

FDA's Compounding Program

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Agenda



- Compounding History
- Statutory Framework
- Policy Overview
- Compounding Guidances
- Section 503A and 503B Bulks Lists
- Section 503A Memorandum of Understanding
- Inspections and Follow-up Actions
- Compounding Risk Alerts
- Stakeholder Collaboration
- Compounding Quality Center of Excellence

Compounding – A Snapshot

- Compounded drugs:
 - Are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing
 - Can qualify for exemptions from key provisions of the Federal Food, Drug and Cosmetic Act if certain conditions are met
 - Can serve an important role for patients whose medical needs cannot be met by an FDA approved drug
- States generally have day-to-day oversight responsibilities of most compounding pharmacies
- FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drugs
- FDA continues to observe egregious conditions, including insanitary conditions, at many of the compounding facilities that it inspects
- Poor quality compounded drugs have led to deaths and other serious patient harm



History

Compounding – History



- Pharmacies have traditionally manipulated drugs to meet the needs of identified individual patients pursuant to prescriptions from licensed practitioners
- FDA addressed this activity in 1992 in a compliance policy guide (CPG), titled *Manufacture, Distribution, and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies*
- The CPG addressed the increasing quantity of entities licensed as pharmacies that were manufacturing, distributing, and promoting unapproved new drugs in a way that is “clearly outside the bounds of traditional pharmacy practice” and that violate the FD&C Act

Compounding – History (cont'd)

Food and Drug Administration Modernization Act of 1997



- Congress passed and the President signed into law the **FDA Modernization Act of 1997 (FDAMA)**, which added section 503A to the FD&C Act addressing compounding by pharmacists and physicians
- Section 503A establishes conditions for compounded drug products to qualify for exemptions from three key provisions of the FD&C Act:
 - New drug approval requirements (section 505)
 - Labeling with adequate directions for use (section 502(f)(1))
 - Current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B))

Compounding – History (cont'd)

Food and Drug Administration Modernization Act of 1997



Joint Explanatory Statement of the Congressional Committee of Conference explained that in enacting section 503A:

“It is the intent of the conferees to ***ensure continued availability*** of compounded drug products as a component of individualized therapy, while **limiting the scope of compounding** so as to **prevent manufacturing under the guise of compounding**. Section **503A** establishes parameters under which compounding is appropriate and lawful . . . ”

Compounding – History (cont'd)



The provisions of section 503A were the subject of subsequent court challenges, which produced conflicting case law and amplified the perceived limitations and ambiguity associated with FDA's enforcement authority over compounding pharmacies. These court challenges resulted in, among other things, a Supreme Court ruling that invalidated provisions of section 503A concerning advertising and promotion for being unconstitutional.

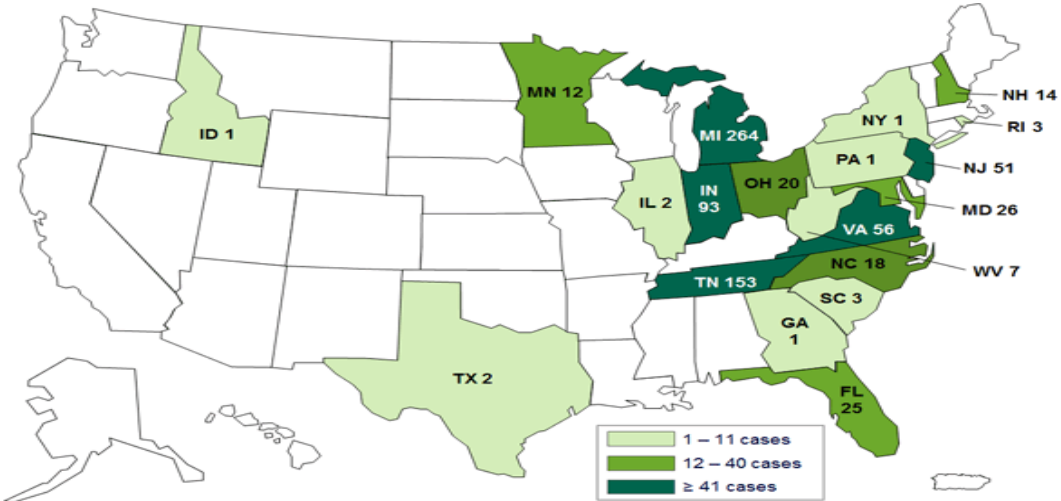
History of Adverse Events Associated with Compounded Drug Products (1997-2012)



1997	Two patients were hospitalized with serious infections after administration of contaminated riboflavin injection prepared by a Colorado pharmacy
2001	Thirteen patients in California were hospitalized and 22 received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result.
2002	Five patients in North Carolina suffered from fungal meningitis resulting from contaminated methylprednisolone acetate made by a South Carolina pharmacy. One person died
2005	Contaminated cardioplegia solution, made by a firm located in Maryland, resulted in five cases of severe system inflammatory infections; three of these patients died
2007	Three people died from multiple organ failure after a Texas compounder sold superpotent colchicine that was as much as 640 percent the labeled strength
2010	FDA investigated a cluster of Streptococcus endophthalmitis bacterial eye infections in patients who received injections of Avastin repackaged by a pharmacy in Tennessee
2011	Nineteen cases of Serratia marcescens bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products
2012	Forty-three patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss

2012 Fungal Meningitis Outbreak

- More than 750 cases of illness in 20 states
- More than 60 deaths
- Caused by contaminated preservative-free methylprednisolone acetate injections compounded by the New England Compounding Center (NECC)



Compounding – History (cont'd)



- In 2013, Congress passed the Drug Quality and Security Act (DQSA), including Title I, the Compounding Quality Act, which added section 503B to the FD&C Act concerning outsourcing facilities
- The DQSA also removed from section 503A provisions that the U.S. Supreme Court held unconstitutional in 2002
- By removing these unconstitutional provisions, the DQSA clarified that section 503A is valid nationwide

Statutory Framework

Statutory Framework

Section 503A (Enacted 1997 FDAMA)	Section 503B (Enacted 2013 DQSA)
<p>Conditions under which drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, qualify for exemptions from three requirements of the FD&C Act:</p> <ol style="list-style-type: none">(1) New drug approval requirements (section 505),(2) Labeling with adequate directions for use (section 502(f)(1)), and(3) Current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B))	<p>Conditions under which drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from three requirements of the FD&C Act:</p> <ol style="list-style-type: none">(1) New drug approval requirements (section 505),(2) Labeling with adequate directions for use (section 502(f)(1)), and(3) Drug supply chain security requirements (section 582). <p>Outsourcing facilities remain subject to CGMP requirements.</p>

Failure to Qualify Under 503A and 503B

- If compounded drug products fail to meet the conditions in sections 503A or 503B, the drug products will not qualify for the exemptions described in each section.
- The drug products will be subject to all applicable requirements of the FD&C Act (e.g., new drug approval requirements).

Compounders Under Section 503A



- Licensed pharmacists in state-licensed pharmacies (e.g., hospital pharmacies, home infusion pharmacies) or Federal facilities, and licensed physicians
- Number in the many thousands
- Generally do not register with FDA
- Pharmacies primarily overseen by the states
- Frequency and depth of state oversight of pharmacies varies from state-to-state
- Quality standards vary from state-to-state
- Compounding physicians are generally not routinely overseen by any regulatory body

Production Requirements: Compounders under Section 503A

- Compounding production standards are set by the states, and vary from state-to-state
 - A number of states require compliance in whole or in part with United States Pharmacopeial Convention (USP) Chapters <795> and <797> addressing nonsterile and sterile compounding, respectively.
- Drugs that meet the conditions under section 503A are exempt from CGMP requirements, but other federal laws remain applicable, including the federal prohibition concerning insanitary conditions (see section 501(a)(2)(A)).

Outsourcing Facilities Under Section 503B

- Section 503B(d)(4)(A) defines “outsourcing facility” as a facility at one geographic location or address that:
 - Is engaged in the compounding of sterile drugs
 - Has elected to register as an outsourcing facility
 - Complies with all of the requirements in section 503B
- 73 outsourcing facilities registered with FDA as of 7/16/21
- <https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities>
- In addition, an outsourcing facility:
 - Is **NOT** required to be a licensed pharmacy (section 503B(d)(4)(B)), but compounding must be by or under the direct supervision of a licensed pharmacist to qualify for the exemptions (section 503B(a))
 - May or may not obtain prescriptions for identified individual patients (section 503B(d)(4)(C))
 - Is subject to increased federal oversight through FDA inspection
 - Is subject to CGMP requirements

Production Requirements:

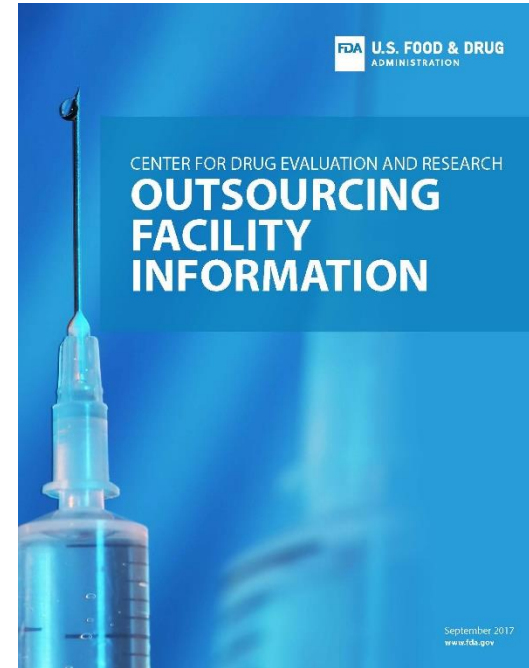
Outsourcing Facilities under Section 503B



- Outsourcing facilities are required to comply with CGMP requirements under section 501(a)(2)(B). FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211.
- Federal prohibition concerning insanitary conditions under section 501(a)(2)(A) also applies to outsourcing facilities.

Outsourcing Facility Information

- Posted September 2017
- Describes in one place various resources available to outsourcing facilities.
 - Advantages to becoming an outsourcing facility and statutory requirements
 - Resources available to outsourcing facilities, including guidance documents, meetings with FDA, and preoperational reviews
 - How to register as an outsourcing facility and submit product reports
 - FDA inspections of outsourcing facilities and subsequent actions



Outsourcing Facility Product Reports

- FDA posts information submitted by outsourcing facilities in product reports
 - Section 503B(b) of the FD&C Act requires, upon initial registration as an outsourcing facility, and each June and December, that each outsourcing facility that registers with FDA submit to FDA a report identifying drug products that they compounded by the outsourcing facility during the previous six-month period.
 - FDA is posting portions of these reports, in part, to assist the public in identifying outsourcing facilities that have produced certain drug products that they need.
- This database contains information reported to FDA within the last two years (last four reporting periods).
- This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future.

<https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm>

Statutory Framework



Drugs compounded under Section 503A (pharmacies, physicians)	Drugs compounded under Section 503B (Outsourcing Facilities)
<ul style="list-style-type: none">• Conditions to qualify for exemptions – e.g.:<ul style="list-style-type: none">• Patient specific prescriptions -- 503A(a)• “Compounds the drug product using bulk drug substances...” -- 503A(b)(1)(A)• “Does not compound regularly or in inordinate amounts ... any drug products that are essentially copies of a commercially available drug product” -- 503A(b)(1)(D)• Not subject to CGMP if conditions are met• MOU between FDA/States	<ul style="list-style-type: none">• Conditions to qualify for exemptions -- e.g.:<ul style="list-style-type: none">• “The drug is compounded in an outsourcing facility that does not compound using bulk drug substances ..., unless...” -- 503B(a)(2)• “The drug is not essentially a copy of one or more approved drugs” -- 503B(a)(5)• Prohibition on wholesaling -- 503B(a)(8)• Labeling provisions -- 503B(a)(10)• No patient-specific prescriptions required (can produce office stock)• Subject to CGMP• Requirements for registration, reports of drugs compounded, adverse event reporting -- section 503B(b)

Policy Overview

Policy Goals



1. Address significant public health concerns
2. Provide clarification on provisions of the law and answer questions presented by industry
3. Decrease regulatory burden to the extent possible without sacrificing critical public health protections
4. Clarify responsibilities of FDA and the States

Policy Considerations: Access



- **Access**
 - Compounded drug products can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product.
 - FDA seeks to develop policies that preserve access to compounded drugs when patients have a medical need for them.

Policy Considerations: Quality

- **Quality**
 - FDA has investigated numerous outbreaks of infections and deaths associated with contaminated or otherwise substandard drugs.
 - FDA has observed insanitary conditions at many of the compounding facilities it has inspected.
 - DQSA created outsourcing facilities to supply compounded drugs made according to CGMP requirements.
 - FDA seeks to develop policies that promote the compounding of drugs under appropriate conditions.

Policy Considerations: Necessity



- **Necessity**
 - Compounded drugs can pose a higher risk to patients than FDA-approved drugs.
 - Compounding can reduce the incentives for investing in and seeking approval of new drugs.
 - FDA seeks to develop policies that encourage use of FDA-approved drugs to meet a patient's medical needs.

Policy Overview Since DQSA

- More than 40 draft, revised draft, and final guidances and other policy documents published
- 10 proposed and final rules and *Federal Register* notices
 - 3 rules have been finalized
 - 2 proposed rules in progress
 - 5 proposed *Federal Register* notices re: the 503B bulks list
- 10 Pharmacy Compounding Advisory Committee meetings
 - 59 bulk drug substances considered for use in compounding under section 503A or section 503B
 - 6 categories of drug products considered for “Difficult to Compound” lists
 - 31 drug products considered for “Withdrawn or Removed” list
- Draft and final guidances are available on the Regulatory Policy Information webpage: <https://www.fda.gov/drugs/human-drug-compounding/regulatory-policy-information>

Final Guidances and Regulations Issued



- Final Guidances (non-exhaustive)
 - Compounded drugs that are essentially copies of a commercially available drug product under section 503A
 - Compounded drugs that are essentially copies of FDA-approved drugs under section 503B
 - Mixing, diluting, and repackaging biological products outside the scope of a BLA
 - Prescription requirement under section 503A
 - Repackaging drugs
 - Interim policies on compounding from bulk drug substances under sections 503A and 503B
 - 503B Electronic Drug Product reporting
 - 503B Adverse event reporting
 - 503B Registration
 - Pharmacy Compounding under section 503A
 - Entities considering whether to register under section 503B
 - Fees for outsourcing facilities
 - Insanitary conditions at compounding facilities
 - Facility definition
- Final Rules
 - Modifications to the withdrawn or removed list under sections 503A and 503B
 - Additions to the 503A Bulks List

Compounding Guidances

Prescription Requirement

Under section 503A(a), there are two situations in which a drug product can be compounded:

- “on the prescription order for such individual patient” (section 503A(a)(1)); **OR**
- “in limited quantities before the receipt of a valid prescription order for such individual patient” if:
 - The compounding is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product; and
 - The orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order.

Section 503A(a)(2).

Final Guidance: Prescription Requirement Under Section 503A



PURPOSE	PRESCRIPTION REQUIREMENT
<p>Set forth policies that both (a) preserve access to compounded drugs for patients who have a medical need for them, and (b) protect patients from compounding practices that could cause serious harm. The prescription requirement:</p> <ul style="list-style-type: none">• Ensures that compounding under section 503A is based on individual patient need	<p>To qualify for the exemptions under section 503A, a drug product must be compounded based on the receipt of a valid prescription order or a notation for an identified individual patient. There are two situations in which a drug product can be compounded:</p> <ul style="list-style-type: none">• In limited quantities before the receipt of such a prescription, or• Based on the receipt of the prescription. <p>Note: Outsourcing facilities may or may not obtain prescriptions for identified individual patients</p>

Prescription Requirement Under Section 503A: Case Study



- Main Street Family Pharmacy
- Compounded methylprednisolone acetate and other drugs
- 26 cases of fungal infections in patients in 17 states in 2013
- Drugs distributed without patient-specific prescriptions
- Co-owner pleaded guilty to misdemeanor criminal violation of FD&C Act and signed civil consent decree.



Essentially a Copy Under Section 503A

- To qualify for the exemptions under section 503A, a drug product must be compounded by a licensed pharmacist or physician who does not compound “regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.” (section 503A(b)(1)(D))
- A compounded drug product is not essentially a copy of a commercially available drug product if “there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.” (section 503A(b)(2))

Essentially a Copy under Section 503B

- To qualify for the exemptions under section 503B, the drug must not be “essentially a copy of one or more approved drugs.” (section 503B(a)(5))
- A compounded drug is “essentially a copy of an approved drug” if:
 - It is a drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on FDA’s drug shortage list at the time of compounding, distribution, and dispensing (section 503B(d)(2)(A)); or
 - It is a drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug (section 503B(d)(2)(B))

Final Guidances: Compounded Drugs that are Essentially Copies



PURPOSE	POLICY
<p>The restrictions in section 503A(b)(1)(D) and section 503B(a)(5) help to limit compounders from compounding drugs for patients who could use an approved (503B) or commercially available (503A) drug product.</p> <p>Compounded copies undermine the FDA approval process and can put patients at unnecessary risk for receiving a substandard drug product.</p>	<p>Guidances describe FDA’s policies regarding the “essentially a copy” provisions of sections 503A and 503B, and clarify certain statutory terms such as:</p> <ul style="list-style-type: none">• 503A: “regularly or in inordinate amounts” and “commercially available”• 503B: “identical or nearly identical”

Copies: Case Study



- Franck's Compounding Lab
- In 2012, more than 40 patients experienced infections, many resulting in permanent vision loss, from contaminated triamcinolone acetate and brilliant blue G ophthalmic injections distributed nationwide.
- FDA-approved triamcinolone acetate may have been medically appropriate for the patients.

Final Guidance: Mixing, Diluting, or Repackaging Biological Products



PURPOSE	POLICY
<p>Biological products subject to licensure under section 351 of the Public Health Service Act (PHS Act) are not eligible for exemptions for compounded drugs under sections 503A and 503B of the FD&C Act.</p> <p>Policy addresses concerns about access and patient safety raised with FDA.</p>	<p>Guidance describes conditions under which FDA does not intend to take action when certain biological products are mixed, diluted, or repackaged in a manner not described in their approved labeling.</p>

Mixing, Diluting, or Repackaging Biological Products

– Case Study

- Eastern Pharmacy
 - At least 37 patients experienced eye infections after receiving intravitreal injections of repackaged Avastin and Lucentis, that was contaminated.
 - Long beyond-use-dates
 - Repackaged under non-sterile conditions
- Since 2007, more than 100 adverse events associated with repackaged Avastin that may have been contaminated



Final Guidance: Repackaging

PURPOSE	POLICY
<p>Drugs repackaged by State-licensed pharmacies, Federal facilities, or outsourcing facilities are not eligible for exemptions under sections 503A or 503B.</p> <p>Policy addresses concerns about access and patient safety raised with FDA.</p>	<p>Guidance describes conditions under which FDA does not intend to take action regarding violations of certain requirements of the FD&C Act, in the context of repackaging.</p>

Repackaged Drugs: Case Study

- Specialty Compounding
- Nationwide distributor
- Repackaged calcium gluconate under insanitary conditions and assigned long beyond-use-dates
- 15 patients infected
- 2 patients died



Temporary COVID-19 Guidances (2020)

- Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency
- Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency
- Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency Guidance for Industry
- Temporary Policy on Repackaging or Combining Propofol Drug Products During the COVID-19 Public Health Emergency
- Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency
- Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic

Spring 2021 Unified Agenda

- Proposed Rules:
 - Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food Drug and Cosmetic Act
 - Amendment to Records and Reports Concerning Adverse Drug Experiences on Marketed Prescription Drugs for Human Use Without Approved New Drug Applications
- Final Rule:
 - Amendments to the List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

Revised Draft Guidance: CGMP Requirements for Outsourcing Facilities

PURPOSE	POLICY – DRAFT GUIDANCE
<p>This guidance reflects FDA’s intent to recognize the differences between outsourcing facilities and conventional drug manufacturers, while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.</p>	<p>The draft guidance restates applicable CGMP requirements in detail to help outsourcing facilities to comply with the law. When finalized, it will describe FDA’s policies regarding compliance with CGMP requirements for outsourcing facilities.</p>

Final Guidance: Insanitary Conditions

PURPOSE	POLICY
<p>This guidance is intended to provide examples of insanitary conditions within the meaning of section 501(a)(2)(A) of the FD&C Act to assist compounding facilities in identifying such conditions at their facilities and to assist state inspectors.</p>	<p>Under section 501(a)(2)(A) of the FD&C Act, a drug is deemed to be adulterated if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health. This guidance provides examples of insanitary conditions related to:</p> <ul style="list-style-type: none">• Aseptic practices• Equipment/facilities• Sterilization• Cleaning and disinfecting

Section 503A & 503B Bulks Lists

Development of the 503A/503B Bulk Drug Bulks Lists



- 503A bulks list (rulemaking)
- 503B bulks list (*Federal Register* notice)
- Interim policy guidances

Drug Products are Compounded with Bulk Drug Substances

Section 503A

Under section 503A(b)(1)(A)(i), for a compounded drug product to qualify for the exemptions under section 503A, the bulk drug substances used to compound it:

- Must comply with the standards of an **applicable** United States Pharmacopeia (USP) or National Formulary (NF) **monograph**, if one exists, and the USP chapter on pharmacy compounding;
- If an applicable USP/NF monograph does not exist, must be a **component** of an **FDA-approved drug**; or
- If such a monograph does not exist and the substance is not a component of an FDA-approved drug, must appear on a **list of bulk drug substances** that can be used in compounding under section 503A developed by FDA through regulations

Section 503B

Under section 503B(d)(2)(A)(i), for a drug product compounded using bulk drug substances to qualify for the exemptions under section 503B:

- The bulk drug substances that are used must appear on a **list** established by the Secretary identifying bulk drug substances for which there is a clinical need, or
- The drug compounded from the bulk drug substance must appear on FDA's **drug shortage list** at the time of compounding, distribution, and dispensing

Bulk Drug Substances



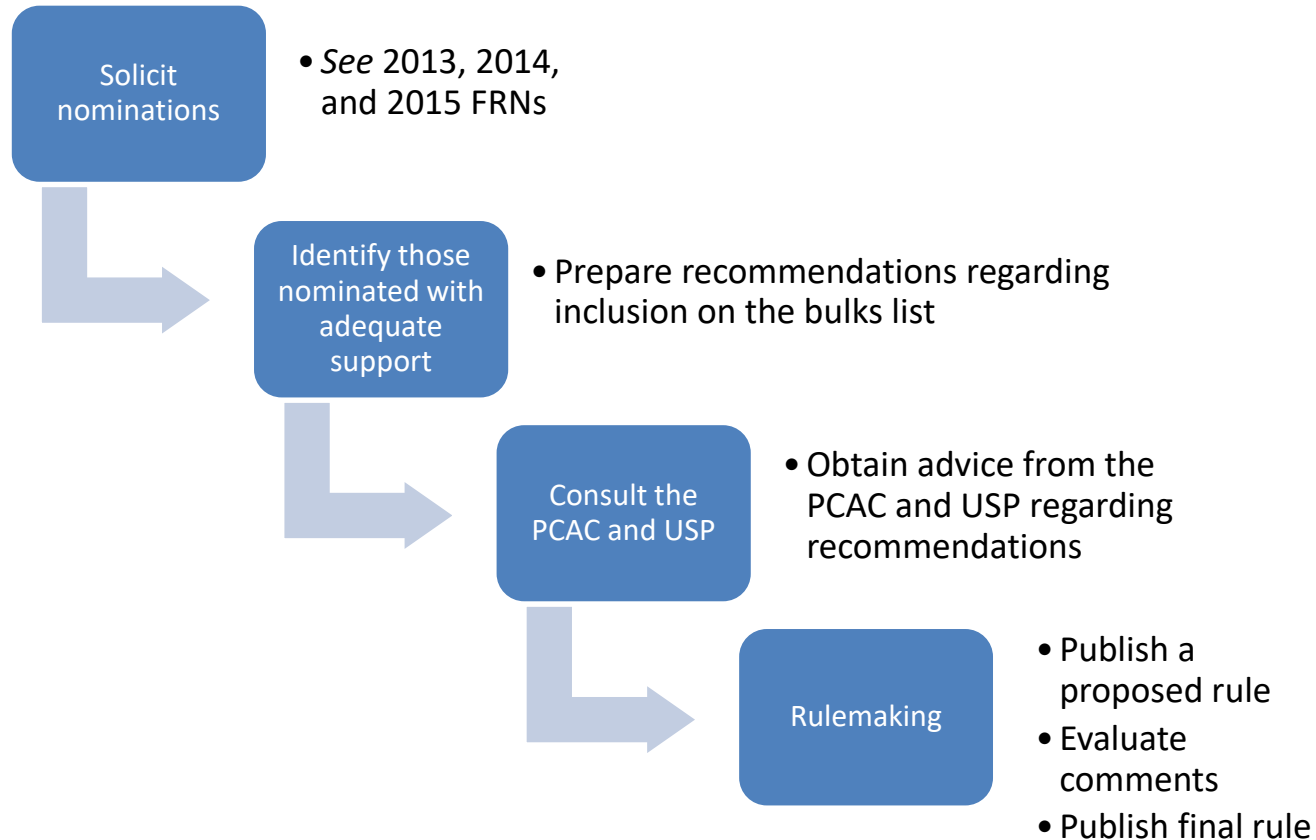
- Sections 503A(b)(1)(A) and 503B(a)(2) define a “bulk drug substance” by referencing the definition in 21 CFR 207.3(a)(4): “the same as active pharmaceutical ingredient as defined in 21 CFR 207.1(b)”
- Active pharmaceutical ingredient is defined in 21 CFR 207.1(b) as “any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body,” but the term “does not include intermediates used in the synthesis of the substance”



Development of 503A Bulks List

- FDA must develop the 503A Bulks List through regulations and in consultation with the United States Pharmacopeial Convention (USP) and the Pharmacy Compounding Advisory Committee (PCAC) (section 503A(c))
- 59 bulk drug substances have been presented to the PCAC

503A Bulks List: General Process



Pharmacy Compounding Advisory Committee

- Provides advice on scientific, technical, and medical issues concerning certain provisions of sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act
- 10 meetings
- 59 bulk drug substances considered
- 6 categories considered for the difficult to compound list
- 31 substances considered for the withdrawn or removed list

Current 503A Bulks List

- 503A Bulks List codified at 21 CFR § 216.23(a):
 - (1) Brilliant Blue G, also known as Coomassie Brilliant Blue G-250.
 - (2) Cantharidin (for topical use only).
 - (3) Diphenylcyclopropenone (for topical use only).
 - (4) N-acetyl-D-glucosamine (for topical use only).
 - (5) Squaric acid dibutyl ester (for topical use only).
 - (6) Thymol iodide (for topical use only).

503A Bulks List: Rulemaking



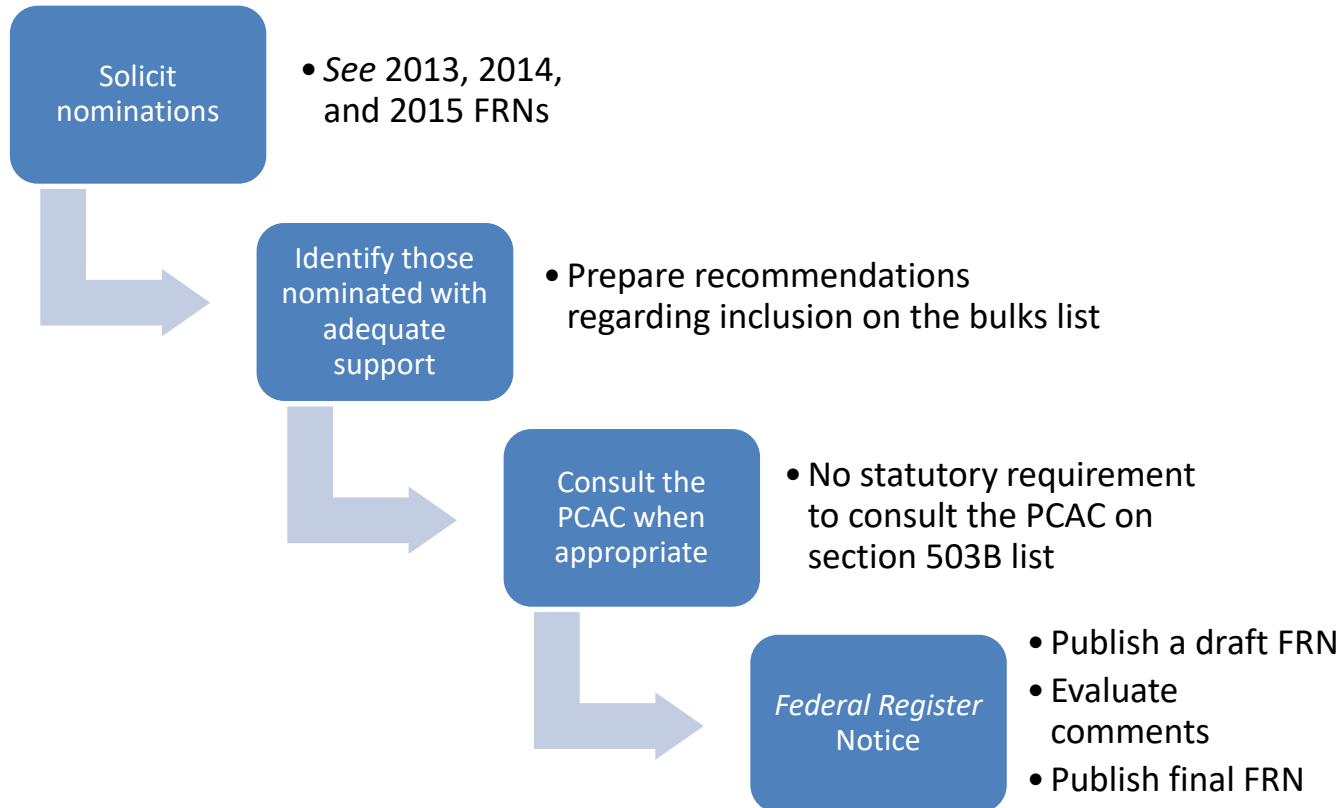
- We plan to address nominated bulk drug substances in rules on a rolling basis, seeking public comment on each proposal.
- Finalize proposed rule
 - Proposed rules address 41 bulk drug substances nominated for inclusion on the 503A bulks list
 - 11 bulk drug substances recommended for inclusion
 - 30 bulk drug substances recommended against inclusion
- Proposed rule
 - FDA is working on addressing additional substances in future rulemaking



Development of 503B Bulks List

- Section 503B(a)(2)(A) condition: the drug is compounded in an outsourcing facility that does not compound using bulk drug substances, unless --
 - The bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need, **or**
 - The drug compounded from such bulk drug substance appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing

503B Bulks List: General Process



503B Bulks List: Federal Register Notice

- Establish a list identifying bulk drug substances for which there is a “clinical need.”
- We plan to address nominated bulk drug substances in *Federal Register* notices (FRN) on a rolling basis, seeking public comment on each proposal.
 - 5 FRNs addressed 42 bulk drug substances nominated for inclusion on the 503B Bulks List
 - 5 bulk drug substances recommended for inclusion
 - 35 bulk drug substances recommended against inclusion
 - 2 bulk drug substances not added to the 503B Bulks List
 - FDA is working on addressing additional substances in future FRNs

Identifying Bulk Drug Substances for Which There is a Clinical Need Under 503B

Final guidance published March 2019: Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B

Guidance explains that the 503B Bulks List may include a bulk drug substance if:

- There is a **clinical need** for an outsourcing facility to compound the drug product, and
- The drug product must be compounded using the bulk drug substance.

Final Guidances: Interim Policies for 503A and 503B Bulks



PURPOSE	POLICY
<p>Prevent unnecessary disruptions in patient access to drugs compounded from bulk drug substances while FDA develops the lists of substances that can be used in compounding.</p>	<p>While the bulks lists are in development, FDA does not intend to object to the compounding of drugs from bulk drug substances that are not on the lists provided that certain conditions are met, including that they were nominated with adequate supporting information for FDA to evaluate them and do not appear to present significant safety risks.</p>

Section 503A Memorandum of Understanding

Final Standard

Memorandum of Understanding



PURPOSE	POLICY
<p>MOU addresses the distribution of inordinate amounts of compounded human drug products interstate and provides for appropriate state agency investigation of complaints associated with compounded drug products distributed outside the state.</p> <ul style="list-style-type: none">• Congress did not intend for compounders operating under the exemptions in section 503A to grow into conventional manufacturing operations, making unapproved drugs and operating a substantial portion of their business interstate.• If a substantial proportion of a compounder’s drugs are distributed outside of a State’s borders, adequate regulation of those drugs poses significant challenges to State regulators.<ul style="list-style-type: none">• States face logistical, regulatory, and financial challenges inspecting compounders located outside their jurisdiction.• It can be difficult to investigate and address adverse events associated with drugs distributed to multiple states.	<ul style="list-style-type: none">• Inordinate amounts means greater than 50% of compounded drugs distributed interstate. (Note: if a pharmacy is located in a state that has not entered into an MOU, the statute limits distribution out of state to 5%).• States notify FDA of serious adverse events and product quality issues within 5 business days.• “Distribution of compounded human drug products interstate” means that a pharmacy or physician has sent (or caused to be sent) a compounded drug product out of the State in which the drug was compounded.

Inspections and Follow-up Actions

When FDA Conducts a Compounding Inspection

For-Cause (>210 inspections conducted)

- Serious adverse events
- Product quality or facility concerns (e.g., contamination, insanitary conditions)
- Complaints (e.g., compounding without patient-specific prescriptions)

Surveillance (>340 inspections conducted)

- Outsourcing facilities
- Limited surveillance of pharmacies of which FDA is aware

Follow-Up (>275 inspections conducted)

- Follow-up on corrective actions implemented after prior FDA inspections or regulatory actions

*Inspection figures from FY'14-FY'21 YTD (8/20/21)

Frequent Inspectional Findings

- Insanitary conditions
- CGMP violations (only applicable to outsourcing facilities and pharmacies not in compliance with the conditions of section 503A)
- Non-compliance with the conditions of section 503A
 - Lack of patient-specific prescriptions
 - Drugs on the withdrawn or removed list
- Non-compliance with the conditions of section 503B
 - Labeling deficiencies
 - Failure to submit a product report

Insanitary Condition Example



Visible
microbial
contamination
on a ceiling tile
in a clean room

Insanitary Condition Example



Filth under the hood including multiple pieces of medical supply waste and dust build up in the pre-filter for the ISO 5 hood

Insanitary Condition Example



The glove box that provides ISO 5 conditions where aseptic processing operations occur, was located in an unclassified carpeted room where the room air was not HEPA filtered. Note the wooden stool.



Insanitary Condition Example



Gowned employee working in the cleanroom, exposing legs

Insanitary Condition Example



The HEPA filter located immediately above the ISO 5 workbench was observed to have been stained on the filter surface.



The HEPA filter stain was due to drug product which had exploded due to excessive pressure applied when forcing non-sterile product through a sterilizing filter. The device used to force the product sterilizing filter was a stainless steel caulking gun that was not sterilized.

Insanitary Condition Example



Sleeve used in the aseptic glove box for aseptic manipulations is damaged

Insanitary Condition Example



Toaster oven used to dry heat sterilize and depyrogenate glassware; oven was not capable of reaching high enough temperature to be effective

Insanitary Condition Example



Ceiling above the doorway
to cleanroom with exposed
insulation



Insanitary Condition Example



Kitchen home dishwasher (supplied with tap water) and Cascade brand detergent used to clean equipment and utensils that comes in contact with product intended to be sterile – no subsequent cleaning step



Insanitary Condition Example



Insects
(vermin) dead
or alive



FDA Actions

Frequent actions taken with respect to compounders:

- Recalls
 - Informal recommendations for voluntary recalls
 - Formal FDA requests for voluntary recalls
- Advisory Actions
 - Untitled letters
 - Warning letters
- Enforcement Actions
 - Civil injunctions
 - Criminal actions
- Referrals
 - State referral letters



Voluntary Recalls

- Since November 2013 there have been approximately 257 recall events involving compounded drugs, many due to conditions and practices resulting in a lack of drug sterility assurance
 - FY 2013 – 28 recall events
 - FY 2014 – 25 recall events
 - FY 2015 – 38 recall events
 - FY 2016 – 51 recall events
 - FY 2017 – 41 recall events
 - FY 2018 – 50 recall events
 - FY 2019 – 32 recall events
 - FY 2020 – 20 recall events
 - FY 2021 YTD – 14 recall events
- Since November 2013 FDA has issued four letters formally requesting firms to recall compounded drugs after they refused informal recommendations

Warning Letters

- Warning letters:
 - Communicate the Agency's position
 - Issued to achieve voluntary and prompt corrective action
 - Generally used when there is no history of repeat violations
- FDA has issued over 265 warning letters since November 2013
 - Insanitary conditions
 - Failure to comply with conditions of sections 503A or 503B
 - Violations of new drug approval, labeling with adequate directions for use, and CGMP provisions of the Act



Civil and Criminal Enforcement Actions



- Civil Injunctions - 13 (from FY 2013 to present)
- Criminal Enforcement Actions - 7 (from FY 2013 to present)

Compounding Risk Alerts

Compounding Risk Alerts

- FDA inspections and subsequent actions are often triggered by reports of incidents from healthcare practitioners, patients, and others.
- FDA frequently conducts extensive follow-up of such reports, and endeavors to share the results publicly when in the interest of public health.
- Compounding risk alerts are posted to inform healthcare practitioners and patients of adverse events associated with compounded drugs.

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570188.htm>

Compounding Risk Alerts (cont'd)



- Compounded curcumin emulsion product for injection (2017)
- Hemorrhagic occlusive retinal vasculitis (HORV) following injections of compounded triamcinolone, moxifloxacin, and vancomycin (2017)
- Adverse events associated with compounded glutamine, arginine, and carnitine product for injection (2017)
- Compounded triamcinolone-moxifloxacin drug product (2017)
- Significant safety risks associated with cesium chloride (2018)
- Differences in strength expression on product labels may lead to dosing errors (2018)
- Using dietary ingredient glutathione to compound sterile injectables (2020)
- Risks associated with intraocular use of compounded moxifloxacin (2021)
- Potential risks associated with the compounding of remdesivir drug products (2021)

2016: compounded morphine sulfate linked to adverse events in three infants



- Three infants received a compounded morphine sulfate preparation at a strength 20-fold greater than that indicated on the prepared label.
- FDA observed insanitary conditions, including poor sterile production practices, at a subsequent inspection of the compounding facility. The facility recalled all products intended to be sterile.



2017: compounded curcumin product linked to one illness and one death



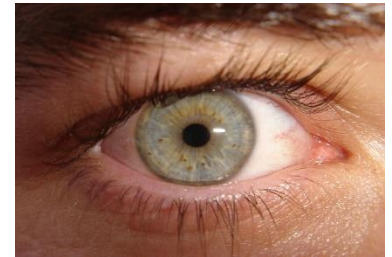
- Two patients given infusions of curcumin (a component of turmeric) compounded with polyethylene glycol (PEG) 40 castor oil reportedly experienced hypersensitivity reactions. One patient subsequently died.
- Risks illustrated by this case include the
 - Lack of a label warning about hypersensitivity reactions associated with PEG 40 castor oil
 - Use of a non-pharmaceutical grade ingredient that may contain impurities such as diethylene glycol
 - IV administration of curcumin when its safety profile by this route of administration and its effectiveness in treating eczema and thrombocytopenia have not been established



2017: eye injections of a compounded drug linked to vision problems in 43 patients



- At least 43 patients received eye injections of a drug containing triamcinolone (steroid) and moxifloxacin (anti-infective) compounded by a Texas pharmacy.
- Patients developed vision impairment (blurred or decreased vision), loss of color perception, glare, halos, pain, and loss of balance among other symptoms.





Stakeholder Collaboration

State Collaboration



- Objectives:
 - Share updates on FDA/State policy and enforcement matters
 - Identify opportunities for improved FDA/State collaboration
 - Clarify areas of primary responsibility
 - Discuss emerging issues of mutual concern
- Opportunities for collaboration:
 - Annual Intergovernmental Working Meetings
 - Action items to improve collaboration
 - Frequent teleconferences with state officials regarding specific compounders
 - States invited to join FDA on all inspections of compounders
 - Monthly meetings with the National Association of Boards of Pharmacy (NABP)
 - Engagement under the FDA-State MOU

Stakeholder Engagement



- Objectives
 - Learn stakeholders' views regarding the compounding sector, policy and regulatory oversight, and their impact on:
 - Public health
 - Drug product quality
 - Compounding ecosystem
 - Current practices and activities
 - Improve compliance by responding to questions and providing guidance on ways to comply with statutory requirements
- Opportunities for engagement
 - Stakeholder listening sessions (2021 listening sessions engaged over 100 stakeholder organizations such as pharmacy, medical, hospital, consumer groups, and outsourcing facilities)
 - Compounding Quality Center of Excellence engagement efforts (e.g., Annual Conference)
 - Numerous inquiry responses
 - Notice-and-comment guidance development process



Compounding Quality Center of Excellence

Compounding Quality Center of Excellence



- COE established in 2019 to develop training courses for outsourcing facilities on current Good Manufacturing Practices (CGMP) and FDA policies related to compounding.
- FDA sponsored the development and delivery of four instructor-led multi day courses, each offered multiple times, for outsourcing facilities on topics related to CGMPs.
- 6 self-guided web-based trainings on compounding policy and CGMPs are available.
- [Trainings](#) have been taken over 700 times by stakeholders.
- Inaugural COE Virtual Conference: Working Together for Patient Safety held in September 2020.
 - Over 350 participants attended
 - Open to all registered outsourcing facilities and related stakeholders including state regulators, federal partners, and relevant trade organizations
- Future COE Conferences are planned

COE Self-Guided Online Trainings



Web-based, on-demand trainings:

- Regulatory Framework for Human Drug Compounding
- Airflow
- Insanitary Conditions and Sterility Assurance
- Stability and Beyond Use Dates
- Outsourcing Facility Guide
- Investigations and Corrective and Preventive Actions (CAPA)



Web-Based Training - Self-Study

ID 1089314

Skill Level: Introductory

1.5h

★★★★☆ (31 Ratings)

Enhance your understanding of federal law and policies applicable to human drug compounding, including an introduction to human compounding, a brief regulatory history and overview of sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act. The course also covers the FDA inspection process and compounding oversight, including Form 483s, warning letters, and regulatory meetings.

▼ [Show More](#)

Moving Forward



Compounding Policy	Inspections and Enforcement	Stakeholder Collaboration and Outreach
Finalize or revise guidance documents, and proposed rules	Conduct inspections of outsourcing facilities and other compounders-based on certain risk criteria	Collaborate with stakeholders and coordinate and collaborate with our state regulatory partners
Develop policies to address other provisions of the law and answer questions presented by industry	Take appropriate action in response to incidents, complaints, and inspectional findings	Conduct outreach to inform interested stakeholders about compounding



U.S. FOOD & DRUG
ADMINISTRATION

Questions?