4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-2023-N-0061]

RIN 0910-AI31

Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is proposing to establish criteria for the lists of drug products or categories of drug products that present demonstrable difficulties for compounding (Demonstrable Difficulties for Compounding Lists or DDC Lists) under certain sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Additionally, the Agency is proposing to identify the first three categories of drug products on both DDC Lists. Drug products or categories of drug products that appear on the DDC Lists cannot qualify for certain statutory exemptions. Additional drug products or categories of drug products are under consideration and may be addressed in future rulemaking.

DATES: Either electronic or written comments on the proposed rule must be submitted by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system

will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://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 https://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): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, 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-2023-N-0061 for "Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- 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 https://www.regulations.gov. Submit both copies to the Dockets Management Staff. 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: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://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 Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Ian Reynolds, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 240-402-7079.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to implement parts of the FD&C Act to establish criteria the Agency will use in evaluating drug products or categories of drug products considered for inclusion on

the lists of drug products or categories of drug products that present demonstrable difficulties for compounding (DDC Lists) under each section. FDA also proposes to identify three categories of drug products on both DDC Lists. Drug products or categories of drug products that appear on the DDC Lists cannot qualify for the statutory exemptions under the applicable section.

B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to amend its regulations to add two lists identifying drug products or categories of drug products that present demonstrable difficulties for compounding under the FD&C Act. FDA is also proposing to establish criteria for evaluating drug products or categories of products for inclusion on one or both of these lists.

For evaluating drug products or categories of drug products for inclusion on the DDC Lists, FDA is proposing to establish the following criteria: the formulation complexity, drug delivery mechanism complexity, dosage form complexity, complexity of achieving or assessing bioavailability, compounding process complexity, and complexity of physicochemical or analytical testing of the drug product or category of drug products. FDA proposes to consider these criteria and the risks and benefits to patients of the compounded drug product or category of drug products in determining whether to add the drug product or category of drug products to one or both lists.

Based on the results of FDA's evaluation of certain categories of drug products that the public has nominated for consideration as presenting demonstrable difficulties for compounding, as well as in consultation with the Pharmacy Compounding Advisory Committee (PCAC), FDA is proposing to include the following three categories of drug products on the DDC Lists: (1) oral solid modified-release drug products that employ coated systems (MRCs), (2) liposome drug products (LDPs), and (3) drug products produced using hot melt extrusion (HMEs).

C. Legal Authority

The compounding provisions of the FD&C Act, in conjunction with our general rulemaking authority in the FD&C Act, serve as our principal legal authority for this proposed rule.

D. Costs and Benefits

FDA evaluated three categories of drug products for this proposed rule (MRCs, LDPs, and HMEs) and is currently proposing to place all three of these categories of drug products on the DDC Lists. We expect that this proposed rule may create benefits for compounders by reducing regulatory uncertainty. At this time, we are not aware of any compounding and marketing of the three proposed categories of drug products for human use. Therefore, we expect that the proposed rule would only create administrative costs to read and understand the rule. We estimate that, over 10 years, the annualized costs of the proposed rule would equal $0.42 million at a 7 percent discount rate and $0.36 million at a 3 percent discount rate.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
ANDA	Abbreviated New Drug Applications
API	Active Pharmaceutical Ingredient
CGMP	Current Good Manufacturing Practice
CFR	Code of Federal Regulations
DDC	Demonstrable Difficulties for Compounding
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GI	Gastrointestinal
HME	Hot Melt Extrusion
LDP	Liposome Drug Product
MRC	Oral Solid Modified-Release Drug Product That Employs Coated Systems
PCAC	Pharmacy Compounding Advisory Committee
NDA	New Drug Application
PEG	Polyethylene Glycol

III. Background

A. FDA's Current Regulatory Framework and Need for DDC Lists

Under sections 503A and 503B of the FD&C Act (21 U.S.C. 353a and 353b), certain conditions must be satisfied for compounded drug products to qualify for the statutory exemptions set forth in each section. Section 503A of the FD&C Act describes the conditions that must be satisfied for a human drug product compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or by a licensed physician, to qualify for exemptions from section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements), section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)) of the FD&C Act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355). Section 503B of the FD&C Act describes the conditions that must be satisfied for a drug product compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), section 505 (concerning the approval of drugs under NDAs or ANDAs), and section 582 (concerning drug supply chain security requirements) of the FD&C Act (21 U.S.C. 360eee-1). Both sections contain conditions that concern whether the compounded drug product is one identified by the Secretary of Health and Human Services (the Secretary) as presenting demonstrable difficulties for compounding (see generally sections 503A(b)(3)(A) and 503B(a)(6) of the FD&C Act).[1]

A condition for the statutory exemptions in section 503A of the FD&C Act is that a drug product is not identified by the Secretary by regulation as a drug product that presents

[1] The functions of the Secretary described herein have been delegated to FDA.

demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (see section 503A(b)(3)(A) of the FD&C Act). Section 503A(c)(1) of the FD&C Act provides that before issuing regulations to implement paragraph (b)(3)(A), 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.

Similarly, a condition for the statutory exemptions in section 503B of the FD&C Act is that a drug compounded by an outsourcing facility is not identified (directly or as part of a category of drugs) on a list published by the Secretary of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients, or the drug is compounded in accordance with all applicable conditions identified on the list as conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (see section 503B(a)(6) of the FD&C Act). Section 503B(c) of the FD&C Act provides that the Secretary will implement the list described in paragraph (a)(6) through regulations and that before issuing regulations to implement paragraph (a)(6), the Secretary will convene and consult an advisory committee on compounding.

This proposed rule, if finalized, would implement sections 503A(b)(3)(A) and 503B(a)(6) of the FD&C Act.

B. History of This Rulemaking and Request for Nominations

In July 2000, the PCAC discussed and provided FDA with advice about the Agency's efforts to develop a list of drugs that present demonstrable difficulties for compounding. FDA

published a notice of that meeting in the *Federal Register* of June 29, 2000 (65 FR 40104). However, before a list could be developed, the constitutionality of provisions of section 503A of the FD&C Act concerning restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs were challenged in court. These provisions were held unconstitutional by the U.S. Supreme Court in 2002 (see *Thompson* v. *Western States Med. Ctr*., 535 U.S. 357 (2002)). After the court decision, FDA suspended its efforts to develop the difficult-to-compound list.

The Drug Quality and Security Act, enacted in 2013, removed from section 503A of the FD&C Act the provisions that had been held unconstitutional and added new section 503B to the FD&C Act. In the *Federal Register* of December 4, 2013 (78 FR 72840), FDA established a docket and invited interested persons to nominate drug products or categories of drug products to be identified as ones that present demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act. Approximately 70 unique drug products or categories of drug products were nominated. In the *Federal Register* of July 28, 2017 (82 FR 35214), FDA established another public docket so that interested parties could nominate drug products or categories of drug products that were not previously nominated, resubmit previous nominations with additional supporting information, or submit comments. Since establishing the new public docket, several new unique drug products or categories of drug products have been nominated and additional information regarding previous nominations and general comments has been submitted.

On June 18, 2015, March 9, 2016, November 3, 2016, May 9, 2017, and November 21, 2017, FDA consulted with the PCAC (see sections 503A(c)(1) and 503B(c)(2) of the FD&C Act) about criteria for evaluating whether drug products and categories of drug products present

demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act and the three categories of drug products that are addressed in this proposed rule (Refs. 1 to 10). The criteria were presented and discussed at the June 2015 PCAC meeting. The criteria were subsequently revised to clarify the description of each factor and were then presented and discussed at the March 2016 PCAC meeting (Ref. 7). In general, the PCAC agreed with the proposed criteria and the approach taken by the Agency in evaluating the proposed categories of products that present demonstrable difficulties for compounding. In addition, the PCAC agreed with FDA's recommendation to identify each of the categories of drug products described in this proposed rule as ones that present demonstrable difficulties for compounding. Since the PCAC meetings, FDA is not aware of information regarding the difficulties presented by compounding the categories of drug products addressed in this proposed rule that would change the analysis the Agency last presented to the PCAC. The Agency has considered the PCAC's recommendations in developing this proposed rule, and the Agency intends to continue to consult with the PCAC in evaluating drug products or categories of drug products for the DDC Lists.

IV. Legal Authority

Section 503A of the FD&C Act describes the conditions that must be satisfied for a human drug product compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or by a licensed physician, to qualify for exemptions from section 501(a)(2)(B) (concerning CGMP requirements), section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and section 505 (concerning the approval of drugs under NDAs or ANDAs) of the FD&C Act. Section 503B of the FD&C Act describes the conditions that must be met for a drug product compounded by or under the direct supervision of a licensed

pharmacist in a facility registered as an outsourcing facility to qualify for exemptions from section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), section 505 (concerning the approval of drugs under NDAs or ANDAs), and section 582 (concerning drug supply chain security requirements) of the FD&C Act. Sections 503A and 503B of the FD&C Act contain conditions concerning drug products that have been identified as presenting demonstrable difficulties for compounding and address how lists of drug products or categories of drug products that present demonstrable difficulties for compounding must be established under each section. Specifically, section 503A(c)(1) of the FD&C Act requires that FDA issue regulations to implement paragraph (b)(3)(A), which refers to the DDC List under section 503A, and section 503B(c)(1) of the FD&C Act states that FDA must implement the list described in paragraph (a)(6) that refers to the DDC List under section 503B, through regulations. 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.

V. Description of the Proposed Rule

FDA is proposing to add § 216.25 to title 21 of the Code of Federal Regulations (CFR) (21 CFR 216.25) to establish criteria to evaluate drug products and categories of drug products for inclusion on one or both of the DDC Lists in § 216.25(a), and to codify the initial DDC List for section 503A and the initial DDC List for section 503B of the FD&C Act in § 216.25(b) and (c), respectively. FDA is proposing to create two separate DDC Lists, a 503A DDC List and a 503B DDC List, that would implement the DDC statutory provisions and reflect the differences in compounding standards under each section. Having two separate lists will make it easier to address situations that could arise where a drug product or category of drug products would

present demonstrable difficulties for compounding under section 503A but may not present demonstrable difficulties for compounding under section 503B of the FD&C Act. For example, in certain situations, FDA may determine in its consideration of the DDC criteria that a drug product or category of drug products presents demonstrable difficulties for compounding unless it is made in accordance with the manufacturing controls over safety, identity, strength, quality, and purity required under CGMP. In such cases, because drug products compounded in accordance with the conditions of section 503A, but not section 503B, are exempt from CGMP requirements, FDA may decide to include a drug product or category of drug products on the DDC List for section 503A but not the DDC List for section 503B of the FD&C Act.[2] The initial lists, if finalized as proposed, would include three categories of drug products that present demonstrable difficulties for compounding under both sections 503A and 503B of the FD&C Act and, therefore, would not qualify for the exemptions in either section. The proposed criteria and categories of drug products are described below.

A. Criteria for Evaluating Drug Products or Categories of Drug Products for the DDC Lists (Proposed § 216.25(a))

FDA has identified six criteria it proposes to consider in determining whether drug products or categories of drug products present demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act:

1. Complex formulation,
2. Complex drug delivery mechanism,
3. Complex dosage form,
4. Bioavailability achievement complexity,

[2] See section 501(a)(2)(B) of the FD&C Act.

5. Compounding process complexity, and
6. Physicochemical or analytical testing complexity.

In evaluating drug products or categories of drug products for the DDC Lists, the Agency proposes to consider these criteria individually and collectively, and to take into account the risks and benefits to patients of the compounded drug product or categories of drug products. The criteria are not mutually exclusive. A drug product or category of drug products may meet one or more of these criteria that indicate it presents demonstrable difficulties for compounding. FDA proposes to apply the same criteria when considering drug products or categories of drug products for inclusion on either the DDC List for section 503A or the DDC List for section 503B of the FD&C Act, although the application of the criteria may lead to different conclusions for each list. The three categories of drug products identified in this proposed rule are proposed to be included on both the initial 503A and 503B DDC Lists, but this may not always be the case given the differences in the statutory standards that apply to compounding under sections 503A and 503B of the FD&C Act. We also note that these criteria for determining whether a drug product presents demonstrable difficulties for compounding are not intended to provide FDA's interpretation of which drugs are considered complex products in other circumstances, including for purposes of determining whether a proposed generic drug is a complex product as defined in the Generic Drug User Fee Amendments Commitment Letters and which, as appropriate, may use scientifically valid in vivo or in vitro test methods to demonstrate bioequivalence.

In its evaluations for the DDC Lists, FDA intends to take into account the risks and benefits to patients of the compounded drug product or category of drug products under consideration. In doing so, FDA may use available information such as reports submitted to FDA about adverse drug experiences and FDA's scientific and medical expertise to inform its

analysis, as well as information about FDA-approved drug products. FDA may consider actual or potential risks and benefits to patients posed by a drug product or category of drug products. In particular, FDA intends to consider actual or potential risks to patients in connection with the six criteria described in this proposed rule.

The Agency does not intend to consider cost and convenience as factors that would be relevant to the risk-benefit analysis for the DDC Lists.

There may be situations in which FDA's findings, with respect to whether a drug product or category of drug products presents demonstrable difficulties for compounding, indicate that the difficulty in compounding is limited to a subset of such drug products or categories of drug products. In those cases, the Agency may tailor the entry on the DDC Lists to reflect its findings and conditions that the Agency determines are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties. For example, if the Agency were to find a drug product or category of drug products presents demonstrable difficulties for compounding at a specific strength for topical use, it could choose to limit the entry of that drug product or category of drug products on the DDC Lists to a specified strength for topical use.

B. Description of Criteria for the Evaluation of Drug Products or Categories of Drug Products for Inclusion on the DDC Lists[3]

The following is a discussion of the criteria the Agency proposes to codify, in proposed § 216.25(a), for including a drug product or category of drug products on the section 503A or section 503B DDC List. A drug product or category of drug products that meets one or more of

[3] These proposed descriptions of terms apply only to those terms when used in proposed 21 CFR part 216 for purposes of determining whether drug products or categories of drug products present demonstrable difficulties for compounding.

the criteria may present demonstrable difficulties for compounding under section 503A or 503B of the FD&C Act.

1. Complex Formulation

Complex formulation refers to a formulation in which the ingredients (active pharmaceutical ingredients (APIs) or excipients) possess (or are required to possess) certain physicochemical characteristics or properties that are necessary to achieve or maintain the proper performance of the drug product. Generally, these attributes may include the solid state (crystalline, amorphous, or a combination thereof), chirality, molecular weight (dispersity/distributions), or particle size distribution of ingredients. For example, for some APIs, the solid state, chirality, or particle size might be critical to the safety and efficacy of certain drug products, whereas for some excipients, the molecular weight, intrinsic viscosity, or relative proportion of the release controlling polymer to an API might be critical to the safety and efficacy of certain drug products. The compatibility or stability (physical and chemical) of the API(s) or excipients in the final dosage form may also contribute to determining whether the compounded drug product has a complex formulation.

2. Complex Drug Delivery Mechanism

Complex drug delivery mechanism refers to the way in which the drug is released from the dosage form or targeted for delivery in the body to achieve the desired therapeutic effect. Complex drug delivery mechanisms include, for example, formulations designed to release the drug at specific onset, rate, and extent through specific region(s) within the gastrointestinal (GI) tract; formulations designed to achieve permeation through the skin at a specific rate; and formulations containing coated beads or liposomes.

3. Complex Dosage Form

Complex dosage form refers to physical dosage units with unique characteristics that are difficult to consistently achieve or maintain. Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system. Drug products may have very simple formulations, such as a single API, and a simple delivery mechanism, such as an injection, but the drug product may be complex because the physical properties of the dosage form are difficult to achieve or maintain. Examples of complex dosage forms include coated beads, osmotic-controlled release systems, and liposomes.

4. Bioavailability Achievement Complexity

Bioavailability refers to the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Drug products may present demonstrable difficulties for compounding if bioavailability is challenging to achieve because of the characteristics of the API or compounded formulation such as low permeability or low solubility. Examples of drug products for which consistent bioavailability is difficult to achieve include Biopharmaceutics Classification System Class 2 drugs (e.g., naproxen, lansoprazole, rifampin, and carbamazepine) and Class 4 drugs (e.g., azathioprine, clarithromycin, oxcarbazepine, and modafinil).

5. Compounding Process Complexity

Compounding process complexity refers to whether compounding the drug requires multiple, complicated, or interrelated steps or specialized facilities or equipment to achieve the appropriate drug product. An example of a complex compounding process includes multistep

and highly interrelated processes such as wet granulation, extrusion, spheronization, fluid bed drying, coating, compression, or curing before processing into the final dosage form.

6. Physicochemical or Analytical Testing Complexity

Physicochemical or analytical testing complexity refers to the challenges presented with confirming the drug product will perform as expected with regard to certain characteristics. Drug products may demonstrate testing complexity when specialized analytical instruments or special training is necessary to show that the drug product will perform as expected. Some examples of complex testing include cell-based assays and use of nuclear magnetic resonance, mass spectrometry, or X-ray powder diffraction to identify constituents of complex formulations.

C. *Evaluation of Drug Products or Categories of Drug Products Proposed for Inclusion on the DDC Lists*

FDA is proposing three categories of drug products that were evaluated by FDA and presented to the PCAC to be included on the initial DDC List for section 503A and the initial DDC List for section 503B of the FD&C Act. The following three categories of drug products are being proposed to be included in § 216.25(b) and (c): MRCs, LDPs, and HMEs. FDA may propose additional drug products or categories of drug products for inclusion on the DDC Lists as it continues its evaluations.

The information that FDA assessed under each of the proposed evaluation criteria for each of the categories of drug products included in this proposed rule was obtained from publicly available sources, including peer-reviewed medical literature. Some of this information was referenced in the nominations, and the remainder was gathered through independent searches of medical and pharmaceutical databases. The nature, quantity, and quality of the information FDA assessed varied considerably from drug product category to drug product category. For some

categories of drug products, reports in the literature were more plentiful and sometimes comprised hundreds or thousands of articles. In those cases, generally, the Agency limited its review to a sample of the best literature sources available (e.g., review articles in widely known, peer-reviewed journals; meta-analyses; reports of randomized controlled trials). The Agency intends to use a similar process when evaluating other drug products or categories of drug products for inclusion on the DDC Lists in future rulemakings.

Three categories of drug products that were nominated, and that FDA evaluated in consultation with the PCAC, are not included in this proposed rule: (1) drug products that employ transdermal or topical delivery systems; (2) metered-dose inhalers; and (3) dry powder inhalers. FDA may address these categories in future rulemaking.

After evaluating the comments on this proposed rule, FDA intends to issue the evaluation criteria and DDC Lists as a final rule, which will be codified at § 216.25. The final rule may include some or all of the categories of products proposed here for inclusion on the DDC Lists, depending on the comments received.

Individuals and organizations may nominate drug products or categories of drug products for the DDC Lists or comment on nominated categories of products. For access to the docket to nominate products or comment on nominated products, go to https://www.regulations.gov and insert Docket No. FDA-2017-N-2562 into the "Search" box and follow the prompts.

FDA intends to consider reevaluating products or categories of products for the DDC Lists if there is a change in circumstances that alters the Agency's analysis. FDA may consider reevaluating products or categories of products for the DDC Lists at any time on its own initiative. Requests for updates to the DDC Lists may be submitted to FDA at any time. With respect to a drug product or category of drug products that has not been addressed in rulemaking,

individuals and organizations may submit nominations of new substances or comments on nominated substances to Docket No. FDA-2017-N-2562. With respect to a drug product or category of drug products addressed in a final rule, individuals and organizations may petition FDA to amend the DDC Lists (see 21 CFR 10.30). FDA intends to review the section 503B DDC List at least once every 4 years.[4]

D. Drug Products or Categories of Drug Products Proposed for Inclusion on the DDC Lists

1. Oral Solid Modified-Release Drug Products That Employ Coated Systems (MRCs)

For purposes of this proposed rule, the Agency defines MRCs as oral solid drug products that consist of, or are intended to consist of, a drug-containing core enclosed within a polymeric coating to release an API at specified rates, patterns, or onsets through the GI tract to produce systemic, enteric, or local action.[5] There are two types of MRCs that affect the rate of API release: diffusion and osmotic systems. The diffusion systems consist of a hydrophilic and/or water-insoluble polymeric coating enclosing a core tablet or multiple cores of active ingredient and excipient. The osmotic systems consist of a semipermeable polymeric membrane coating enclosing a compressed core that is composed of active ingredient, osmotic agent, and other excipients, and one or more mechanical or laser drilled orifices for drug release.

MRCs were evaluated using the six criteria that FDA proposes to use to determine whether drug products or categories of drug products present demonstrable difficulties for

[4] See section 503B(c)(4) of the FD&C Act.

[5] Modified release solid oral dosage forms include both delayed and extended release drug products. See FDA's guidance for industry on "(SUPAC-MR) Scale-Up and Postapproval Changes for Modified Release Solid Oral Dosage Forms." For this proposed rulemaking, the Agency does not consider matrix-type tablets and capsules to be MRCs, provided that drug release and delivery of an active ingredient from such products is controlled solely by disintegration or dissolution through the polymeric matrix. Moreover, with regard to certain fillable capsules, the Agency does not consider enteric coated capsules of immediate release formulations to be MRCs because of the fact that such enteric coating is designed to control disintegration onset of the coated capsule and not the release rate of active ingredient at a targeted location in the GI tract. In addition, as noted above, this proposed rule is not intended to provide FDA's interpretation of which drugs are considered complex products in other circumstances, including for purposes of determining whether a proposed generic drug is a complex product.

compounding under sections 503A and 503B of the FD&C Act explained in section V.A. above. MRC formulations are complex because they are required to release a specified amount of active ingredient over a specified period of time for a given therapy. Developed properly, MRCs must be physically stable and exhibit consistent functional properties of active ingredient release rate, pattern, and location within the GI tract. If MRCs are not produced correctly, sub- or supra-therapeutic release, GI mucosa irritation, and variability in performance within and across batches may occur. The mechanism by which active ingredient is released from the MRCs throughout the GI tract is complex because, to perform properly, it requires the design and formation of a system that delivers a specific amount of active ingredient per unit time and, in some cases, in specific regions of the GI tract. Depending on the type of MRC systems, the drug (API) delivery mechanism for an MRC can either be diffusion controlled through polymeric coating or osmotic controlled through a polymeric semipermeable membrane, and, in either case, the delivery mechanism depends on several factors, including the intended time/location of API release in the GI tract and the types of materials used for coating. In addition, because the dose-release profile is impacted by several factors, precise control of the attributes of raw materials, the manufacturing process, and the final product is necessary for ensuring the specifications of the drug product are met.

MRCs' complex formulations and complex drug delivery mechanisms also affect the complexity of their dosage forms for compounding. They require well-designed controls of component attributes and process parameters for predictable release of the active ingredient. In addition, MRCs are designed to maintain their integrity in vivo to minimize local irritation to the GI tract and to ensure that dose dumping does not occur. Various components play a critical role in the dosage form performance. Extensive product development and precise control over raw

material selection and the production process are essential for evaluating the active ingredient release mechanism and profile, and overall MRC performance characteristics. Characterizing and controlling bioavailability of MRCs are also critical. Subtle changes to any of the product's components or manufacturing processes could significantly impact its bioavailability and performance characteristics. In general, for MRCs, in vitro assessments, such as in vitro dissolution testing, alone are insufficient to accurately predict bioavailability and overall clinical effect; rather, in vivo assessments are needed.

Because specialized equipment under appropriate controls is critical for the automated processing and precise control over the manufacturing process, the compounding processes for MRCs are also complex. These processes include technically complex mixing, fluidization coating and drying, compression, filling, and orifice drilling. Poor technique or control during any of these processes will likely result in variable performance of the drug product. MRCs additionally require complex physicochemical and analytical testing of raw material, product quality/performance, and stability because evaluating the physical and chemical properties of the raw materials and finished dosage form, as well as the product-critical performance parameters, requires specialized analytical devices and procedures for accurate measurement. Furthermore, to assess and ensure consistent purity of the drug product, chemical impurities must be quantitated through various sensitive analytical techniques developed specifically for these impurities.

With respect to the risks and benefits to patients, compounded MRCs present a significant safety risk given the complexities described above. MRC design and the relationship between excipient and active ingredient directly impact release rate and pattern and performance. Release rate and pattern and performance in turn affect drug product effectiveness and safety.

Substituting or removing excipients, such as release retarding polymers, plasticizers, solubilizers, and permeation enhancers, would likely change the release characteristics of the product and, in turn, may adversely impact product performance. Also, precise and consistent quality controls of raw materials, the manufacturing process, and final product are essential for predictable and reproducible active ingredient release, performance, and safety profiles. MRCs are designed to release a specified amount of active ingredient to a specific region of the GI tract over a specified period of time, for a given therapy. MRCs are designed to maintain their integrity in vivo to minimize local irritation to the GI tract and to ensure that dose dumping does not occur. The complexities associated with the manufacture of MRCs create a heightened risk that compounded products would not deliver the active ingredient as intended, which would present a safety concern to patients. The Agency is not aware of compounded MRCs for human use. FDA is also not aware of a rationale for why a patient would have a medical need for compounded MRCs, as opposed to an FDA-approved product, nor is it aware of any actual or potential benefit that would outweigh the risks to patient safety that would be presented by compounded MRCs.

Based on an analysis of the evaluation criteria, taking into account the risks and benefits to patients, FDA proposes to include MRCs on the lists of drug products or categories of drug products that present demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act. On May 9, 2017, FDA proposed to the PCAC that MRCs be identified as presenting demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act (Ref. 9). The PCAC voted to agree with FDA's proposal (Ref. 4).

2. Liposome Drug Products (LDPs)

For this proposed rule, the Agency defines an LDP as a drug product in which the API is generally contained in or intended to be contained in liposomes.[6] The Agency has broadly evaluated LDPs, including those containing liposomes that would not fall within what is commonly considered to be the nanoscale-size range, for inclusion on the DDC Lists.[7]

Liposomes are vesicles composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment. LDPs were evaluated using the six criteria explained in section V.A. above. Because of: (1) the attributes of lipids, including chemistry and structure; (2) the attributes of inactive ingredients (e.g., cholesterol and polyethylene glycol (PEG) or PEG derivatives), including grade, ratio, and concentration range; and (3) the stability of the liposome, which can be affected by a number of formulation-related factors (e.g., the size and size distribution of the lipid vesicles, morphology, surface coating, pH, buffer, or counter ions), LDPs have complex formulations. LDPs also have a complex drug delivery mechanism. The mechanism by which an API is released from an LDP is complex because it involves precisely designing and formulating a system that delivers a specific amount of API per unit time and, in most cases, in a specific region (e.g., tumor tissues, intracellular compartments). In addition, because the in vivo biodistribution and release characteristics are

[6] With respect to FDA-approved liposome drug products, see the guidance for industry "Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation." See also FDA's final guidance for industry "Drug Products, Including Biological Products, that Contain Nanomaterials."

[7] Within the context of this rule, preparations such as liposomal creams or gels are not considered LDPs, provided that, the principal use of amphipathic molecules such as phospholipids in the form of liposome alone or in combination with other inactive components (i.e., other than the drug or active pharmaceutical ingredient) in such preparations is intended for other than cure, mitigation, treatment or prevention of any underlying human disease; or intended not to affect, the structure or any function of a human body.

affected by several factors, precise control of raw materials, the manufacturing process, and the final product is critical to achieving a safe and effective drug product.

LDPs are complex dosage forms because they have complex formulations and mechanisms by which the API is delivered in vivo. Characteristics of the physical dosage units of liposome suspensions or lyophilized powders for suspension are difficult to consistently achieve or maintain, including: (1) well-defined and controlled particle size and particle size distribution; (2) the status of the API (e.g., whether it is contained within the liposome); and (3) the surface chemistry of the liposomes. These characteristics have a significant impact on the safety and effectiveness of LDPs. In addition, various formulation components play a critical role in dosage form performance and product stability. Such components can vary for different drug products that have different routes of administration. For example, the components of an injectable drug product may include different inactive ingredients than potential topical or inhalation drug products. Extensive product development and precise control over raw materials and optimization of the process parameters are essential to produce safe, effective, and high-quality LDPs.

Characterizing and controlling the bioavailability of LDPs is also a contributing factor to the complexity of LDPs. Subtle changes to the formulation composition, lipid raw material purity, or manufacturing processes could significantly impact the biodistribution and release characteristics of an API from liposomes, which in turn influence the availability of an API in systemic circulation at tissue or subcellular targets. Different API forms may have different absorption, distribution, metabolism, and elimination, and the difficulty in determining the amount of various forms of API makes it complex to characterize and control bioavailability. Depending on the types of lipids used in formulating liposomes, interactions between liposome

surface and blood proteins may affect the drug release and pharmacological properties of a liposome drug product in vivo. Such interactions can have safety implications because of "dose dumping." For parenteral LDPs, in vitro assessments (e.g., in vitro drug release testing) are often used in conjunction with in vivo testing to predict the availability of drug at its intended target. LDPs involve complex compounding processes. The production of LDPs is complex because of unique equipment and unit operations involved and the critical need for in-process controls to ensure consistent product quality. Poor control over these unit operations may lead to variability in product quality, which may potentially lead to a negative impact on product efficacy and safety. In addition, LDPs involve comprehensive and complex physicochemical testing to ensure quality of the raw material, consistency of the product quality, and predictable in vivo performance. Furthermore, suitable analytical methods need to be employed to properly characterize LDPs, which can often be difficult given the complexity of liposome formulations. Use of inappropriate methods could produce false results, thereby calling data reliability and, hence, product quality into question.

With respect to the risks and benefits to patients, compounded LDPs present a significant safety risk for compounding given the complexities described above. Many of the APIs used in LDPs are cytotoxic. In addition, improper selection of inactive ingredients or improper mixing of liposomes with APIs present safety risks that the APIs will not be encapsulated properly or be released prematurely, causing the drug product to be potentially ineffective or hazardous. LDPs are used to alter the biodistribution of an API and can improve drug dissolution, stability, deliverability, biodistribution, and bioavailability. However, the Agency is not aware of compounded LDPs for human use or of any actual or potential benefit that would outweigh the risks to patient safety that would be presented by compounded LDPs.

Based on an analysis of the evaluation criteria, taking into account the risks and benefits to patients, FDA proposes to include LDPs on the lists of drug products or categories of drug products that present demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act. On November 21, 2017, FDA proposed to the PCAC that LDPs be identified as presenting demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act (Ref. 10). The PCAC voted to agree with FDA's proposal (Ref. 5).

In addition, FDA is considering whether the difficulty in compounding for this category of drug products is limited, including, for example, whether an outsourcing facility's compliance with CGMP requirements would sufficiently mitigate any difficulties associated with compounding certain LDPs. Accordingly, FDA is soliciting comments about whether the entry for the 503B DDC List should include any limitations, such as, for example, to address certain LDPs that an outsourcing facility compounds from FDA-approved liposome drug products.

3. Drug Products Produced Using HMEs

For this proposed rule, the Agency defines HME as a continuous process operation that achieves or is intended to achieve the molecular mixing of APIs and inactive ingredients (e.g., polymers) at temperatures above their glass transition temperatures and/or melting temperatures within an extruder. The objective of an HME process is to enhance the solubility of poorly water-soluble drugs by converting the formulation components into an amorphous phase (not crystalline) product with uniform content.

HME is a process by which heat and shear are applied to melt a mixture of API and inactive ingredients within an extruder that is then pushed through an orifice with the objective of converting the ingredients into an amorphous phase material with uniform content, referred to as the "extrudate." HMEs were evaluated using the six criteria that FDA proposes to use to

determine whether drug products or categories of drug products present difficulties for compounding under sections 503A and 503B of the FD&C Act explained in section V.A. above. HMEs have complex formulations because the extrudate must remain a stable and amorphous solid solution of API within a matrix throughout the shelf life of the final drug product in order to achieve proper product performance. This formulation is necessary to ensure that the API has higher solubility, resulting in the desired bioavailability of the drug product. To avoid a negative impact on the safety and efficacy of the product, the extrudate should have a uniform distribution of API in the matrix and a controlled level of impurities. It is critical for these formulations to be thermally stable during the extrusion process and physically stable afterwards. Raw material selection and control and ingredient ratios influence several attributes of the extrudate and, in turn, the final product. If HMEs are not formulated correctly, taking into account the principles discussed above, it could lead to significant variability in performance within and across batches, and may impact bioavailability. The drug delivery mechanism, or the mechanism by which API is released from the HMEs, can also be complex because it is dependent on a product design (e.g., immediate or sustained) that implicates API dissolution and solubility in an amorphous state within the extrudate to ensure appropriate drug delivery. Product design involves achieving and maintaining an amorphous state of the API in the extrudate, extrudate incorporation into the final dosage form, and selection of a carrier/API matrix that will release the drug at a predetermined rate. In addition, in order to achieve a proper dose-release profile, precise control of raw materials, the extrusion process, and the final product is critical.

Some dosage forms of HMEs are complex because of the structural arrangement or distribution of the extrudate within the dosage form, the function or role of the extrudate in the dosage form's drug delivery mechanism, or the interaction of extrudate with other ingredients

within the dosage form. HMEs require well-designed controls of ingredient attributes and process parameters for predictable API release from a dosage form. These controls may vary from dosage form to dosage form, depending on what downstream incorporation steps the extrudate will undergo. Extensive product development and precise control over raw material selection and the production process are essential to evaluating the API release mechanism and profile, and other product performance characteristics. Characterizing and controlling the bioavailability of HMEs is also a contributing factor to the complexity of HMEs. Subtle changes to any components or production processes could significantly impact a drug product's solubility and intrinsic dissolution, which may in turn influence local and systemic bioavailability. In general, for compounded HMEs, in vitro assessments, such as dissolution testing, alone are insufficient to accurately predict bioavailability and overall clinical effect. Rather, in vivo assessments are needed.

The manufacturing process for HMEs typically requires specialized equipment under sophisticated controls, critical for ensuring product quality, and thereby making compounding of HMEs complex. To achieve and maintain critical product quality attributes, the extruder must be properly calibrated based on the characteristics of the ingredients fed into the extruder and desired characteristics of the extrudate. Poor technique or control at any step will likely result in a product that does not achieve or maintain critical quality attributes. Physicochemical and analytical testing before, during, and after HME to evaluate thermal properties, recrystallization, dissolution, and uniformity requires specialized analytical devices and procedures for accurate measurement. A rigorous characterization of the ingredients processed by HME is important to avoid a negative impact on the safety and effectiveness of HMEs. Physicochemical characterization of the extrudate formed during HME is complex and necessary to properly

assess its properties and performance in the finished drug product. In addition, the measurement system to properly characterize the extrudate is complex because it incorporates multiple complementary methods to interpret similar properties, such as a limit of detection for crystallinity and thermal history of amorphous phase. Ensuring the stability of an HME is a major challenge during production, storage, and administration.

With respect to the risks and benefits to patients, compounded HMEs present a significant safety risk given the complexities described above, which include HME process-design complexities and the relationship between inactive ingredient and API of HMEs, which directly impacts bioavailability, release, and performance. Bioavailability, release, and performance in turn affect drug product effectiveness and safety. Substituting or removing inactive ingredients, such as polymers, plasticizers, or surfactants, would likely change the solubility and release characteristics of the product and, in turn, may adversely impact product performance. Also, consistent quality controls for raw materials, the extrusion process, and final product are essential for predictable and reproducible API release, which directly affects the safety and effectiveness of the product. HMEs can have enhanced bioavailability, controlled delivery rates, and stabilized formulations. Such products can be produced with taste-masking properties suitable for children or are in dosage forms that are suitable for patients with swallowing difficulties. However, the Agency is not aware of compounded HMEs for human use or a rationale for why patients would have a medical need for compounded HMEs, as opposed to an FDA-approved product; or of any actual or potential benefit that would outweigh the risks to patient safety that would be presented by compounded HMEs.

Based on an analysis of the evaluation criteria, taking into account the risks and benefits to patients, FDA proposes to include HMEs on the lists of drug products or categories of drug

products that present demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act. On November 21, 2017, FDA proposed to the PCAC that HMEs be identified as presenting demonstrable difficulties for compounding under sections 503A and 503B of the FD&C Act (Ref. 10). The PCAC voted to agree with FDA's proposal (Ref. 5).

VI. Proposed Effective Date

The Agency proposes that any final rule based on this proposal become effective 30 days after the date of publication of the final rule in the *Federal Register*.

VII. Preliminary 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 we expect that the proposed rule would have a small impact, if any, on small entities, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) 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 $177 million, using the most current (2022) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

We evaluated three categories of drug products for this proposed rule. We are proposing to place all three of these categories of drug products on the DDC Lists for sections 503A and 503B of the FD&C Act. We expect that this proposed rule may create benefits for compounders by reducing regulatory uncertainty. Currently, we are not aware of any marketing of compounded drugs in the three proposed categories of drug products for human use. Therefore, we expect that the proposed rule would only create administrative costs for compounders to read and understand the rule.

In table 1, we summarize the impacts of the proposed rule. The present value of the costs of the proposed rule would equal $3.19 million at a 7 percent discount rate and $3.19 million at a 3 percent discount rate. The proposed rule would result in annualized costs of $0.42 million at a 7 percent discount rate, or $0.36 million at a 3 percent discount rate.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)							
	Annualized Quantified							
	Qualitative	Benefits to compounders from reduced regulatory uncertainty.						
Costs	Annualized Monetized ($m/year)	$0.42	$0.38	$0.48	2021	7%	10 years	
		$0.36	$0.33	$0.41	2021	3%	10 years	
	Annualized Quantified							
	Qualitative							

Transfers	Federal Annualized Monetized ($m/year)							
		From:			To:			
	Other Annualized Monetized ($m/year)							
		From:			To:			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 11) and at https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

VIII. 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.

IX. 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.

X. 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.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. References

The following references are on display at the Dockets Management Staff (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 https://www.regulations.gov. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, Transcript of the June 18, 2015, Meeting of the Pharmacy Compounding Advisory Committee (available at https://wayback.archive-it.org/7993/20170403224128/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458514.pdf), accessed January 10, 2023.

2. FDA, Transcript of the March 9, 2016, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/04-03-2022T19:30/https://www.fda.gov/media/98783/download), accessed January 10, 2023.

3. FDA, Transcript of the November 3, 2016, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/04-03-2022T19:30/https://www.fda.gov/media/105599/download), accessed January 10, 2023.

4. FDA, Transcript of the May 9, 2017, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/04-03-2022T19:30/https://www.fda.gov/media/106182/download), accessed January 10, 2023.

5. FDA, Transcript of the November 21, 2017, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/04-03-2022T19:30/https://www.fda.gov/media/112399/download), accessed January 10, 2023.

6. FDA, Briefing Information for the June 17-18, 2015, Meeting of the Pharmacy Compounding Advisory Committee (available at https://wayback.archive-it.org/7993/20170404155225/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf), accessed January 10, 2023.

7. FDA, Briefing Information for the March 8-9, 2016, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/browse/FDA/01-03-2022T00:42/https://www.fda.gov/advisory-committees/pharmacy-compounding-advisory-committee/briefing-information-march-8-9-2016-meeting-pharmacy-compounding-advisory-committee-pcac), accessed January 10, 2023.

8. FDA, Briefing Information for the November 3, 2016, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/01-03-2022T00:42/https://www.fda.gov/media/100283/download), accessed January 10, 2023.

9. FDA, Briefing Information for the May 8-9, 2017, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/content/FDA/01-03-2022T00:42/https://www.fda.govmedia/104134/download), accessed January 10, 2023.

10. FDA, Briefing Information for the November 20-21, 2017, Meeting of the Pharmacy Compounding Advisory Committee (available at https://public4.pagefreezer.com/browse/FDA/01-03-2022T00:42/https://www.fda.gov/advisory-committees/pharmacy-compounding-advisory-committee/briefing-information-november-20-21-2017-meeting-pharmacy-compounding-advisory-committee-pcac), accessed January 10, 2023.

11. FDA, Preliminary Regulatory Impact Analysis, "Drug Products That Present Demonstrable Difficulties for Compounding Under Section 503A or 503B of the Federal Food, Drug, and Cosmetic Act " (available at https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations).

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, we propose that 21 CFR part 216 be 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. Add § 216.25 to subpart B to read as follows:

§ 216.25 Drug products or categories of drug products that present demonstrable difficulties for compounding under section 503A or 503B of the Federal Food, Drug, and Cosmetic Act.

(a) FDA will use the following criteria in evaluating drug products or categories of drug products considered for inclusion on the lists set forth in paragraphs (b) and (c) of this section:

(1) The complexity of the drug product or category of drug products' formulation;

(2) The complexity of the drug product or category of drug products' drug delivery mechanism;

(3) The complexity of the drug product or category of drug products' dosage form;

(4) The complexity of achieving or assessing bioavailability of the drug product or category of drug products;

(5) The complexity of the drug product or category of drug products' compounding process; and

(6) The complexity of physicochemical or analytical testing of the drug product or category of drug products.

(b) After considering the criteria in paragraph (a) of this section and taking into account risks and benefits to patients, FDA has determined that the following drug products or categories of drug products present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and therefore cannot be compounded under section 503A of the Federal Food, Drug, and Cosmetic Act:

(1) Drug products produced using hot melt extrusion.

(2) Liposome drug products.

(3) Oral solid modified-release drug products that employ coated systems.

(c) After considering the criteria in paragraph (a) of this section and taking into account risks and benefits to patients, FDA has determined that the following drug products or categories of drug products present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, and therefore cannot be compounded under section 503B of the Federal Food, Drug, and Cosmetic Act:

(1) Drug products produced using hot melt extrusion.

(2) Liposome drug products.

(3) Oral solid modified-release drug products that employ coated systems.

Dated: _____.

_____