U.S. FOOD & DRUG ADMINISTRATION

FDA Drug Topics:
Regulatory Framework for Human Drug Compounding

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Disclaimer

- This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Disclosures

- Both presenters have nothing to disclose.

Goals and Objectives

- Discuss the basics of human drug compounding
- Describe the history and regulatory framework of human drug compounding and the differences between sections 503A and 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act
- Explain the evaluation process for bulk drug substances (BDS)* nominated for use in compounding in accordance with section 503A of the FD&C Act (503A Bulks List) and bulk drug substances nominated for use in compounding in accordance with section 503B of the FD&C Act (503B Bulks List), and how the evaluation process differs from the new drug approval process

*Sections 503A and 503B define a **bulk drug substance** as meaning "the same as **active pharmaceutical ingredient** as defined in 21 CFR 207.1" (see 21 CFR 207.3)

Outline of Presentation

- Basics of human drug compounding
- History of compounding and Drug Quality & Security Act of 2013
- Regulatory framework
    - Section 503A
    - Section 503B
- Overview of evaluation process for bulk drug substances
- Examples of substances (active ingredients) evaluated for use under section 503A
- Resources on compounding

The Basics

Human drug compounding is generally regarded as the practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, **combines, mixes, or alters ingredients of a drug to create a medication** tailored to the needs of an individual patient.

The Basics

- Compounded Drugs
  - Are not FDA-approved
  - Are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing
  - Qualify for exemptions from key provisions of the FD&C Act if certain conditions are met
  - Can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product
    - An example of when a provider might choose to prescribe a compounded drug: an FDA-approved opioid product is only available as a tablet for swallowing and the patient cannot swallow. In this case, a pharmacist could provide the opioid in a different dosage form such as a troche (medicated lozenge)
  - Poor quality compounded drugs have led to deaths and life-long patient harm
- States generally have day-to-day oversight of compounders that are not outsourcing facilities

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 (continued)

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 (continued)

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 (continued)

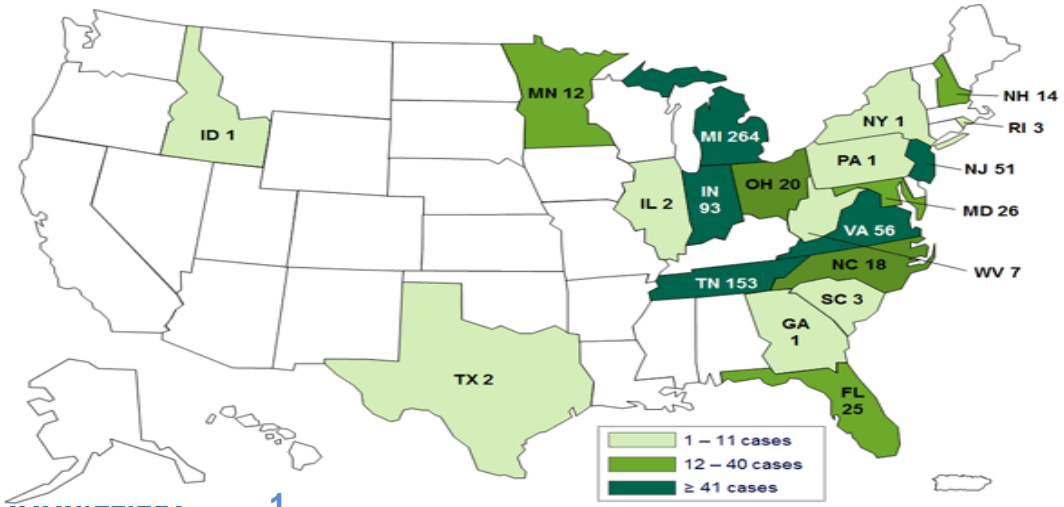
- Certain provisions of section 503A were the subject of subsequent court challenges, which produced conflicting case law and amplified the perceived limitations and ambiguity associated with FDA's enforcement authority over compounding pharmacies. These court challenges resulted in, among other things, 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 (continued)

- 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)
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: (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))	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: (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). **Outsourcing facilities remain subject to CGMP requirements.**

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).

Limits on Compounding

Section 503A	Section 503B
• **Withdrawn or Removed List**: drug products that have been withdrawn or removed from the market because FDA found them to be unsafe or not effective	
• **Demonstrably Difficult to Compound List**: drug products FDA identified as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on safety or effectiveness	• **Demonstrably Difficult to Compound List**: drug product or category of drug products FDA identified as presenting demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on safety or effectiveness taking into account the risks and benefits to patients
• **Essentially Copies**: cannot compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product	• **Essentially Copies**: cannot compound essentially a copy of one or more approved drugs

Limits on Compounding (continued)

Section 503A	Section 503B
• **Patient-Specific Prescriptions**: compounding must be based on the receipt of a valid prescription for an identified individual patient	• **Patient-Specific Prescriptions**: may or may not obtain prescriptions for identified individual patients
• **5% Limit:** limits compounded drug products distributed out of the State in which they are compounded in quantities that do not exceed 5% unless the State has entered into a memorandum of understanding (MOU) with FDA addressing interstate distribution of compounded drugs.	• **Prohibition on Wholesaling**: drugs may not be sold or transferred by an entity other that the outsourcing facility that compounded such drug but does not prohibit administration of a drug in a health care setting or dispensing a drug pursuant to a prescription executed in accordance with section 503(b)(1)
• **503A Bulks List:** directs FDA to create a list of bulk drug substances that may be used in compounding	• **503B Bulks List:** bulk drug substance must be listed for compounded drug product to qualify for an exemption from certain sections of the FD&C Act

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

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 6/20/23
- 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

Section 503A & 503B Bulks Lists

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”
- Active pharmaceutical ingredient is defined in 21 CFR 207.1 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”

Drug Products Compounded with BDS

Section 503A	Section 503B
• Must comply with 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, 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, appear on a **list of bulk drug substances** that can be used in compounding under section 503A developed by FDA through regulations	• Must appear on a **list** developed by FDA **of bulk drug substances** that can be used in compounding under section 503B, 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

- Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the FD&C Act
- Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the FD&C Act

How Entries are Added to the 503A Bulks List

- Nominations for the 503A Bulks List may be submitted to docket FDA-2015-N-3534 at https://www.regulations.gov/document?D=FDA-2015-N-3534-0001
  - The Federal Register notice associated with this link provides instructions on the information that should be submitted with a bulk drug substance nomination
- FDA evaluates substances for inclusion on this list on a rolling basis and publishes notices in the Federal Register to communicate its intentions and decisions regarding groups of substances
  - Substances nominated for the 503A Bulks List with adequate support are reviewed by FDA and presented to the Pharmacy Compounding Advisory Committee which makes a recommendation on whether to add the substance to the list, then FDA publishes a proposed rule in the Federal Register, and a final rule in the Federal Register to add or not add a substance to the list
- The 503A Bulks List is codified at 21 CFR 216.23

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 31 bulk drug substances nominated for inclusion on the 503A bulks list
    - 5 bulk drug substances recommended for inclusion
    - 26 bulk drug substances recommended against inclusion
- Proposed rule
  - FDA is working on addressing additional substances in future rulemaking

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).

Development of 503B Bulks List

- Section 503B 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

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 provides 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.

How Entries are Added to the 503B Bulks List

- Nominations for the 503B Bulk List may be submitted to docket FDA-2015-N-3469 at https://www.regulations.gov/document?D=FDA-2015-N-3469-0001
  - The Federal Register notice associated with this link provides instructions on the information that should be submitted with a bulk drug substance nomination
- FDA evaluates substances for inclusion on this list on a rolling basis and publishes notices in the Federal Register to communicate its intentions and decisions regarding groups of substances
  - Substances nominated for the 503B Bulks List with adequate support are reviewed by FDA, and then FDA publishes its proposal to add or not add the substance to the list in a preliminary Federal Register notice, and then FDA publishes its decision to add or not add a substance to the list in a Federal Register notice
- The 503B Bulks List is housed on FDA's website

Current 503B Bulks List

- 503B Bulks List:
  - (1) Diphenylcyclopropenone (for topical use only).
  - (2) Glycolic Acid (for topical use in concentrations up to 70% only).
  - (3) Quinacrine HCl (for oral use only).
  - (4) Squaric Acid Dibutyl Ester (for topical use only).
  - (5) Trichloroacetic Acid (for topical use only).

Evaluation Process

503A Evaluation Process

- FDA evaluates:
  - Information provided by the nominator
  - Publicly available information from published medical literature, clinical guidelines, various databases/websites, etc.
- FDA assesses each substance according to four criteria:
  1) Physical and chemical characterization
  2) Safety issues raised by use in compounded products
  3) Evidence of effectiveness or lack of effectiveness
  4) Historical use in compounded products
- FDA considers each criterion in the context of the others and balances them

Differences Between NDA and Compounding

New Drug Approval Process	Bulks List Process (Compounding)
New drug application (NDA) is submitted to FDA by a **sponsor (section 505 of the FD&C Act)**	**Nomination** of a bulk drug substance (active pharmaceutical ingredient) to FDA by a **nominator (section 503A or 503B of the FD&C Act)**
Sponsor submits data, required to demonstrate **substantial** evidence of effectiveness and show the drug is safe for intended use. Clinical data usually from adequate and well-controlled trials.	**Nominator** submits publicly available evidence of effectiveness and safety information to support nomination. Nominations must include a bibliography of safety and efficacy information, including any relevant peer-reviewed medical literature.
Sponsor applies for the drug's use in specific **indication(s)**	Nominator provides **proposed use(s)** for the compounded drug product
FDA reviews Chemistry, Manufacturing, and Controls (CMC) information and **final product formulation** (i.e., the finished dosage form containing active and any inactive ingredients).	FDA evaluates **active pharmaceutical ingredient** (drug substance). FDA does not evaluate specific drug product formulations or manufacturing processes.

Differences Between NDA and Compounding (continued)

New Drug Approval Process	Bulks List Process (Compounding)
Drug product labeling must meet content and format requirements (21 CFR 201).	Compounded drugs are **exempt from labeling** of drugs with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1)). For 503B compounded drugs, label and container must contain certain information, such as the statement "This is a compounded drug".
FDA generally performs premarket assessment of the establishments where drug product will be manufactured (part of the NDA approval process).	No premarket inspection and finding of manufacturing quality. FDA conducts surveillance, for-cause inspections (503A) or inspects according to a risk-based schedule (503B). Inspection is not drug-specific.
Drug is **FDA-approved.**	Compounded drugs are **not FDA-approved.** Inclusion on the 503A or 503B list should not be equated with FDA approval, endorsement, or recommendation.

503A Substance Example 1

Melatonin

503A Example: Melatonin Nomination

- Melatonin was nominated for oral use for the treatment of sleep disorders in children and adolescents with autism spectrum disorder (ASD), 0.2 mg - 5 mg
- There are no FDA-approved products for the treatment of insomnia in children and adolescents

503A Example: Melatonin

- A neurohormone that plays a key role in regulating the sleep-wake circadian rhythm
- Sleep disorders are more common and severe in children with neurodevelopmental disorders like ASD
  - 44% to 83% of children with ASD are reported to experience sleep disorders
  - Coexisting sleep disorders can have significant effects on patient health and quality of life, family functioning, and can worsen the core symptoms of ASD

Melatonin: 4-Criteria Evaluation

1. Physical and Chemical Characterization
   - Easily characterized and preparation of melatonin has been well-developed
2. Safety (Nonclinical and clinical data)
   - Relatively safe and without serious adverse events (AEs)
3. Effectiveness
   - Studies showed treatment response for *short-term treatment of sleep disorders* in children with ASD
   - American Academy of Neurology (AAN) and American Academy of Pediatrics (AAP) practice guideline recommend melatonin in ASD population
   - European Medicines Agency (EMA) licensed a prolonged-release dosage form of melatonin in ASD
4. Historical use
   - Used in pharmacy compounding since 2009 in a variety of dosage forms
   - Melatonin is approved for use in Europe, Australia, and Japan

- **The Division of Psychiatry was consulted and provided assistance and input on the review. The Division of Pediatrics and Maternal Health provided assistance and input.**

Melatonin Evaluation

- **June 2021:** Melatonin presented and discussed at PCAC meeting
  - FDA recommendation: a balancing of the four criteria *weighed in favor* of adding melatonin to the list
  - PCAC voted to include on the 503A Bulks List

503A Substance Example 2

Oxitriptan (5-HTP)

503A Example: Oxitriptan

- Oxitriptan (5-hydroxytryptophan, 5-HTP) is a chemical precursor in the biosynthesis of the neurotransmitter serotonin from tryptophan.
- **2014:** Nominated for use in depression and sleep disorders
- **June 2015:** Oxitriptan discussed at PCAC meeting
  - FDA evaluated for inclusion on the list (using 4 criteria) for depression and sleep disorders.
    - Did not recommend adding to the list due to lack of evidence of effectiveness and safety concerns
  - PCAC voted not to include on the 503A Bulks List.

503A Example: Oxitriptan

- **December 2016:** Proposed Rule published to not include on the 503A Bulks List
- **February 2019:** Final Rule published, not included on the List
  - Healthcare providers and caregivers of patients with tetrahydrobiopterin (BH4) deficiency contacted FDA expressing oxitriptan is an essential and standard treatment for BH4 deficiency (rare disease)
  - FDA received a citizen petition that compounded drug products containing oxitriptan are used to treat patients with BH4 deficiency
- **July 2019:** FDA issued guidance it does not intend to take action against compounders who use oxitriptan for BH4 deficiency
- **June 2021:** FDA reevaluated oxitriptan for use in BH4 deficiency

BH4 Deficiency

- BH4 deficiency is a group of treatable genetic neurotransmitter disorders
  - Manifests with hyperphenylalaninemia and deficiency of oxitriptan and L-dopa (precursors to neurotransmitters serotonin and dopamine)
  - Symptoms include motor dysfunction, impaired muscle tone, movement abnormalities, intellectual disabilities, and seizures
- Treatment should be initiated as early as possible
- Late detection and late initiation of effective treatment can lead to irreversible brain damage

BH4 Deficiency and Oxitriptan

- Treatment strategy:
  - Restricted phenylalanine diet and/or BH4 replacement
  - Substitute depleted neurotransmitters with precursors
- Oxitriptan considered first-line treatment according to the International Working Group on Neurotransmitter Related Disorders (iNTD) consensus guideline and a standard therapy per National Organization for Rare Disorders (NORD)
- Recommended pediatric oral dose is 4 to 10 mg/kg/day. Starting dose is 1 to 2 mg/kg/day, divided in 3 to 6 doses per day, with slow titration
- Dose is adjusted depending on clinical response

Oxitriptan: 4-Criteria Evaluation

1) Physical and Chemical Characterization
   - Well-characterized and likely to be stable in solid and solution formulations
2) Safety
   - Nonclinical: Available nonclinical data did not identify safety concerns
   - Clinical: Most common AEs include gastrointestinal symptoms, irritability, motor disorders, sweating. Potential risk of serotonin syndrome.
3) Effectiveness
   - Considered a standard therapy with numerous case reports
4) Historical Use
   - Used in compounding since 2011 based on literature; dosing for children first described in 1975

The Division of Rare Diseases and Medical Genetics was consulted and provided assistance and input on the review.

Oxitriptan Evaluation

- **June 2021:** Oxitriptan presented and discussed at PCAC meeting
  - FDA recommendation: a balancing of the four criteria *weighed in favor* of adding oxitriptan to the list
  - PCAC voted to include on the 503A Bulks List

Resources on Human Drug Compounding

- Guidance for Industry *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* Guidance (March 2019) https://www.fda.gov/media/121315/download

- Guidance for Industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017) https://www.fda.gov/media/94402/download

- Guidance for Industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (January 2017) https://www.fda.gov/media/94398/download

Resources on Human Drug Compounding

- FDA's website on Human Drug Compounding: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding
- Section 503A of FD&C Act Provisions: https://www.fda.gov/drugs/human-drug-compounding/section-503a-federal-food-drug-and-cosmetic-act
- Section 503B of FD&C Act Provisions: https://www.fda.gov/drugs/human-drug-compounding/text-compounding-quality-act
- Laws and policies that govern our work: https://www.fda.gov/drugs/human-drug-compounding/compounding-laws-and-policies
- Other FD&C Act Provisions relating to Compounding: https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding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