



FDA Update

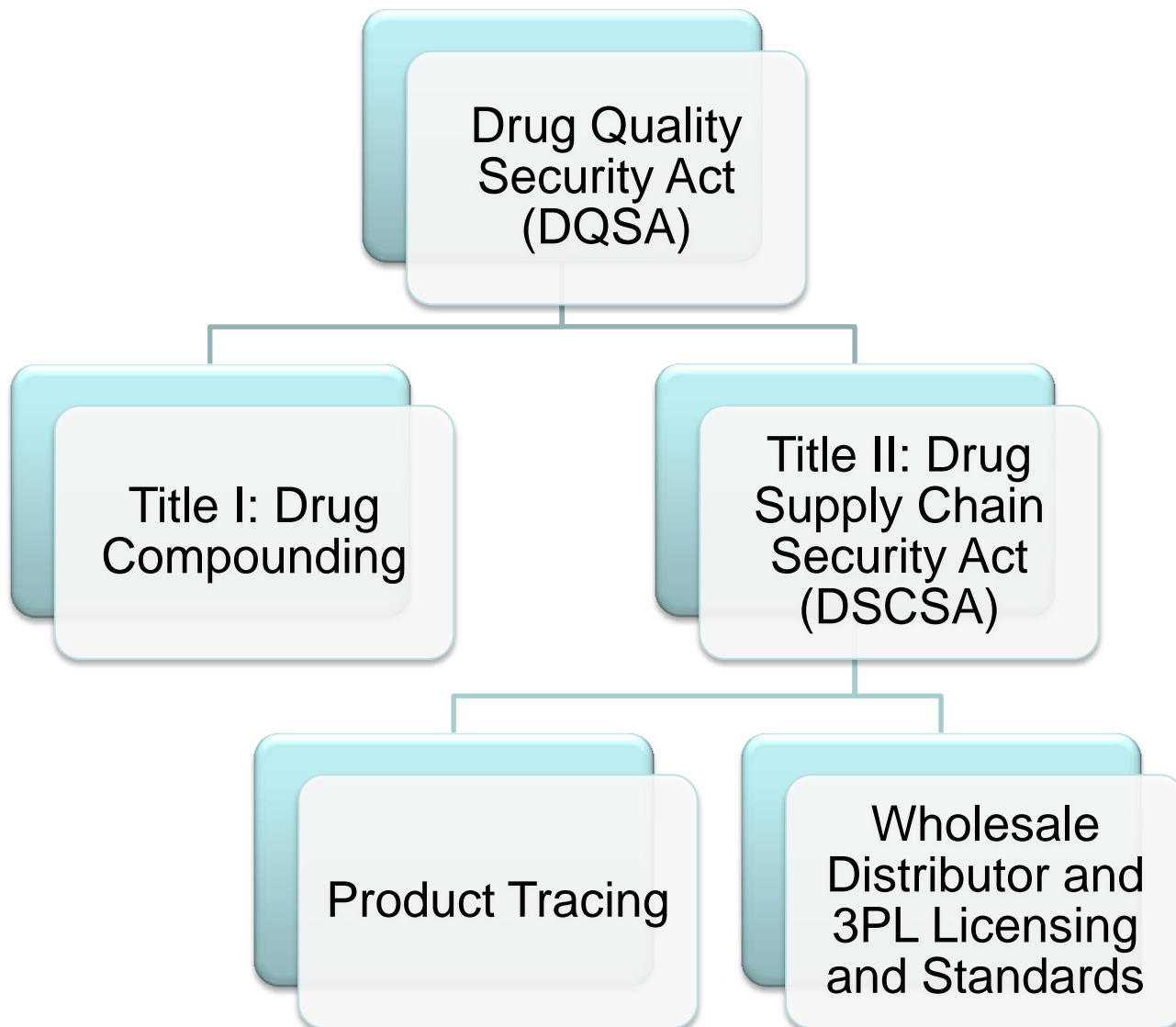
Drug Quality Security Act & Drug Shortages

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NABP District 4 Meeting
November 5, 2014

Objectives

- Overview of the Drug Quality Security Act (DQSA)
 - Title I: Drug Compounding
 - Title II: Drug Supply Chain Security Act (DSCSA)
- Drug Shortages





Title I: Drug Compounding

Overview

- Historical context
- Overview of 503A and 503B
- Implementation Efforts

Section 503A

- 503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:
 - FDA approval prior to marketing (section 505)
 - Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B)); and
 - Labeling with adequate directions for use (section 502(f)(1))
- Pharmacies that qualify for the exemptions are primarily regulated by the states, although some Federal requirements still apply (e.g., no insanitary conditions)
- Compounding performed by licensed pharmacist in a licensed pharmacy or Federal facility, or by licensed physician
- Prescription for an identified individual patient; anticipatory compounding in limited quantities before receipt of prescription

Compounding -- 503A (2)

- If bulk active ingredients used, must meet certain criteria
- Cannot compound:
 - Drugs on FDA list of drugs withdrawn or removed from the market for safety or efficacy reasons
 - Regularly or in inordinate amounts, drugs that are essentially copies of commercially available products,
 - Drugs on FDA list of drugs that present demonstrable difficulties for compounding
- Memorandum of Understanding (MOU) between FDA and States
 - Compounder cannot distribute or cause to be distributed interstate more than 5% of the total prescription orders dispensed or distributed by that pharmacy or physician unless they are located in a state that has entered into a Memorandum of Understanding with FDA that provides for appropriate investigation of complaints related to drugs distributed outside the state and addresses the distribution of inordinate amounts of compounded drug products interstate

Compounding Quality Act

November 27, 2013

- Removes certain provisions from section 503A related to solicitation of prescriptions and advertising and promotion that were held unconstitutional by the U.S. Supreme Court in 2002
- Clarifies that section 503A is applicable to compounders nationwide
- Adds new section 503B: “Outsourcing Facilities”

A registered outsourcing facility

- Must comply with CGMP requirements;
- Will be inspected by FDA according to a risk-based schedule; and
- Must meet certain other conditions to be exempt from the new drug approval requirements, the requirements for adequate directions for use, and the track and trace requirements.
- Registered outsourcing facilities must:
 - Report to FDA twice a year information about the products they compounded during previous six months
 - Report adverse events
 - Label their products with certain information

Other conditions for outsourcing facilities

- Outsourcing facilities cannot compound drug products that appear on FDA lists
 - of drug products that have been withdrawn or removed from the market because the drug products or their components have been found to be unsafe or not effective,
 - of drug products that present demonstrable difficulties for compounding
- The outsourcing facility cannot compound a drug that is essentially a copy of one or more FDA-approved drugs.
- The outsourcing facility cannot compound a drug that is subject to a REMS with elements to assure safe use or from a bulk drug substance that is a component of such drug unless the outsourcing facility demonstrates it will use controls comparable to the REMS

Outsourcing facility fees

- An outsourcing facility will not be considered registered until it has paid the applicable annual establishment fee
- An outsourcing facility could have registered without paying a fee until September 30, 2014; entities registering after October 1, 2014 must pay fee
- Full establishment fee for FY 15 is \$16,442
- Statute also authorizes reinspection fees

By definition a registered outsourcing facility...

- Is engaged in the compounding of STERILE drugs
- Has elected to register as an outsourcing facility
- Complies with all of the conditions in section 503B
- 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

Compounders that do not register as outsourcing facilities

- A compounder that:
 - does not register as an outsourcing facility and comply with the conditions under section 503B, and
 - compounds drugs that do not qualify for the exemptions under section 503A
- Is subject to all of the requirements in the FDCA applicable to conventional manufacturers.

FDA is moving swiftly to implement the new law

- On Dec, 2, 2013, FDA issued three draft guidances:
 - How to register under section 503B as an outsourcing facility
 - How outsourcing facilities may report to FDA required information about the products they have compounded
 - Compounding under section 503A, and regarding sections that require rulemaking or other FDA action to implement (bulks list, difficult to compound list, MOU)
- FDA published Federal Register Notices soliciting nominations for:
 - The list of drugs that are difficult to compound under 503A and 503B
 - The list of bulk drug substances that may be used to compound under section 503A
 - The list of bulk drug substances that may be used to compound under section 503B (based on clinical need); nominations later reopened
 - Pharmacy Compounding Advisory Committee

Other documents issued

- Draft fee guidance, March 2014;
- Final 503A guidance, July, 2014
- Proposed rule that would add 25 drugs to the list of drugs that cannot be compounded because they have been withdrawn or removed from the market for safety and efficacy reasons
- Draft Interim CGMP Guidance for outsourcing facilities;

Oversight of outsourcing facilities

- As of September 30, 2014, 56 outsourcers were registered
- FDA is inspecting outsourcing facilities, focusing first on those that have not been inspected by FDA before they registered
 - Looking at processes for producing sterile drugs, and
 - Compliance with certain other conditions under section 503B such as the specified labeling requirements
- See:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm>

FDA working with States

- State partners participated in many recent inspections of compounders; some were initiated at the state's request
- FDA has held two 50-state meetings, most recently in March, 2014, to discuss plans for implementing the new law and get input on how best to partner to improve oversight of compounding
 - Several disclosure related issues:
 - Consider how to share adverse event reports with states
 - Inspection and enforcement issues



Title II: DSCSA

The Drug Supply Chain Security Act

Overview of the DSCSA (enacted 11/27/2013)

- Product tracing
- Product verification
 - Quarantine and investigation (steps for detection and response)
 - Notification
 - Recordkeeping
- Product identification
- Wholesaler standards for licensure
- Third-party logistics provider standards for licensure
- Enhanced system – 10 years
- Penalties
- National uniform policy

Definitions

- Dispenser
- Distribute
- Illegitimate product
- Manufacturer
- Package
- Product
- Product identifier
- Quarantine
- Repackager
- Return
- Standardized numerical identifier
- Suspect product
- Trading partner
- Transaction
- Transaction history
- Transaction information
- Transaction statement
- Wholesale Distributor
- Among others...

Definitions: Scope

Product

- What's covered:
 - Prescription drug in finished dosage form for administration to a patient without further manufacturing (such as capsules, tablets, lyophilized products before reconstitution)
- What's not covered:
 - Blood or blood components intended for transfusion
 - Radioactive drugs or biologics
 - Imaging drugs
 - Certain IV products
 - Medical gas
 - Homeopathic drugs
 - Lawfully compounded drugs

Transaction

- Transfer of product where a change of ownership occurs
- Exempt
 - Intercompany distributions
 - Distribution among hospitals under common control
 - Public health emergencies
 - Dispensed pursuant to a prescription
 - Product sample distribution
 - Blood and blood components for transfusion
 - Minimal quantities by a licensed pharmacy to a licensed practitioner
 - Charitable organizations
 - Distributions pursuant to a merger or sale
 - Certain combination products
 - Certain medical kits
 - Certain IV products
 - Medical gas distribution
 - Approved animal drugs

Product Tracing

- Beginning 1/1/2015, manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies beginning 7/1/2015) in the drug supply chain will provide information about a drug and who handled it each time it is sold in the U.S. market.
- This transaction documentation consists of:
 - Transaction **information (TI)** which include lot number of product (except for certain wholesale drug distributor transactions)
 - Transaction **history (TH)**
 - Transaction **statement (TS)**
- FDA is required to establish standards for the exchange of transaction documentation no later than 11/27/2014.

Definitions: Transaction Information, History, and Statement

Transaction Information (TI):

- Proprietary or established name or names of the product;
- Strength and dosage form of the product;
- National Drug Code number of the product;
- Container size;
- Number of containers;
- Lot number of the product;
- Date of the transaction;
- Date of the shipment, if more than 24 hours after the date of the transaction; and
- Business name and address of the person from whom and to whom ownership is being transferred.

Transaction History (TH): A statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.

Transaction Statement (TS): A

statement, in paper or electronic form, that the entity transferring ownership in a transaction—

- Is authorized as required under DSCSA;
- Received the product from a person that is authorized as required under DSCSA;
- Received transaction information and a transaction statement from the prior owner of the product, as required under the law;
- Did not knowingly ship a suspect or illegitimate product;
- Had systems and processes in place to comply with verification requirements under the law;
- Did not knowingly provide false transaction information; and
- Did not knowingly alter the transaction history.

Authorized Trading Partners

- **Manufacturers and Repackagers:** valid registration with FDA
- **Wholesale distributors:** valid State or Federal license and compliance with reporting requirements; considered authorized before federal licensing regulations effective if possesses “valid license under State law”
- **Third-party logistic provider:** valid State or Federal license and compliance with reporting requirements; considered authorized before federal licensing regulations effective, unless FDA makes certain findings and gives notice
- **Dispensers:** valid State license

Beginning 1/1/2015 - trading partners must be “authorized”

Product Verification

- No later than 1/1/15, manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) shall establish systems and processes to be able to comply with the verification requirements
 - Must be able to respond to verification requests from Secretary about suspect product
 - Quarantine and investigate suspect product to determine if illegitimate product (includes validating applicable TI and TH)
 - Notify trading partners and FDA of illegitimate product (within 24 hours of determination)
 - Respond to notifications of illegitimate product
 - Recordkeeping
- Verification requirements change once product is serialized.
(starting in 2017 for M, 2018 for R, 2019 for WD and 2020 for D)

Product Identification (Serialization)

- No later than 4 years (11/27/2017), manufacturers, followed by repackagers (11/27/2018) shall place a unique product identifier on certain prescription drug packages
 - 2D bar code
- Product identifier
 - National Drug Code
 - Serial number
 - Lot number
 - Expiration date
- After 6 years (11/27/2019), wholesalers, followed by dispensers (11/27/2020), will only trade products with product identifiers.
- Verification requirements change once product is serialized.
(starting in 2017 for M, 2018 for R, 2019 for WD and 2020 for D)



Definitions- WD and 3PL

WHOLESALE DISTRIBUTOR (WD) — a person (other than a manufacturer...) engaged in wholesale distribution (as defined in section 503(e)(4))

- **Wholesale Distribution** is defined as the distribution of a drug... to a person other than a consumer or patient, or receipt of a drug... by a person other than the consumer or patient
- **Contains a number of exceptions** for example : intracompany distribution, transfers to and from third-party logistics providers and common carriers, distribution of certain drugs in medical convenience kits, IV fluid replenishment and dialysis drugs, medical gases, etc.

THIRD-PARTY LOGISTICS PROVIDER (3PL) — entity that provides or coordinates warehousing, or other logistics services of a product in interstate commerce on behalf of a manufacturer, wholesale distributor, or dispenser of a product, but does not take ownership of the product, nor have responsibility to direct the sale or disposition of the product.

Wholesaler Licensing and Standards

- No later than 11/27/2015, FDA is required to develop new federal standards for licensing of wholesale drug distributors and a federal system for wholesale drug distributor licensing for use when a state system does not meet federal standards.
- Beginning 1/1/2015, wholesale drug distributors shall report their licensing status and contact information to FDA. This information will then be made available in a public database.
- Coordination with appropriate state officials

Third-Party Logistics Provider (3PL) Licensing and Standards

- No later than 11/27/2015, FDA is required to develop new federal standards for licensing of 3PLs and a federal system for 3PL licensing for use when a state system does not meet federal standards.
- The licensing regulations go into effect 1 year after regulations are finalized. At that time, 3PLs are required by federal law to obtain a state or federal license.
- Beginning 11/27/2014, 3PLs shall report their licensing status and contact information to FDA.

State Licensing Fees

- WDDs – The DSCSA does not prohibit States from collecting fees from wholesale distributors in connection with State licensing.
- 3PLs – For program establish by a State, the State can collect fees from a 3PL for issuing a license. If a State does not established program, the State is prohibited from collecting fees from 3PL.

Enhanced System – 10 years

- Establishes package level requirements for the interoperable, electronic tracing of products that shall go into effect 10 years after enactment of this Act, including those relating to:
 - Electronic exchange of transaction information for each sale of certain prescription drugs
 - Verification of product identifiers at the package level
 - Prompt response to suspect and illegitimate products when found
 - Improved efficiency of recalls

Uniform National Standards (Section 585)

- Product tracing and other requirements:
 - No state or local government may establish or continue in effect requirements for tracing products through the distribution system which are *inconsistent with, more stringent than, or in addition to*, any requirements applicable under 503(e) (as amended by such Act) or the subchapter, or which are inconsistent with any waiver, exception, exemption, or restrictions under sections 581 or 582.

- Wholesale distribution and 3PL standards:
 - Prohibits any state or local government from establishing or continuing any standards, requirements, or regulations with respect to the licensing of wholesale prescription drug distributors or 3PLs that are *inconsistent with, less stringent, directly related to, or covered by* standards and requirements applicable under section 503(e) (as amended by such Act) or section 584 (for 3PLs).
 - No state shall regulate 3PLs as wholesale distributors

The effect of Section 585....

- Q&A Guidance for Industry; published on 10/8/2014
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417564.pdf>
- To assist industry and State and local governments in understanding the effects of section 585 of the FD&C Act
 - immediate effects of the law
 - Clarifies effect on State product tracing and standards and requirements for wholesale distributor and third-party logistics provider licensing

Action Items for your Board to Consider (1)

- Familiarize yourself with the DSCSA
- Obtain a good understanding of how the DSCSA will impact your future role of licensing WDs and 3PLs
- Identify if your state plans to continue to license WDs once the new federal regulations take effect
 - WDs will need to comply with the new federal requirements effective 2 years after federal regulations are finalized.
 - Will your board update your statutes and/or regulations to meet the new federal standards for licensure?

Action Items for your Board to Consider (2)

- Identify if your state plans to create a new licensure program for 3PLs
 - 3PLs will need to comply with the new federal requirements effective 1 year after federal regulations are finalized.
 - Will your board create a new 3PL licensure program?
 - Will your board update your statutes and/or regulations to meet the new federal standards for licensure?
 - Would you recognize a national 3rd party accreditation program to fulfill that role?
- **DSCSA web page**
<http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm>



Email questions/comments to:

DSCSA

drugtrackandtrace@fda.hhs.gov

wdd3plrequirements@fda.hhs.gov

Compounding

compounding@fda.hhs.gov



Drug Shortages

Drug Safety and Availability

• Drug Shortages

Drug Shortages: Additional News and Information

Frequently Asked Questions About Drug Shortages

Resources for You

- Drug Shortage Manual of Policies and Procedures (MaPP) (PDF - 1.1MB)
- American Society of Health-System Pharmacists: Drug Shortages [@](#)
- American Society of Health-System Pharmacists: Guideline on Managing Drug Shortages [@](#)
- Guidance for Industry: Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage (PDF - 226kB)
- FDA Drug Shortages RSS Feed [@](#) (XML - 37kB)
- Sign up for Drug Shortages

Drug Shortages

Search Our New [Drug Shortages Database](#)

FDA takes great efforts, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations. The agency works closely with manufacturers of drugs in short supply to communicate the issue and to help restore availability. FDA also works with other firms who manufacture the same drug, asking them to increase production, if possible, in order to prevent or reduce the impact of a shortage.

The majority of drug shortage information is provided to FDA by manufacturers. Communication between FDA and the public is an essential component of preventing and mitigating drug shortages. To ensure information is current, FDA appreciates all information and updates about shortages provided by manufacturers. Shortage notifications and updates may be reported to FDA at drugshortages@fda.hhs.gov.



Spotlight

- FDA updates on saline drug shortage
- Drug Shortages Report to Congress
- FDA Takes Two Important Actions on Drug Shortages
- Strategic Plan for Preventing and Mitigating Drug Shortages (PDF - 381KB)
- Federal Register Notice for Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products, Proposed Rule

Information for You

- Consumers: FDA Works to Lessen Drug Shortage Impact
- From a Clinical Perspective
- Drug Shortages: Additional News and Information
- Health Professionals: FDA Working to Lessen Patient Impact from Drug Shortages
- Industry: FDA and Manufacturers Work to Prevent Drug Shortages

Shortages and the FDA response

What we CAN require:

- Notification by manufacturers
 - Interruptions that could lead to a meaningful supply disruption, discontinuations
 - No penalty for not reporting
- Notification of manufacturing changes

What we CANNOT require:

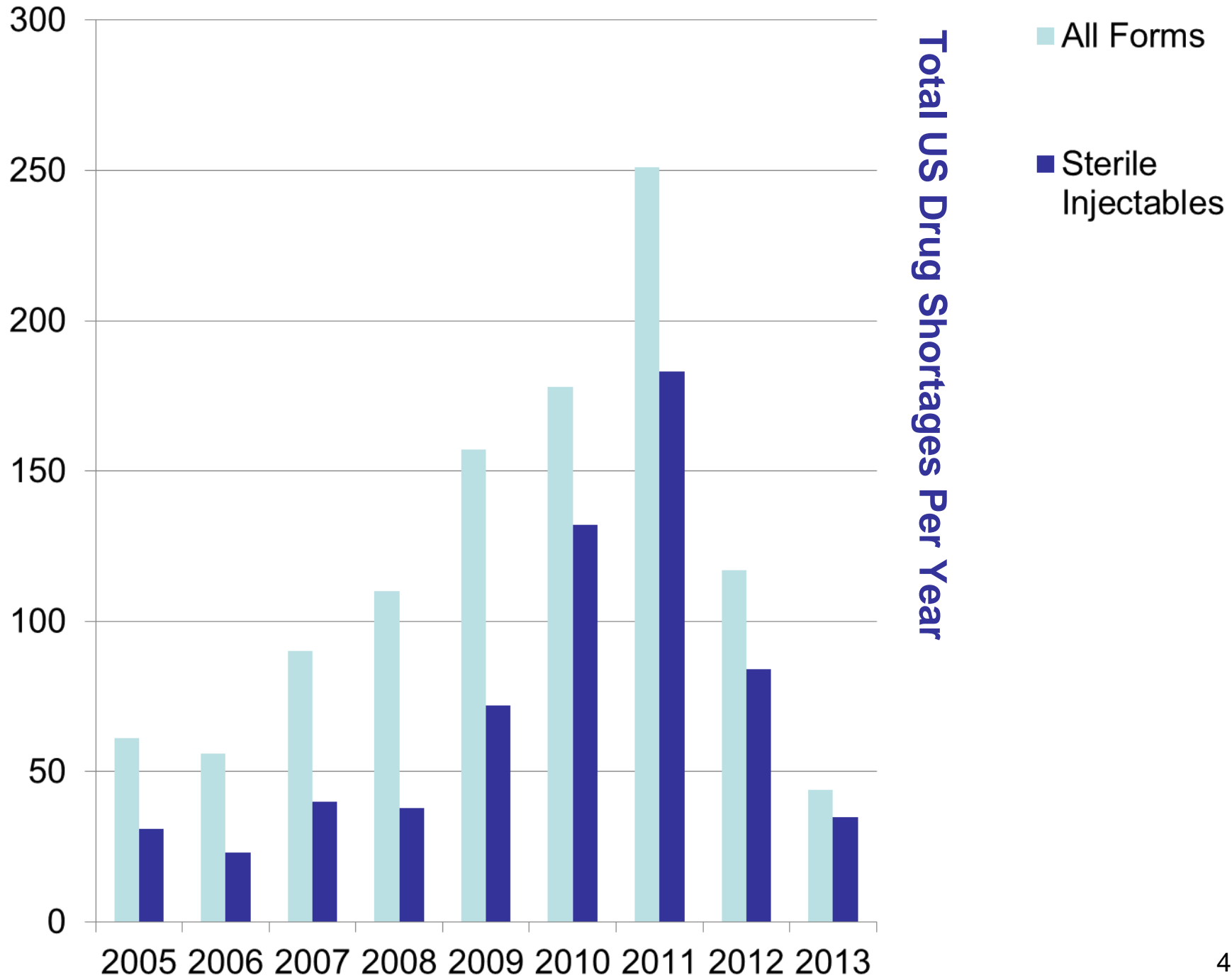
- A company to make a drug
- A company to make more of a drug
- How much and to whom the drug is distributed

Drug shortage data

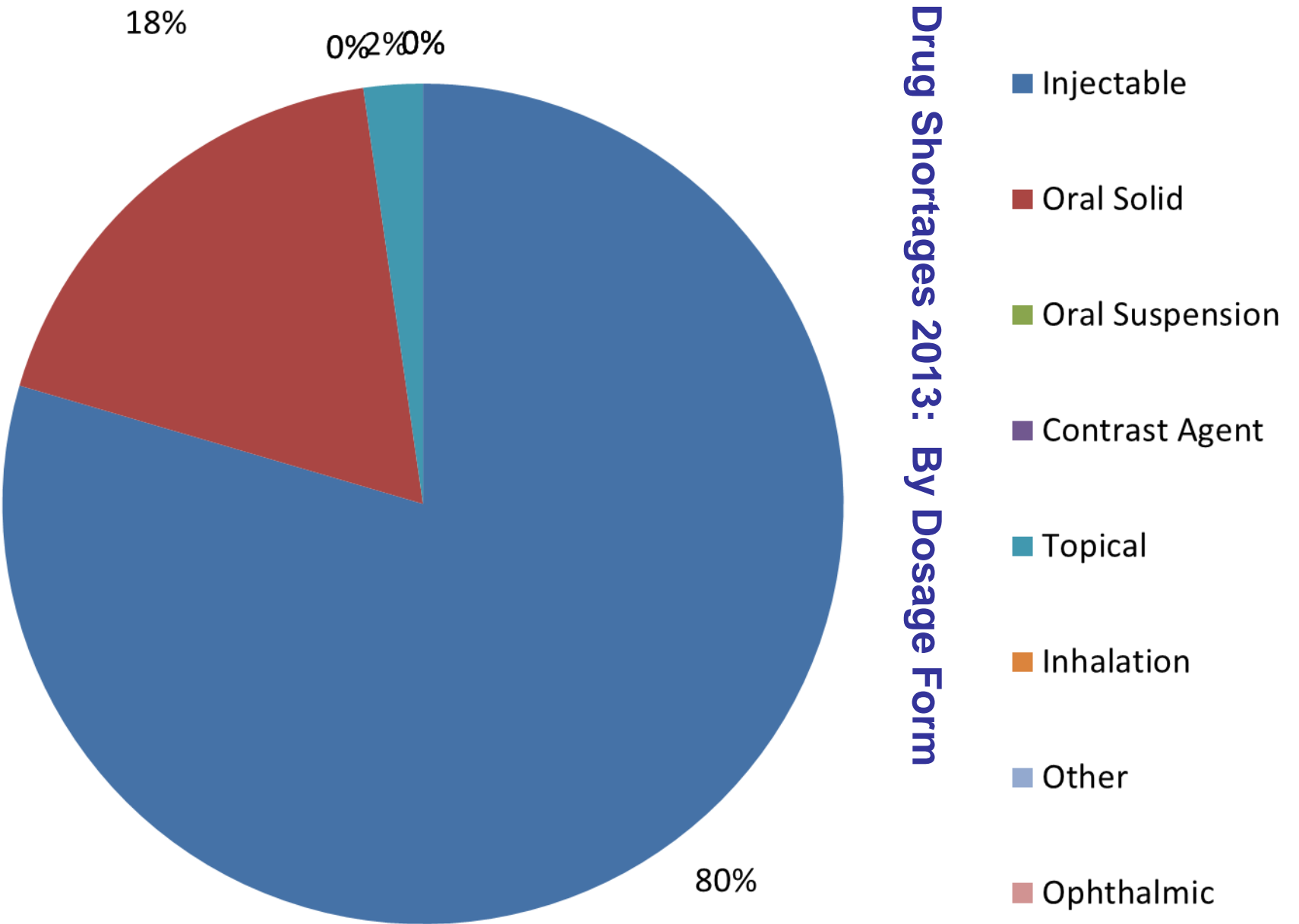
- 2011: 251 shortages reported
- 2012: 117 shortages reported
- 2013: 44 shortages reported

- A high percentage are sterile injectables

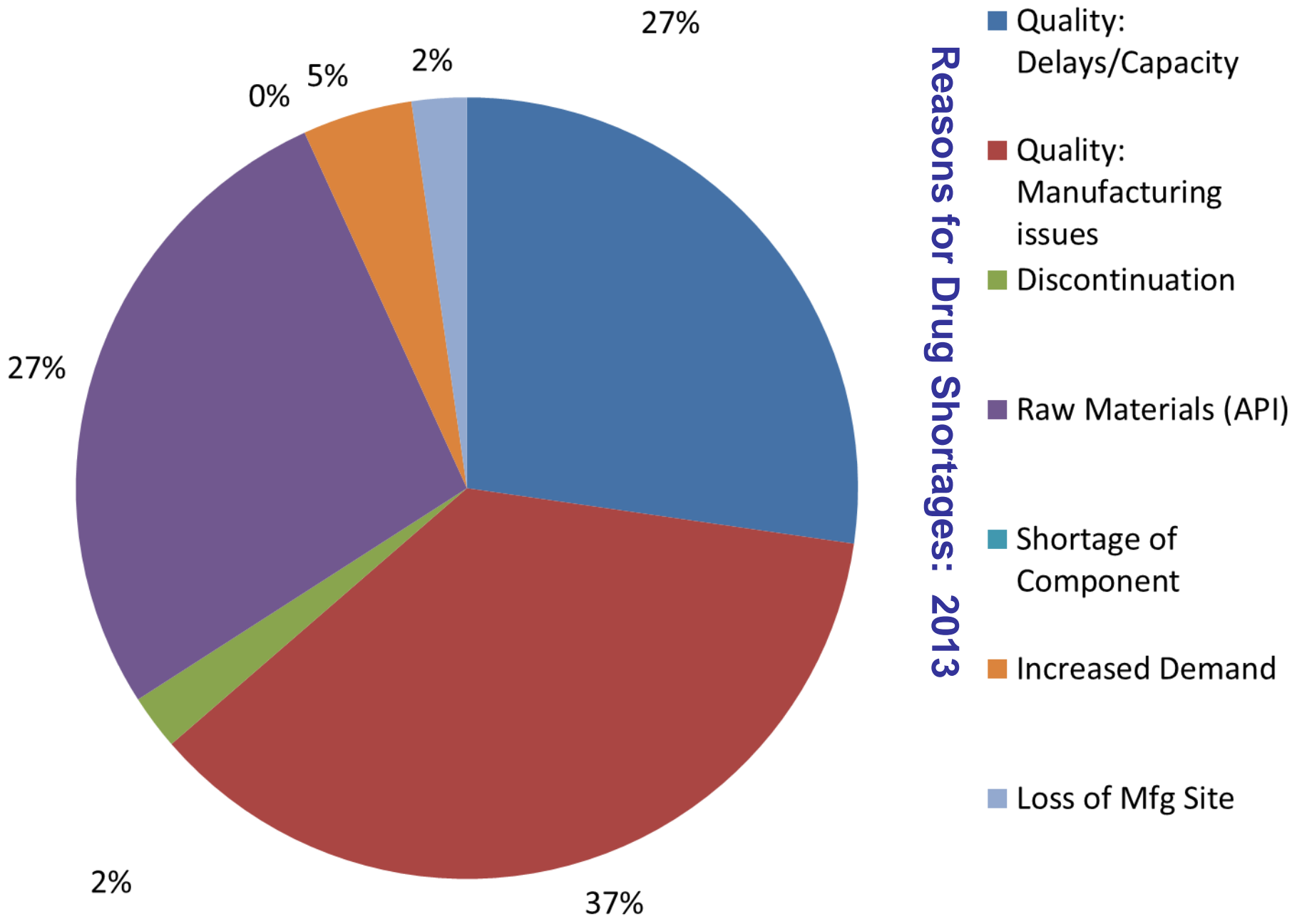
When there are quality or production problems for sterile injectables, the result is almost always a shortage



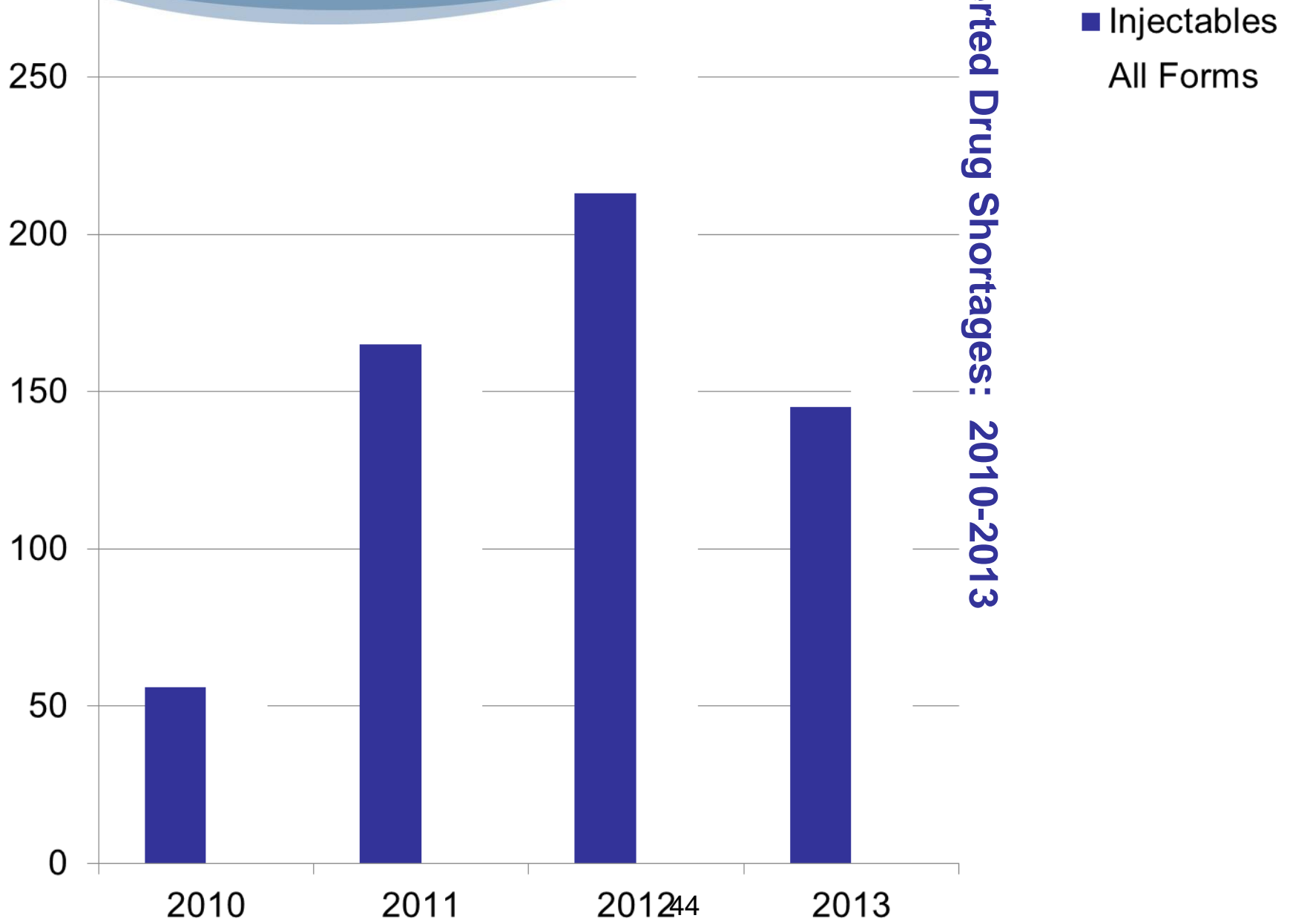
Drug Shortages 2013: By Dosage Form



Reasons for Drug Shortages: 2013



Averted Drug Shortages: 2010-2013



Causes of shortages: sterile injectables

- Quality and manufacturing issues:
 - Sterility: Bacterial and fungal contamination
 - Particulates: Glass, metal or fiber in vials
 - Crystallization: Drug may form crystals
 - Precipitate: Reaction between drug and container or diluent
 - Impurities: Can be toxic (heavy metals)
 - Degradants: Lead to less effective drug product
 - Equipment breakdown
 - Natural disasters

FDA's approach to prevention and mitigation

- Prioritize products that are medically necessary
- Risk/Benefit of the drug in question
- Maintain availability while minimizing risk to patients
- Work with firms to address problems
 - We can advise, assist and expedite but the manufacturer must fix the problem
 - Early notification is key!!
- Be flexible, creative and fast!

FDA toolbox

- Regulatory Discretion
 - Allows for manufacture of medically necessary products to continue
 - May require additional safety controls
 - Filters with product; extra testing at plant; 3rd party oversight of production; special instructions for safe use
- Request other firms to increase production
- Expedite reviews
 - New manufacturing sites, increased expiry date, new raw material source, changes in specifications, etc.
- In rare cases, temporary importation from unapproved sources
 - 2013: sodium bicarbonate, phosphate injection, trace elements (pediatric and adult), IV lipids, calcium chloride injection, zinc injection
 - 2014: IV Saline, nitroglycerin injection, PD Solution, Irrigation solution





Drug shortages: Strategic plan

Issued October 2013

- First strategy is to strengthen FDA response
 - Streamlining internal processes
 - Improving data tracking
 - Better communication including targeted communication
- Second strategy is to implement new efforts to prevent quality issues from occurring
 - Exploring incentives for manufacturers
 - Creation of a new Office of Pharmaceutical Quality
 - Working to develop ways to identify early warning signals at manufacturers
 - Working with outside stakeholders to better understand the range of factors that contribute to shortages

<http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>

Drug shortages summary...

- FDA work will continue....
 - Working with manufacturers, progress is being made to prevent and mitigate critical shortages
 - Challenges remain: a single shortage of a critical drug is unacceptable
 - FDA has strategic vision, but cannot solve drug shortages alone
 - Industry commitment to a culture of quality manufacturing is needed



THANKS!!!

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