDA does intend to consult with Advisory Committee as described in section II.C.3.

D. Miscellaneous Comments

(Comment 12) One comment stated that nowhere within the proposed rule is there a formal process for reviewing, updating, and informing the compounding community of changes or updates to the list of drugs withdrawn or removed from the market for safety and efficacy reasons. The comment contends this is of grave concern to the pharmacy community and one which must be addressed.

(Response) FDA agrees that the compounding community should be informed of and have an opportunity to review and comment on proposed revisions to the list of drugs at § 216.24, that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. The process outlined in section II.C.3 provides notice and an opportunity to comment to the compounding community and to the general public. Further, as noted elsewhere, members of the compounding community and other members of the public can submit a citizen petition at any time under § 10.30, requesting that FDA modify or remove an entry on the list (with adequate data to support their request), and FDA will consider and respond to the petition.

(Comment 13) One comment suggested that the Secretary establish minimum criteria that must be met before any drug product may be added to the withdrawn or removed list.

(Response) FDA disagrees with this comment. The criteria that must be met to place a drug on the withdrawn or removed list are laid out in the statute. Under sections 503A and 503B of the FD&C Act, drug products on the withdrawn or removed list are those 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. At this time, FDA does not believe it would be helpful to issue guidance or regulations to further define or interpret this standard. Instead, FDA intends to discuss in any rulemaking the basis for the Agency's proposal to add a drug product to the list or to modify an entry on the list.

(Comment 14) One comment observed that under both sections 503A and 503B of the FD&C Act, drugs may be added to the list if they have been found to be not effective. The comment went on to note that without the crucial check in the rulemaking process afforded by

public review, FDA would be able to ban from compounding any drug on the pretext of it being “not effective.”

(Response) As described in section II.C.3, FDA intends to revise the list by using notice-and-comment rulemaking and, generally, to consult the Advisory Committee. Interested members of the public will have the opportunity to submit their views through this process. In addition, in the preamble to the July 2014 proposed rule, FDA observed that as with the original list, the primary focus of the July 2014 proposed rule was on drug products that have been withdrawn or removed from the market because they have been found to be unsafe. FDA further stated that FDA may propose at a later date to add to the list other drug products that have been withdrawn or removed from the market because they have been found to be not effective, or to update the list as information becomes available to the Agency regarding products that have been removed from the market because they have been found to be unsafe.

(Comment 15) One comment suggested that when updating the list, a process be considered by which FDA will consider exemptions (for example, when a drug or drug component may be compounded for a specific formulation, strength, or route of administration).

(Response) FDA agrees that sometimes it may be appropriate to except a specific formulation (including strength), dosage form, or route of administration of a drug on the list. Indeed, as discussed further in FDA’s response to the following comment, FDA has already engaged in this practice when it deems such exceptions appropriate. Going forward, when FDA is considering an addition or modification to the list, FDA will continue to consider the appropriateness of such exceptions on a case-by-case basis.

(Comment 16) One comment advised that ingredients should be banned completely and absolutely with great caution.

(Response) With respect to whether drugs on the withdrawn or removed list may be used in compounding, as FDA indicated in the preamble to the July 2014 proposed rule, 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 because it has been found to be unsafe or not effective. 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.

In addition, FDA notes that just because a drug is on the withdrawn or removed list does not mean it is banned completely and absolutely from compounding. In certain circumstances, if warranted, drugs that have been withdrawn or removed from the market could be made available for use under FDA regulations on expanded access at 21 CFR part 312, subpart I. If conditions in the regulations are met, expanded access programs allow the use of a drug in a clinical setting to treat patients with a serious or immediately life-threatening disease or a condition that has no comparable or satisfactory alternative therapies to diagnose, monitor, or treat the patient's disease or condition (see Guidance for Industry, Expanded Access to Investigational Drugs for Treatment Use--Questions and Answers (June 2016), available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf>).

FDA will apply the statutory standard for placing drugs on the withdrawn or removed list, and intends to follow the process described in section II.C.3 to consult with the Advisory Committee and provide the public with notice and opportunity for comment.

IV. Legal Authority

Sections 503A and 503B of the FD&C Act provide the principal legal authority for this final rule. As described in section I 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).

Therefore, sections 503A and 503B of the FD&C Act and our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)) together serve as our principal legal authority for this final 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

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.

VI. Economic Analysis of Impacts

FDA has examined the impacts of the 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 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 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 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 issuing “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 rule to result in any 1-year expenditure that would meet or exceed this amount.

This rule amends § 216.24 concerning human drug compounding. Specifically, the rule adds to and modifies 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). The rule adds 24 entries to the list and modifies the description of one drug entry on the list. The Agency is not aware of any routine compounding of these drug products 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.

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 certifies that this rule will not have a significant economic impact on a substantial number of small entities.

VII. Paperwork Reduction Act of 1995

The submission of comments on this rule were 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 Office of Management and Budget 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 rule contains no other collection of information.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that this final 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, the Agency concludes 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

In addition to the references placed on display in the Division of Dockets Management for the proposed rule under Docket No. FDA-1999-N-0194 (formerly 99N-4490), the following reference is on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket No. FDA-1999-N-0194 (formerly 99N-4490) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <http://www.regulations.gov>. (FDA has verified the Web site address in this reference section as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.)

1. Briefing Information for the February 23-24, 2015, Meeting of the Pharmacy Compounding Advisory Committee (available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm433803.htm>).

For the convenience of the reader, the regulatory text of § 216.24 provided with this final rule includes the drug products described in this final rule and the drug products codified by the 1999 final rule.

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, 21 CFR part 216 is amended as follows:

PART 216--HUMAN DRUG COMPOUNDING

1. The authority citation for 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 have been 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 etretinate.

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 dermatologic application).

Nomifensine maleate: All drug products containing nomifensine maleate.

Novobiocin sodium: All drug products containing novobiocin sodium.

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 hydrochloride.

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.

Dated: October 3, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016-24333 Filed: 10/6/2016 8:45 am; Publication Date: 10/7/2016]