



FDA Update on Drug Compounding

Julie Dohm, J.D., Ph.D.

Senior Science Advisor for Compounding, CDER

Agency Lead on Compounding, FDA

Outline

- Regulatory Framework
- Compounding Program
 - Compounding Policy
 - Inspections and Enforcement
 - Stakeholder Engagement

Compounding Provisions of Federal Law

Section 503A (enacted 1997)	Section 503B (enacted 2013)
<p>Conditions under which drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, can qualify for exemptions from certain 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 can qualify for exemptions from certain 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>

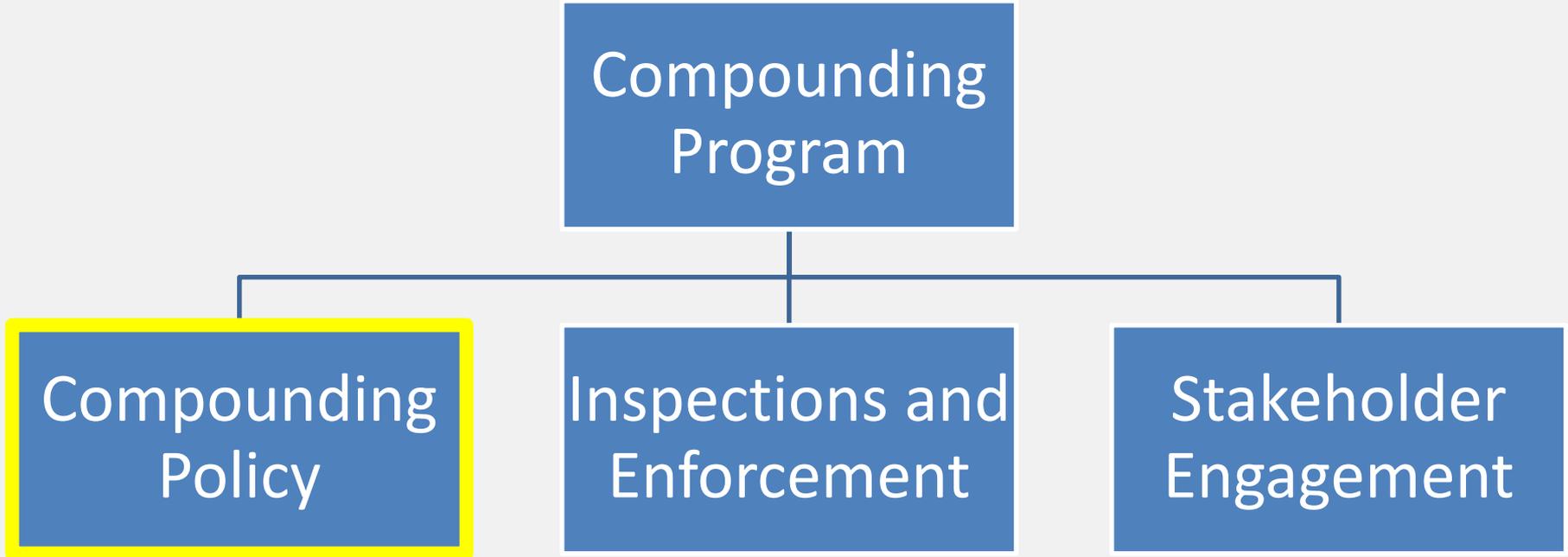
Compounders under Section 503A

- State-licensed pharmacies (e.g., hospital and community pharmacies), Federal facilities, physicians
- Number in the many thousands
- Generally do not register with FDA
- Pharmacies primarily overseen by the states
 - State-to-state variation in quality standards and frequency and depth of state oversight of pharmacies
 - Compounding physicians are generally not routinely overseen by any regulatory body

Outsourcing Facilities under Section 503B

- Section 503B defines “outsourcing facility” as a facility 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
- In addition, an outsourcing facility:
 - Is NOT required to be a licensed pharmacy, but compounding must be by or under the direct supervision of a licensed pharmacist
 - May or may not obtain prescriptions for identified individual patients
- Outsourcing facilities are subject to CGMP requirements
- ~75 outsourcing facilities registered with FDA as of 9/28/18

Policy, Oversight, and Stakeholder Engagement



FDA Compounding Policy Goals and Considerations

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

ACCESS	Preserve access to compounded drugs when patients have a medical need for them.
QUALITY	Promote the compounding of drugs under appropriate conditions.
NECESSITY	Encourage use of FDA-approved drugs when they meet a patient's medical needs.

Final Guidances and Regulations Issued

- Final Guidances
 - Compounding and repackaging of radiopharmaceuticals
 - Compounded drugs that are essentially copies
 - Facility Definition
 - Mixing, diluting, and repackaging biological products
 - Interim policies on compounding from bulk drug substances
 - Repackaging drugs
 - Prescription requirement under section 503A
 - 503B product reporting
 - Compounding under section 503A
 - 503B adverse event reporting
 - 503B registration
 - Entities considering whether to register under section 503B
 - 503B fees
- Final Rules
 - Modifications to the withdrawn or removed list under sections 503A and 503B

Examples of Policy Documents Under Development

- Draft or Revised Draft Guidances
 - Insanitary conditions
 - Evaluation of bulk drug substances under section 503B
 - Hospital and health system compounding
 - CGMP Interim Guidance for Outsourcing Facilities
- Proposed Rules
 - Bulk drug substances list under section 503A
 - Modifications to the withdrawn or removed list under sections 503A and 503B
- Proposed Federal Register Notices
 - Bulk drug substances list under section 503B
- Revised draft memorandum of understanding

Examples of Policies Applicable to Compounders under Section 503A

- FDA-State Memorandum of Understanding
- Compounding using bulk drug substances under section 503A
- Compounded drug products that are essentially copies of a commercially available drug product under section 503A
- Prescription requirement under section 503A

FDA-State Memorandum of Understanding

Statutory Framework

Under section 503A(b)(3)(B), a compounded drug may be eligible for the exemptions only if it is compounded in a State—

- (i) that has entered into an MOU with FDA which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or
- (ii) that has not entered into the MOU and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5% of the total prescription orders dispensed or distributed by such pharmacy or physician.

Why is interstate distribution addressed?

- Compounders operating under section 503A are mainly overseen by their home state regulator.
- Congress did not intend for compounders operating under section 503A to grow into conventional manufacturing operations conducting a substantial portion of their business interstate without adequate oversight.
- If a substantial proportion of a compounder's drugs are distributed outside of a State's borders, adequate regulation of those drugs can pose logistical, regulatory, and financial challenges to State regulators; it can be difficult to investigate and address multi-state outbreaks.

Revised Draft FDA-State Memorandum of Understanding

- The MOU
 - Addresses “the distribution of inordinate amounts of compounded drug products interstate,” and
 - Provides “for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State”
 - Is developed in consultation with the National Association of Boards of Pharmacy (NABP)
- Next Steps
 - 90-day comment period (ending on December 10, 2018)
 - Review comments submitted and make revisions, as appropriate, to address comments
 - Develop and publish final MOU
 - Offer the MOU to states to consider signature for a period (proposal is 180 days) before beginning to enforce the 5% statutory limit on distribution out of the state for compounders located in states that have not signed the MOU

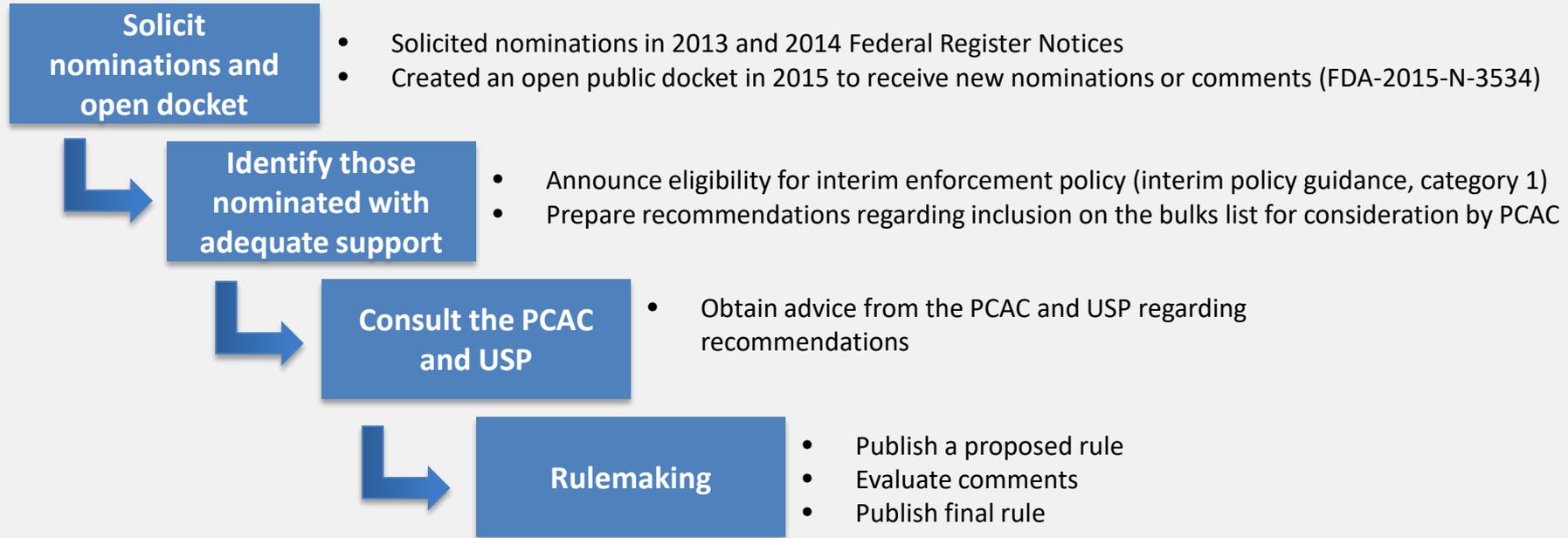
Bulks Provisions under Section 503A

Statutory Framework

A drug may be compounded using bulk drug substances that:

- comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;
- if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
- if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d)

Section 503A Bulks List: Process



Development of Section 503A Bulks List

Pharmacy Compounding Advisory Committee (PCAC)

- Provides advice on scientific, technical, and medical issues concerning certain provisions of sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act
 - PCAC materials are available at:
<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/default.htm>
- Majority of committee members have experience related to drug compounding
- 9 meetings
- 53 bulk drug substances considered

Rulemaking

- Proposed rule describes criteria for evaluating the bulk drug substances and addresses 10 bulk drug substances nominated for inclusion on the 503B bulks list
 - 6 recommended for inclusion
 - 4 recommended against inclusion
- FDA is working on addressing additional substances in future rulemaking

Essentially a Copy under Section 503A

Statutory Framework

- To qualify for the exemptions under section 503A, a drug product must be compounded by a compounder that 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.”
- 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.”

Importance of Copies Provision

- Copies provisions are important to help to:
 - Ensure that patients do not receive a compounded drug when an approved or commercially available drug would meet their medical needs. Patients should not be unnecessarily exposed to drug products that have not been shown to be safe and effective.
 - Protect the integrity and effectiveness of the drug approval process. Distribution of compounded copies undermines the incentive for sponsors to seek approval of innovative, life-saving new drugs, or of generic drugs.

Final Guidance: Compounded Drug Products that Are Essentially Copies of a Commercially Available Drug Product under Section 503A

- The guidance sets forth FDA’s policies regarding
 - the statutory terms, including “commercially available,” “essentially a copy of a commercially available drug product,” and “regularly or in inordinate amounts”
 - the prescriber’s determination of significant difference
 - Documentation
 - No particular format (e.g., “No Dye X, patient allergy)
 - The significant difference that the prescriber identifies must be produced by the change between the compounded drug and the comparable commercially available drug

Prescription Requirement under Section 503A

- Statutory Framework
 - Section 503A(a) of the FD&C Act requires that compounding under this section be based on the receipt of a valid prescription for an identified individual patient
 - Compounding can occur:
 - In limited quantities before the receipt of such a prescription, or
 - After the receipt of the prescription.
- Importance of Prescription Requirement
 - Ensures that compounding under section 503A is based on individual patient need
 - Establishes clear lines of accountability between FDA and States
 - Distinguishes compounders under section 503A from outsourcing facilities under section 503B. Outsourcing facilities may or may not obtain prescriptions for their compounded drugs.
- FDA Final Guidance issued December 2016

Office Stock and Access

- Some stakeholders have expressed concerns that:
 - Outsourcing facilities cannot meet healthcare providers' needs for compounded drugs for office use.
 - Many compounding pharmacies that want to distribute office stock cannot register as outsourcing facilities because CGMP compliance is too onerous.
- FDA is engaged in numerous efforts to help outsourcing facilities meet their intended role in the continuum of care for patients.
 - FDA posts lists of drug products that outsourcing facilities report making over prior six-month periods to help health care practitioners identify and access specific compounded drugs.
 - FDA is developing a risk-based approach to CGMP requirements for outsourcing facilities that may make it more feasible for certain smaller compounders to become outsourcing facilities.

Examples of Policies Applicable to Outsourcing Facilities under Section 503B

- CGMP interim draft guidance for outsourcing facilities
- Compounding using bulk drug substances under section 503B
- Compounded drug products that are essentially copies of approved drug products under section 503B

Draft CGMP Interim Guidance for Outsourcing Facilities

- Outsourcing facilities are subject to CGMP requirements for finished pharmaceuticals in 21 CFR Parts 201 and 211. FDA is working on CGMP regulations specific to outsourcing facilities. In the interim, FDA has issued guidance that, when final, will describe FDA's expectations regarding compliance with CGMP requirements in part 210 and 211 until the new regulations are developed.
- FDA is currently revising its July 2014 draft guidance in response to stakeholder feedback, and is considering how CGMP requirements should be applied in light of the size and scope of an outsourcing facility's operations.
- Policy goal is to make it more feasible for more compounding pharmacies that can meet the more stringent production standards to register as 503B outsourcing facilities. This should promote more patient access to higher quality compounded medicines.

Bulks Provisions under Section 503B

- Bulk drug substances used in compounding under section 503B must either:
 - Appear on a list established by FDA identifying bulk drug substances for which there is a clinical need (“bulks list”), or
 - The drug compounded from such bulk drug substance must appear on the drug shortage list at the time of compounding, distribution, and dispensing.
- In March 2018, FDA published the draft guidance, titled *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B*
 - The draft guidance describes the criteria it intends to apply to evaluate whether there is a clinical need for outsourcing facilities to compound with nominated bulk drug substances.
 - Limiting the 503B list to substances for which there is a clinical need:
 - Reduces patient exposure to drugs that have not been demonstrated to be safe and effective to those situations in which the drug is necessary for patient treatment
 - Preserves incentives for sponsors to invest in the research and testing required to obtain FDA approval

Section 503B Bulks List: Process

Solicit nominations and open docket

- See 2013, 2014, and 2015 FRNs

Identify substances nominated with adequate support

- Announce eligibility for enforcement policy
- Prepare recommendations regarding inclusion on the bulks list

Federal Register Notice and PCAC consultation as needed

- Publish proposed determinations on specific bulks
- Consult PCAC if needed
- Publish final determinations on specific bulks

Proposal in Federal Register Regarding Three Bulk Drug Substances

- FDA has issued a proposal not to include three bulk drug substances –bumetanide, nicardipine hydrochloride, and vasopressin—on the 503B Bulks List.
 - Substances are components of FDA-approved drug products.
 - Nominations did not indicate why the FDA-approved drug products containing these substances could not be either used or adapted instead of a bulk drug substance.
- Proposal in FRN states that at this time we do not find clinical need for an outsourcing facility to use these bulk drug substances to compound finished products.
- Public comment on the proposals ends on October 29, 2018.

Collaborative Agreements

- New research collaborations to support development of the 503B bulks list with the University of Maryland and Johns Hopkins University - two of FDA's Center of Excellence in Regulatory Science and Innovation (CERSI) partners.
- [University of Maryland](#) will be working closely with medical specialty groups and researching information about the use of drug products including certain bulk drug substances historically and in current clinical practice.
- [Johns Hopkins University](#) will focus on bulk drug substances identified as used to compound drugs for patients with autism spectrum disorder by systematically studying any available information concerning the safety and effectiveness and use in clinical practice of such substances.
- These projects will help inform the FDA's regulatory decision-making, including whether to place the evaluated substances on the 503B bulks list.

Essentially a Copy under Section 503B

Statutory Framework

- To qualify for the exemptions under section 503B, the drug must not be essentially a copy of one or more approved drugs.
- A compounded drug is essentially a copy if:
 - It is **identical or nearly identical** to a marketed unapproved OTC drug or an approved drug that is not on FDA's drug shortage list at the time of compounding, distribution, and dispensing; or
 - It is not identical or nearly identical, but it **contains a bulk drug substance that is a component of an approved drug** or a marketed unapproved OTC drug, unless—
 - a prescriber determines that there is a change between the compounded drug and the comparable approved drug that produces a clinical difference for an individual patient.

Final Guidance

- Sets forth policies regarding
 - statutory terms, including “identical or nearly identical,” and
 - the prescriber determination of clinical difference

Examples of Policies Applicable to Compounders under Sections 503A and 503B

- Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
- Mixing, diluting, or repackaging biological products outside the scope of an approved biologics license application
- Insanitary Conditions

Repackaging

- Many compounders, including pharmacies and outsourcing facilities, repackage drugs. However, repackaging is not addressed in section 503A or section 503B, and repackaged drugs are generally subject to all provisions of the FD&C Act that apply to the production of drugs.
- Final guidance, “Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities,” describes conditions under which FDA does not intend to enforce new drug approval, labeling with adequate directions for use, and, except with respect to outsourcing facilities, current good manufacturing practice requirements, when state-licensed pharmacies, Federal facilities, and outsourcing facilities repackage drugs.
- Examples of the conditions:
 - Drug product is assigned a beyond-use-date in accordance with the guidance
 - State-licensed pharmacy (not an OF) or federal facility distributes the repackaged drug only after receipt of a valid prescription for an identified individual patient

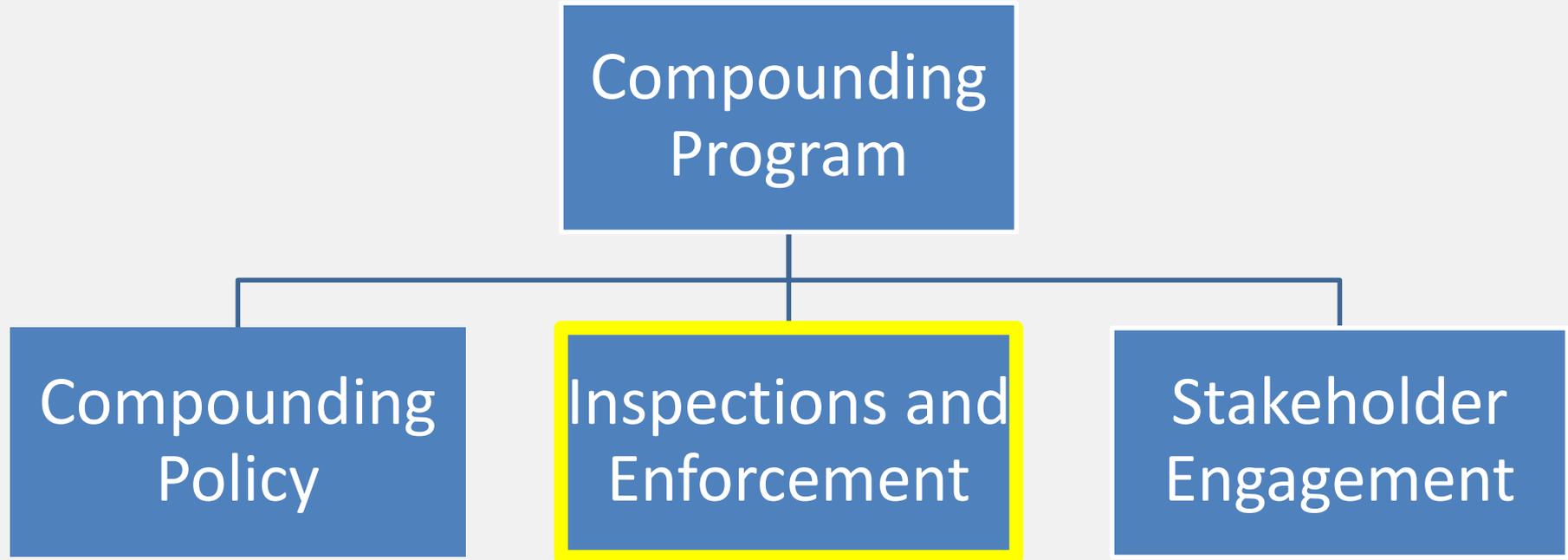
Mixing, Diluting, or Repackaging Biological Products

- Biological products subject to licensure in a biologics license application under the Public Health Service Act are not covered by sections 503A or 503B, and therefore are not eligible for the exemptions in those sections.
- Guidance explains conditions under which FDA does not intend to take action for certain violations of the law when certain biological products are mixed, diluted, or repackaged in a manner not described in their approved labeling.
- These conditions are intended to reduce the public health risks of mixing, diluting, or repackaging biological products, while preserving access to those products. For example:
 - Limited beyond use dates, with mechanism for outsourcing facilities to assign beyond use dates to repackaged biological products based on data
 - Mixing, diluting, or repackaging does not conflict with approved product labeling (e.g., storage and handling conditions)

Insanitary Conditions

- Federal law provides that a drug is adulterated if it was prepared, packed, or held under insanitary conditions whereby it may become contaminated with filth or rendered injurious to health.
- Under federal law, the prohibition on insanitary conditions applies to compounders that meet the conditions of section 503A and outsourcing facilities that meet the conditions of section 503B, and other entities that produce drugs.
- FDA revised draft guidance issued September 2018 provides examples of insanitary conditions related to:
 - Aseptic practices
 - Equipment/facilities
 - Sterilization
 - Cleaning and disinfecting
- The 60-day comment period ends November 26, 2018.

Inspections and Enforcement



FDA Oversight Priorities

- Focus oversight on entities whose practices may have the greatest impact on public health
 - Conduct oversight of the outsourcing facility sector to evaluate compliance with the law, encourage voluntary compliance, and pursue regulatory action when necessary.
 - Conduct risk-based oversight of entities that are not outsourcing facilities, but that engage in multi-state, large volume distribution of compounded drugs. These compounders' interstate operations may present challenges for state regulators, and their practices may have widespread, nationwide impact.
 - In general, FDA does not intend to engage in routine surveillance of state-licensed pharmacies that operate within their state.

When FDA Conducts a Compounding Inspection

For-cause (>180 inspections conducted)

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

Surveillance (>230 inspections conducted)

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

Follow-Up (>130 inspections conducted)

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

Examples of Frequent Adverse Inspectional Findings

- Insanitary conditions
- CGMP violations (only applicable to outsourcing facilities and pharmacies not in compliance with 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



Ceiling above the doorway to cleanroom with exposed insulation



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

(b) (4)

Insanitary Condition Example



Equipment,
located in
cleanroom, used
to produce
injectable drugs
visibly dirty

Insanitary Condition Example



Gowned employee
working in the
cleanroom,
exposing legs

Insanitary Condition Example



Poor personnel practices – leaning into ISO-5

Average normal human sheds about 37 million CFU/hour

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



Observed conditions:
Stain due to product which had exploded due to excessive pressure applied when forcing product through a sterilizing filter. The device used to force through filter was a non-sterilized caulking gun.



Insanitary Condition Example



Coffee filters used to filter particulates in suspensions prior to filling and autoclaving



Insanitary Condition Example



Insects (vermin)
dead or alive

Frequent FDA actions taken

VOLUNTARY RECALLS

Informal recommendations
for voluntary recalls

Formal FDA requests for voluntary
recalls

ADVISORY ACTIONS

Warning letters

Untitled letters

ENFORCEMENT ACTIONS

Civil injunctions

Criminal actions

Seizures

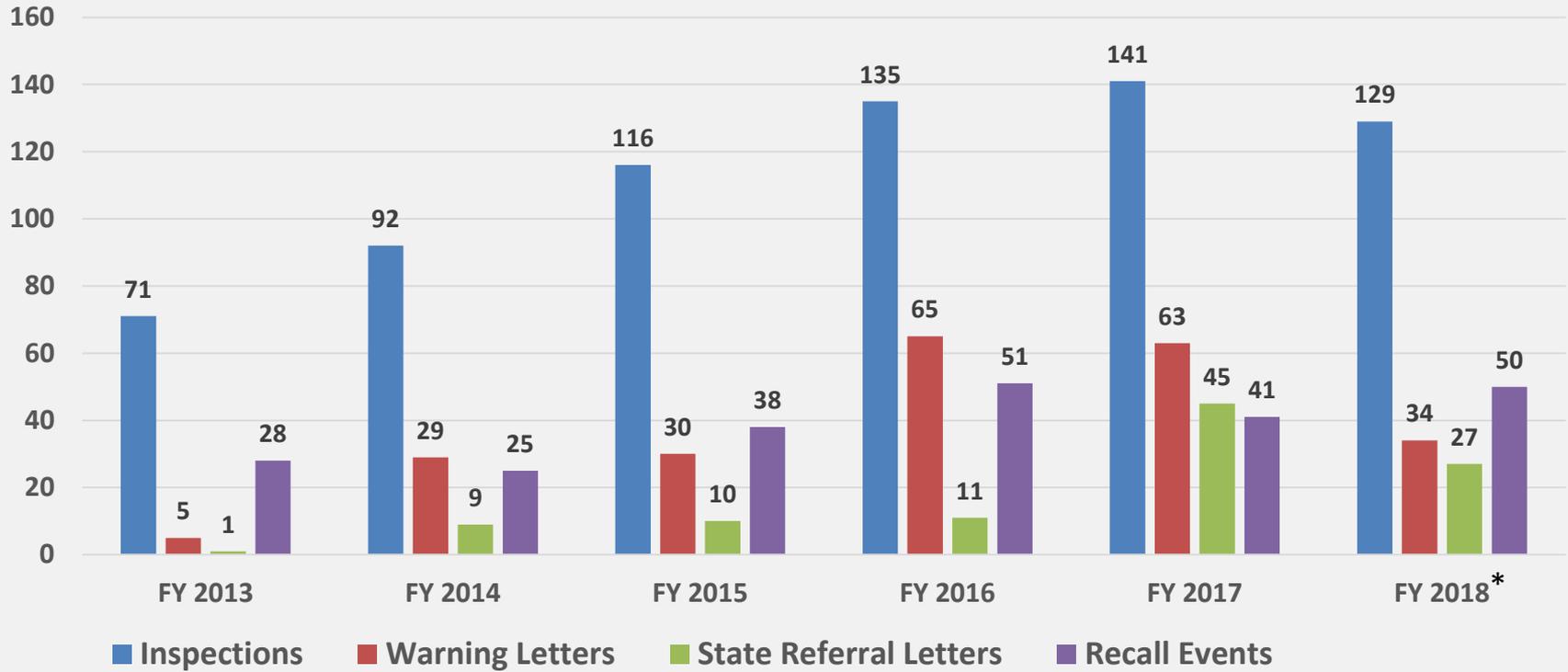
STATE REFERRALS

For 503A facilities

Inspectional findings

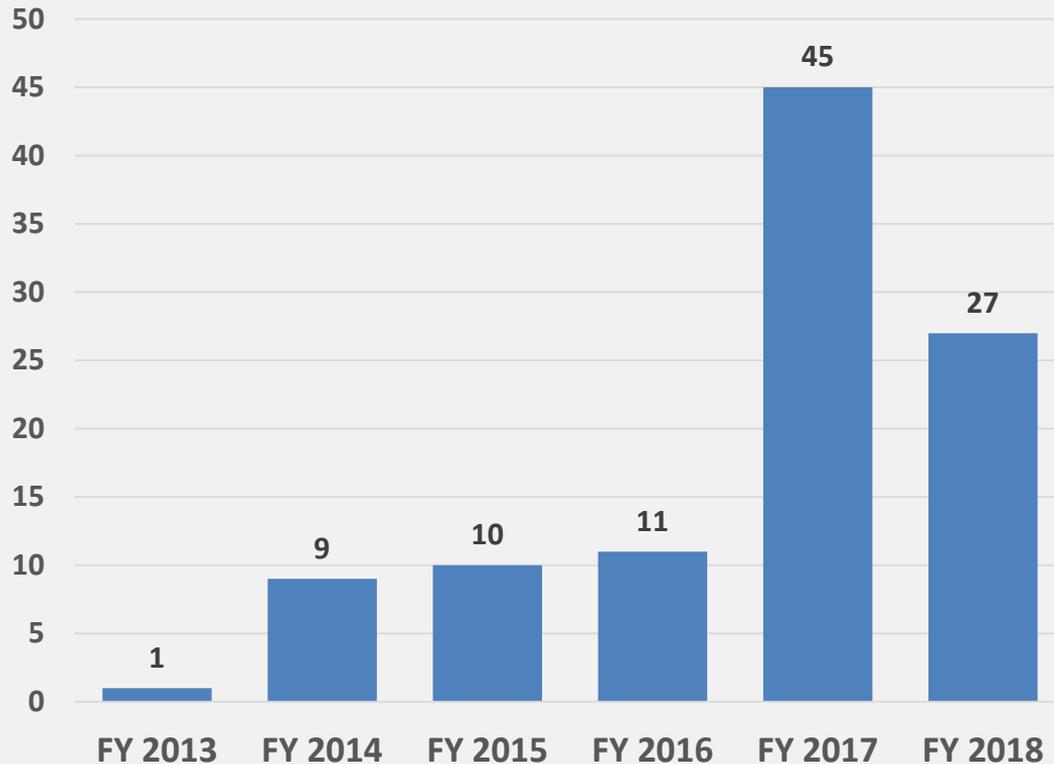
Complaints

Inspections, Oversight Actions, and Recalls



*Preliminary data

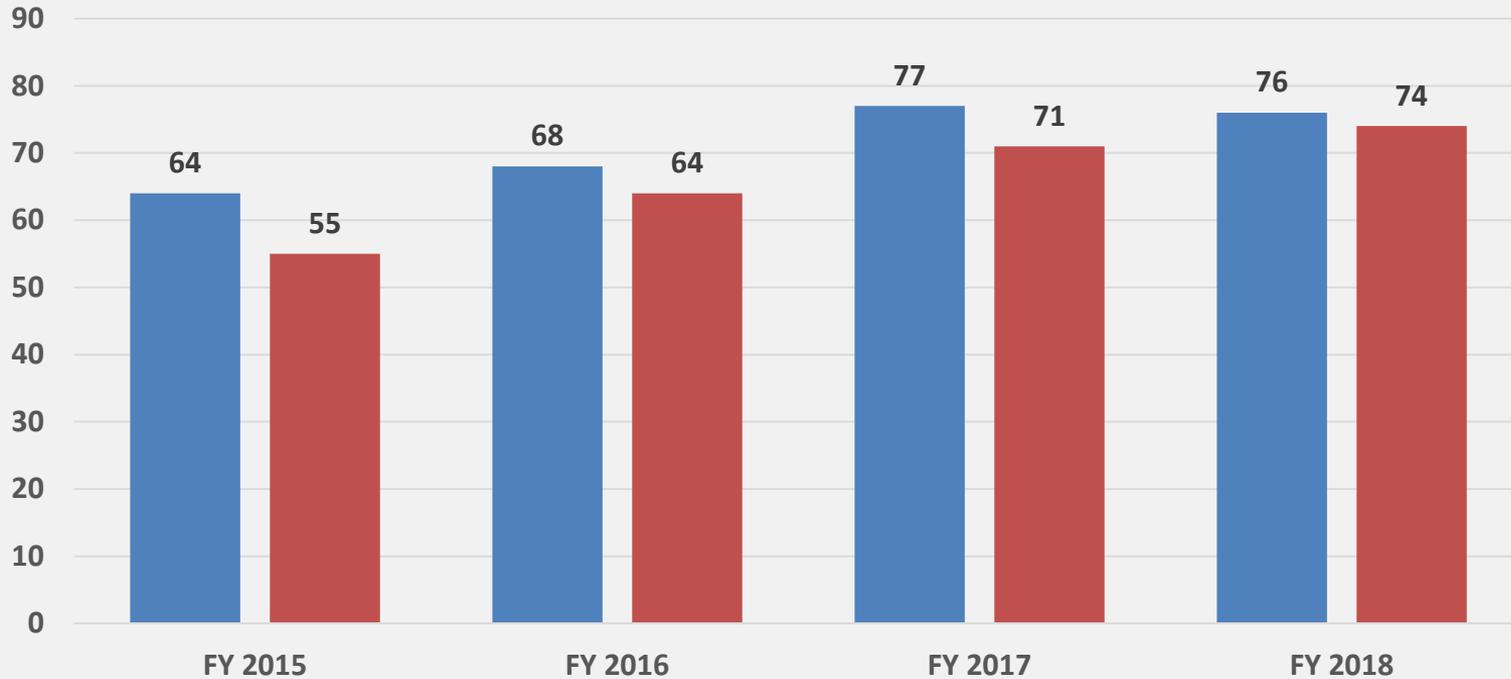
Compounding State Referral Letters



FDA refers inspectional findings for a pharmacy to a state for further action when a pharmacy

- Appears to be obtaining prescriptions for identified individual patients,
- Has promised to correct deviations, and
- Corrective actions can be appropriately overseen by the state.

Outsourcing Facility Registration



■ Total Outsourcing Facilities Registered
■ Outsourcing Facilities Registered at End of FY

Stakeholder Engagement



Stakeholder Collaboration

- Objectives
 - Learn stakeholders' views regarding proposed policies, including feedback about adequacy of public health protections and implications for current practice
 - Improve compliance by responding to questions and providing guidance on ways to comply with statutory requirements
- Opportunities for collaboration
 - Annual listening sessions with up to 75 stakeholder groups each year
 - Numerous inquiry responses
 - Notice-and-comment guidance development process
 - Ad hoc listening sessions with individual organizations as resources permit
 - Conferences

State Regulator Collaboration

- Objectives
 - Clarify areas of primary responsibility
 - Discuss emerging issues of mutual concern
 - Share updates on FDA/State policy and enforcement matters
 - Identify opportunities for improved FDA/State collaboration
- Opportunities for collaboration
 - Annual Intergovernmental Working Meetings
 - States invited to join FDA on all inspections of compounders
 - Monthly meetings with the National Association of Boards of Pharmacy

Compounding Risk Alerts

- FDA began in 2017 to post “compounding risk alerts” to inform healthcare practitioners of adverse event reports associated with compounded drugs.
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570188.htm>
- Some FDA inspections are initiated when FDA receives adverse event reports from healthcare practitioners, patients, and others.
- FDA provides the information in the compounding risk alerts to health care professionals to help further the goal of promoting patient safety

2017-18: eye injections of a compounded drug linked to vision problems in at least 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.
- FDA testing of Guardian's product and in-house samples revealed:
 - 12% w/v poloxamer 407. This amount is much > the poloxamer amounts in FDA-approved ophthalmic products (e.g., 0.1-0.2%), and poloxamer 407 is not used in any FDA-approved drug product intended for intravitreal injection.
 - Poloxamer 407 degraded upon autoclaving and sonication.
- FDA alert: <https://www.fda.gov/Drugs/DrugSafety/ucm569114.htm>



2018: differences in strength expression on compounded product labels may lead to dosing errors

- FDA received two Medwatch reports and multiple complaints concerning medication errors associated with overdoses of compounded injectable products that were labeled with the strength per mL in large font (e.g., 50 mcg/mL) and the strength per total volume (2,500 mcg/50 mL) in smaller font.
- These types of dosing errors could be avoided for small volume parenteral products by expressing the drug strength per total volume as the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses.
- FDA Alert:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm621769.htm>



THANK YOU

ANY QUESTIONS?