FDA Update on Compounding

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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 (FD&C Act) if certain conditions are met
  - Can serve an important patient need when FDA approved drugs are not available
- 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

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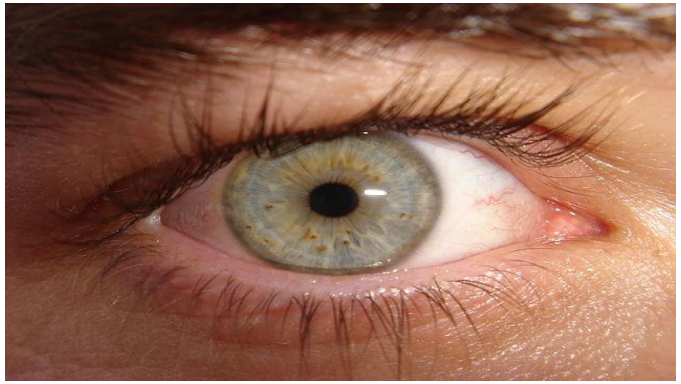
2017: eye injections of a compounded drug linked to vision problems in 43 patients

- 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.



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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 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 containing 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

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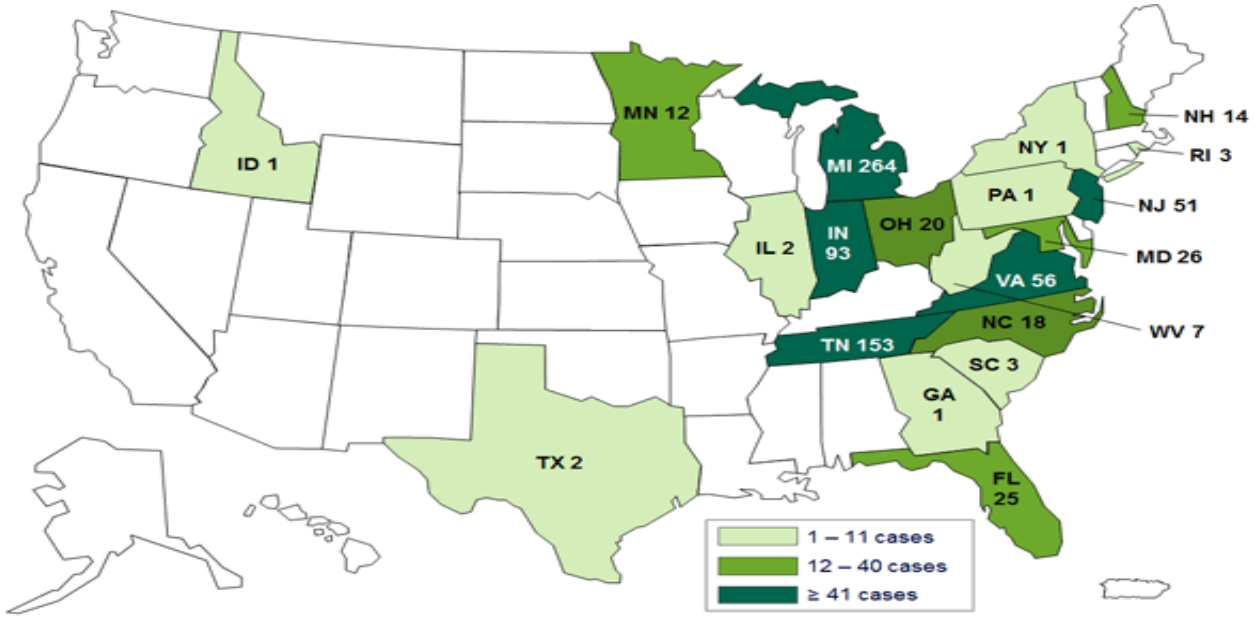
2016: compounded morphine sulfate linked to adverse events in three infants

- 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.

2012 Fungal Meningitis Outbreak

More than 750 cases of illness in 20 states

More than 60 deaths



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Drug Quality and Security Act of 2013

- Made clear that existing federal law applicable to drug compounding by licensed pharmacies and physicians—section 503A of the FD&C Act—was enforceable throughout the country by removing the advertising and promotion provisions that were held unconstitutional by the U.S. Supreme Court in 2002.
- Created new section 503B of the FD&C Act that established a new type of compounder called an "outsourcing facility." These facilities may distribute compounded medicines to hospitals and clinics without first receiving a patient-specific prescription. They are subject to current good manufacturing practice (CGMP) requirements.

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Statutory Framework

Section 503A	Section 503B
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 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** can 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.**

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Policy, Oversight and Enforcement, and Stakeholder Collaboration and Outreach

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FDA Policy Goals for Compounding

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

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Major Policy Considerations

- **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.
- **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, which may supply certain compounded drugs made subject to CGMP requirements.
  - FDA seeks to develop policies that promote the compounding of drugs under appropriate conditions.
- **Necessity**
  - Compounded drugs pose a higher risk to patients than FDA-approved drugs.
  - Compounding can reduce the incentives for investing 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.

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Final Guidances and Regulations Issued

- Final Guidances
  - Prescription requirement under section 503A
  - Repackaging drugs
  - Interim policies on compounding from bulk drug substances for 503A and 503B
  - 503B Product reporting
  - 503B Adverse event reporting
  - 503B Registration
  - Compounding under section 503A
  - Entities considering whether to register under section 503B
  - Fees for outsourcing facilities
- Final Rules
  - Modifications to the withdrawn or removed list under sections 503A and 503B

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Examples of Policy Documents Under Development

- Draft or Revised Draft Guidances
  - Current good manufacturing practice requirements for outsourcing facilities
  - Insanitary conditions
  - 503B facility definition
  - Radiopharmaceutical compounding
  - Compounded drugs that are essentially a copy (guidances for 503A and 503B)
  - Mixing, diluting, or repackaging biological products
  - Hospital and health system compounding
- Proposed Rules or FRNs (for 503A and 503B)
  - Bulk drug substances list
  - Withdrawn or removed list
- Draft memorandum of understanding

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Other Compounding Provisions

- Compounding by or under the direct supervision of a licensed pharmacist. Section 503B(a).
- List of drugs or categories of drugs that present demonstrable difficulties for compounding. Sections 503A(b)(3)(A) and 503B(a)(6).
- Compounding of drugs or components of drugs subject of a risk evaluation and mitigation strategy (REMS) approved with elements to assure safe use. Section 503B(a)(7).
- Prohibition on wholesaling. Section 503B(a)(8).

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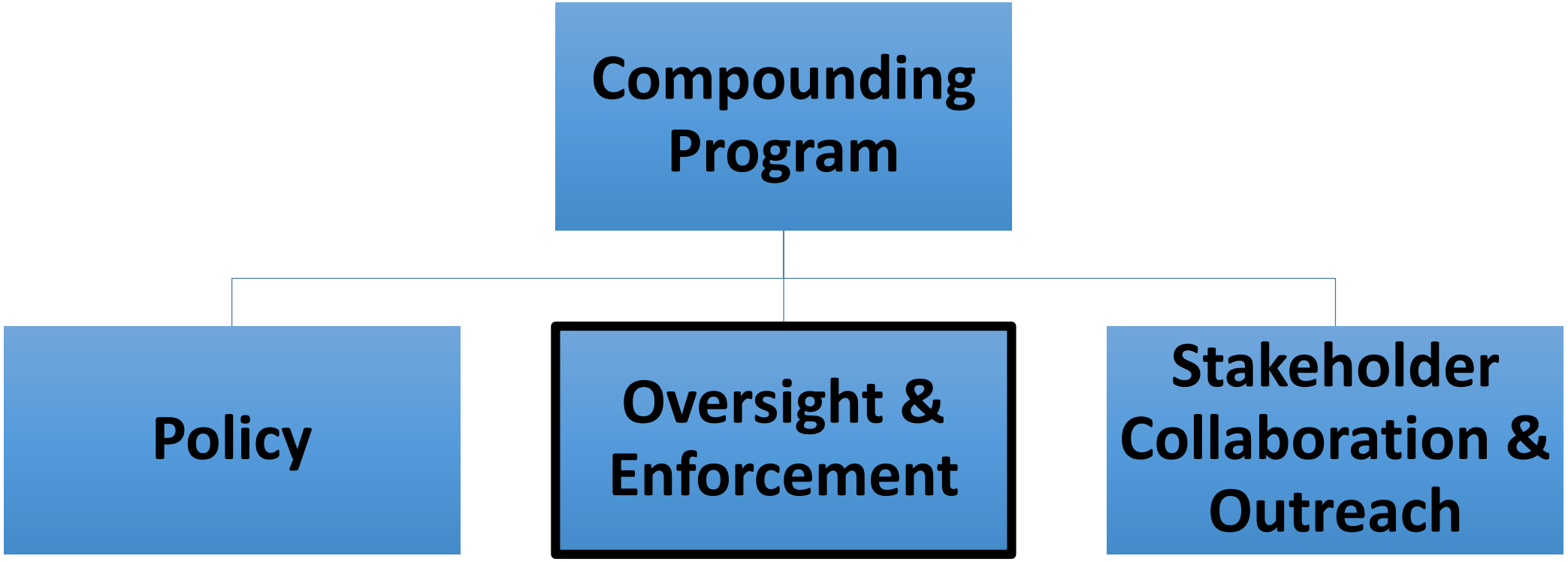

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Outsourcing Facilities under Section 503B

- 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

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Profile of Outsourcing Facilities

Of the 59 outsourcing facilities that FDA has inspected as of August 2017

- 25 engage in both sterile and non-sterile compounding
- 24 engage in both patient-specific and non-patient specific compounding
- 45 compound drugs from bulk drug substances
- Outsourcing facilities are located in 25 states
- 51 ship compounded drugs in interstate commerce
- In a six-month period, outsourcing facilities that submitted drug product reports to FDA compounded 12,305,873 units of drugs.

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Regulation of Outsourcing Facilities

- 72 Outsourcing Facilities, including 15 new registrants in FY17
- 38 Inspections of Outsourcing Facilities in FY 2017 (as of September)
- Must pay annual registration fees
- Must submit biannual product reports
- Must comply with all other conditions of section 503B
- Must comply with CGMP requirements

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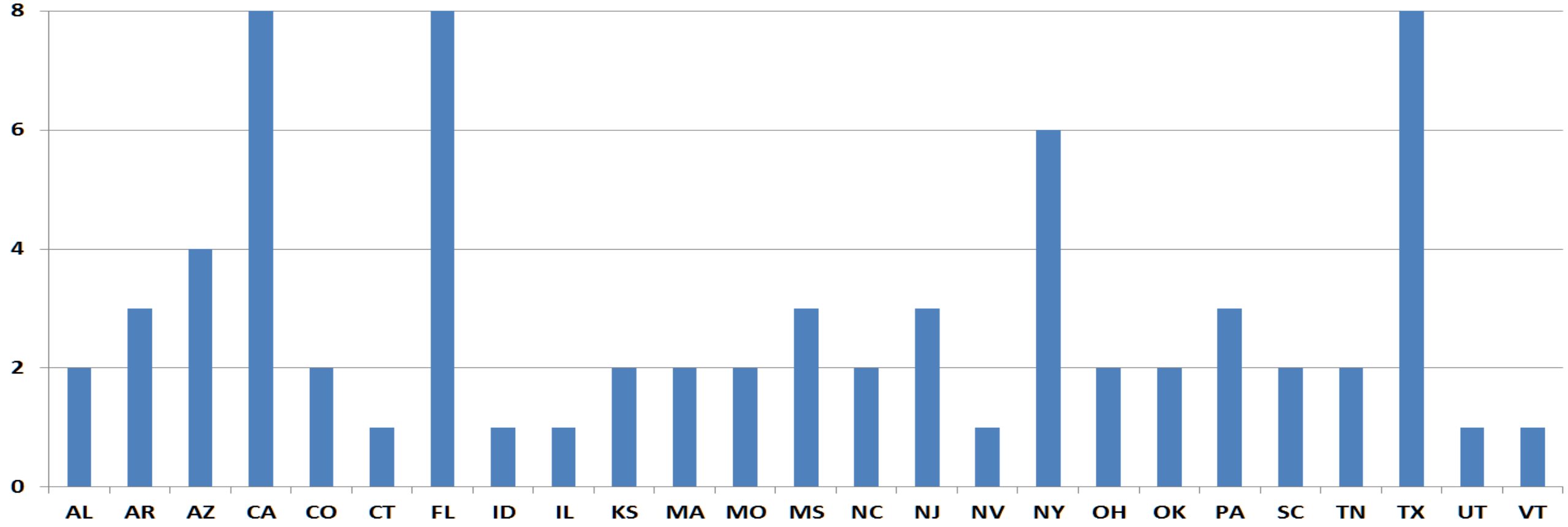
Outsourcing Facilities by State



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Outsourcing Facility Inspections

- FDA inspects outsourcing facilities upon initial registration, and conducts risk-based surveillance inspections thereafter. FDA also conducts for-cause inspections and follow-up inspections.
- FDA does not formally inspect until outsourcing facilities are operational.
- As resources allow, FDA entertains requests for preoperational site visits of outsourcing facilities to assess facility design, standard operating procedures, and other conditions that are critical to producing sterile drug products before the outsourcing facility initiates production for distribution.

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Compounders under Section 503A

- State-licensed pharmacies, Federal facilities, 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
  - Many states adopt in whole or in part USP Chapter 797

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Regulation of Compounders under Section 503A

- ~100 Inspections of compounders not registered as outsourcing facilities in FY 2017 (as of September)
- Must meet conditions of section 503A to qualify for exemptions from three requirements of the FD&C Act
- Must not compound drugs under insanitary conditions

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FDA Surveillance Inspections of Compounders under Section 503A

- FDA intends to focus its surveillance inspections on outsourcing facilities and other compounders that ship large volumes of compounded drugs to multiple states, which could
  - Help FDA identify firms that are distributing non-patient specific compounded drugs and should consider registering as outsourcing facilities;
  - Focus FDA oversight on facilities that, should quality issues occur, have the potential to affect the largest number of patients; and
  - Target FDA oversight in a manner that is useful to states, especially for those who are not able to conduct frequent oversight of nonresident pharmacies.
- FDA does not intend to conduct surveillance inspections of the vast majority of compounders that do not elect to register as outsourcing facilities and are primarily regulated by the states.

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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
  - Conferences

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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

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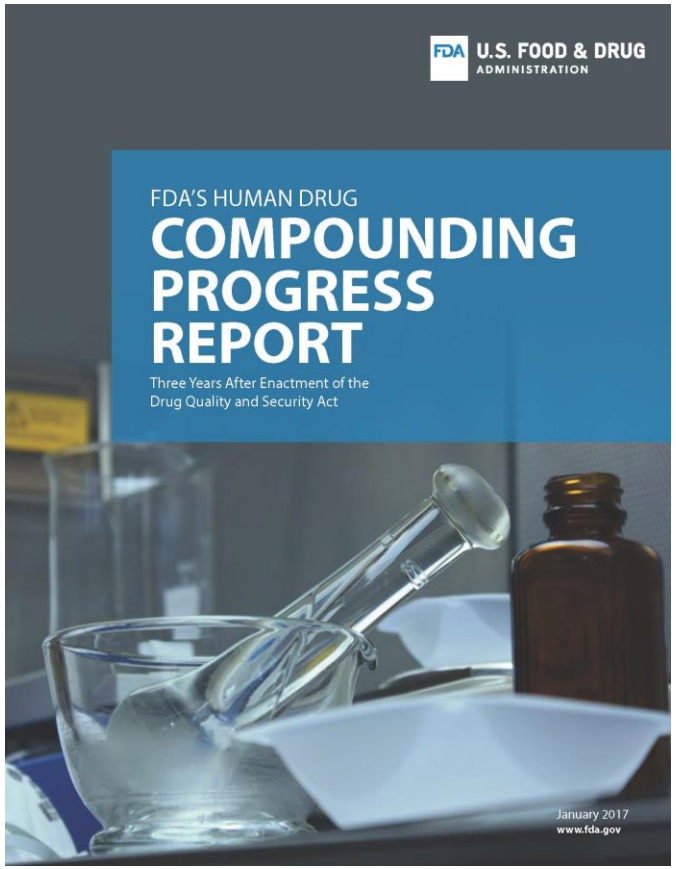
Compounding Progress Report

- Posted January 2017
- Describes FDA's efforts over the past three years
  - Conducting inspections of compounding facilities and taking regulatory actions in response to violations of law that put patients at risk
  - Issuing numerous policy documents
  - Convening many advisory committee meetings to obtain advice on scientific, technical, and medical issues concerning drug compounding
  - Working closely with our state partners
  - Conducting stakeholder outreach



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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.
- Going forward we will be posting “compounding risk alerts” to inform healthcare practitioners of adverse events associated with compounded drugs. **https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570188.htm**

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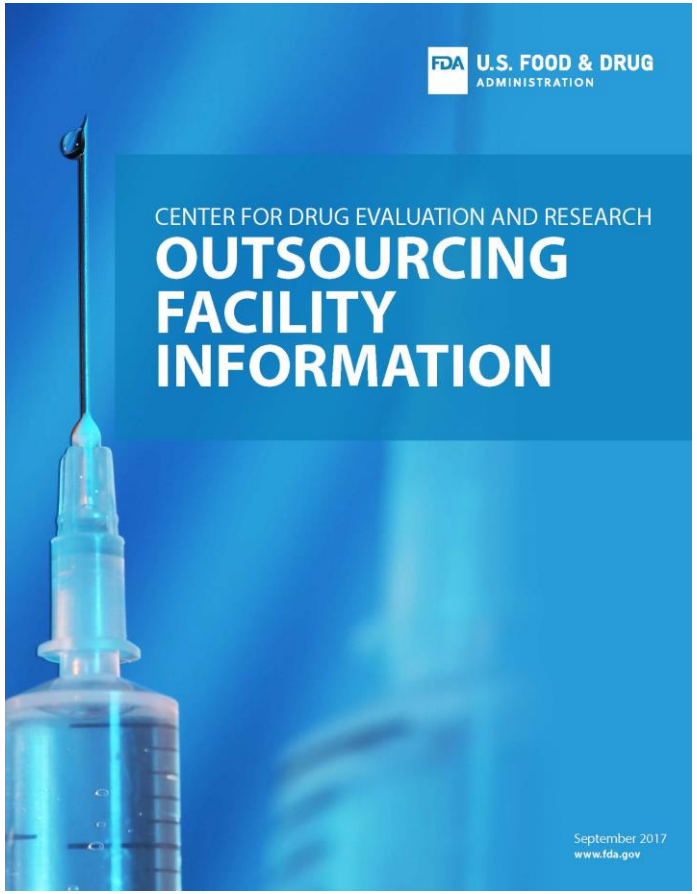
Outsourcing Facility Information

- 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



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Outsourcing Facility Product Reports

- FDA has begun to post information submitted by outsourcing facilities in product reports
  - Section 503B(b) of the FD&C Act requires outsourcing facilities to report to FDA, upon initial registration and each June and December, drug products that they compounded 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.
- Information online covers prior reporting period(s), beginning with the Dec 2016-May 2017.
- May not represent drug products that outsourcing facilities intend to produce in the future.
- Not complete, as not all outsourcing facilities have submitted reports to the agency.
- https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm

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Outsourcing Facility Product Reports

REPORTING YEAR	REPORTING PERIOD	LABELER NAME	PROPRIETARY NAME	PACKAGE NDC	PACKAGE DESCRIPTION
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 2R3122-5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 2R3122-K5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 2R3301-K5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 3120NO	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 3120NO-K	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ephedrine Sulfate 3122NO	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 2R3320-K5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 2R3331-5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 2R3533-5	-	5 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 3320NO-K25	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 3330NO	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Ketamine HCl 3330NO-K25	-	25 mL in 1 SYRINGE
2017	1	Pharmedium Services, LLC	Potassium Chloride 2K5824	-	24 mL in 1 BAG
2017	1	Pharmedium Services, LLC	Potassium Chloride 2K5838	-	6 mL in 1 BAG
2017	1	Pharmedium Services, LLC	Potassium Chloride 2K5839	-	24 mL in 1 BAG
2017	1	Pharmedium Services, LLC	Epinephrine HCl 2R3244	-	5 mL in 1 SYRINGE

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Moving Forward

Policy	Oversight and Enforcement	Stakeholder Collaboration and Outreach
Finalize or revise draft guidance documents, proposed rules, and the MOU	Conduct inspections of outsourcing facilities, as well as other compounding facilities that ship compounded drugs in large volumes to multiple states	Collaborate with stakeholders and coordinate compounding efforts with our state regulatory partners
Develop policies to address other provisions of the law and answer questions raised by industry and other stakeholders	Take appropriate action in response to incidents, complaints, and inspectional findings	Conduct outreach to inform interested stakeholders about compounding

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THANK YOU

QUESTIONS?

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