FDLI

Enforcement, Litigation, and Compliance Conference

December 7-8, 2016
Washington, DC

Compliance Central with FDA Center Compliance Directors: Part I

Tom Cosgrove, Acting Director, Office of Compliance, Center for Drug Evaluation and Research, FDA

Carl Fischer, Senior Advisor, Office of Compliance, Center for Devices and Radiological Health, FDA

Mary Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, FDA

Moderated by: John R. Manthei, Partner, Latham & Watkins LLP

U.S. FOOD & DRUG ADMINISTRATION

CDER Office of Compliance

Thomas J. Cosgrove, J.D.
Acting Director, Office of Compliance

FDLI Enforcement, Litigation, and Compliance Conference
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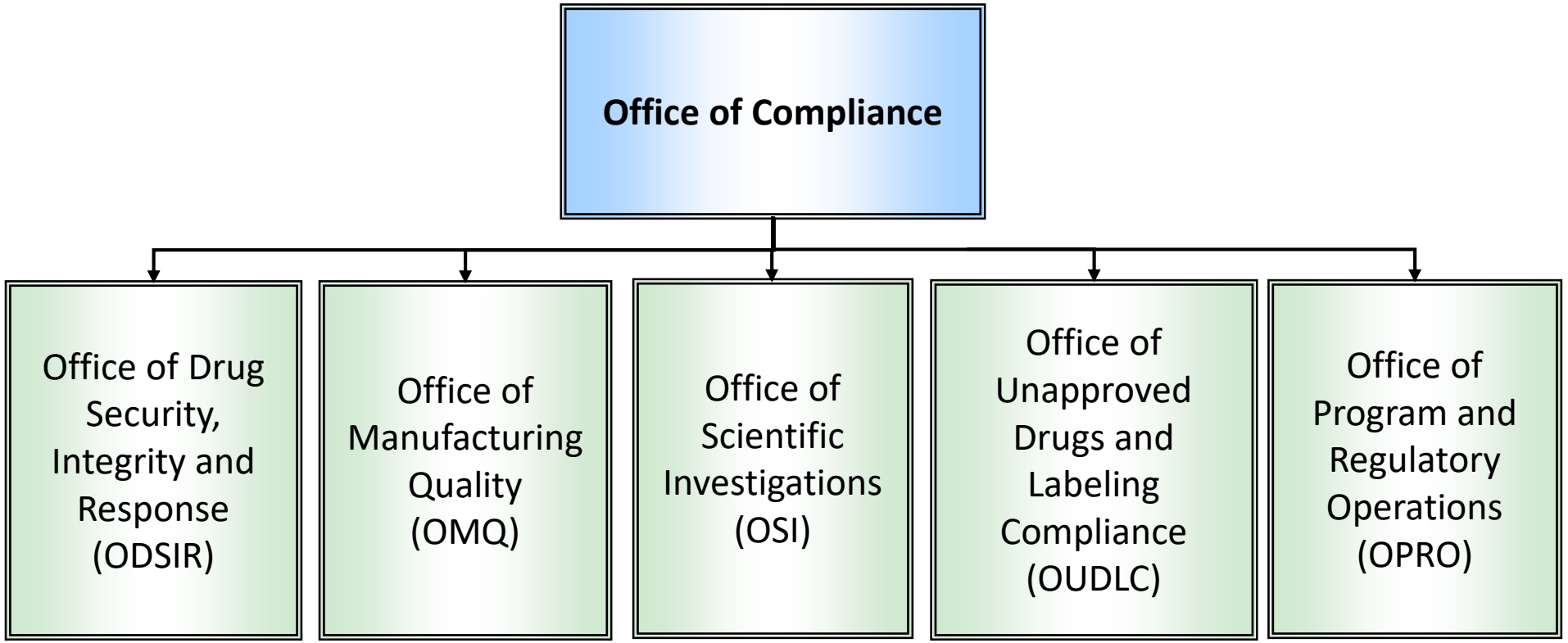
Our mission: to promote and protect the public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.

Our vision: to be a global leader in preventing consumer exposure to unnecessary risk from drugs throughout the drug lifecycle.

Office of Compliance Priorities

- Compliance/enforcement actions
- Quality/safety initiatives
- Data integrity/assurance
- Compounding
- Track and trace
- Clear guidance and standards for compliance
- Program alignment

Office of Compliance Structure



Our Toolbox

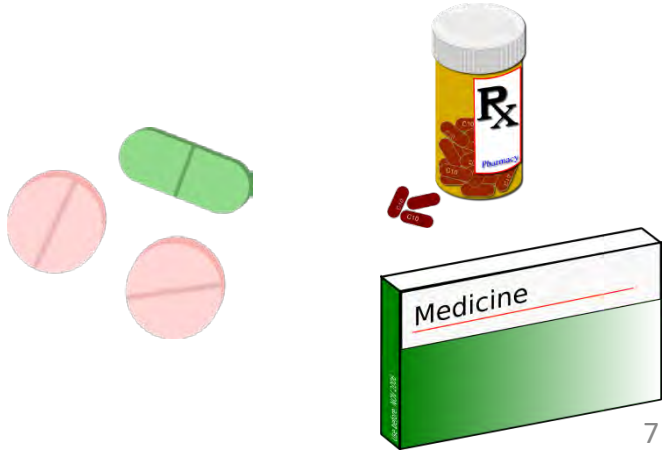
- Industry/firm regulatory meeting
- Injunction/shut down
- Consent decree
- Import alerts
- Seizures
- Warning letters
- Untitled letters
- Disqualifications
- Criminal indictments/convictions
- More

Adulterated
Misbranded
Unapproved
Health fraud
Data integrity
CGMP violations
GCP violations
Compounding
More…

6

Office of Manufacturing Quality (OMQ): Focus

- Compliance and enforcement for:
  - Current Good Manufacturing Practices violations
  - Data reliability issues
  - Compounding
- Global cooperation/training
- Policy/standards development



7

Primary Considerations CGMP Enforcement

Is the drug "adulterated"?

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- For API, standards are set forth in ICH Q7

Most important – patient risk

- High risk ➡ FDA takes quick action.
- Sub or super-potent
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Will FDA Issue an Import Alert?

CGMP Import Alert issued if:

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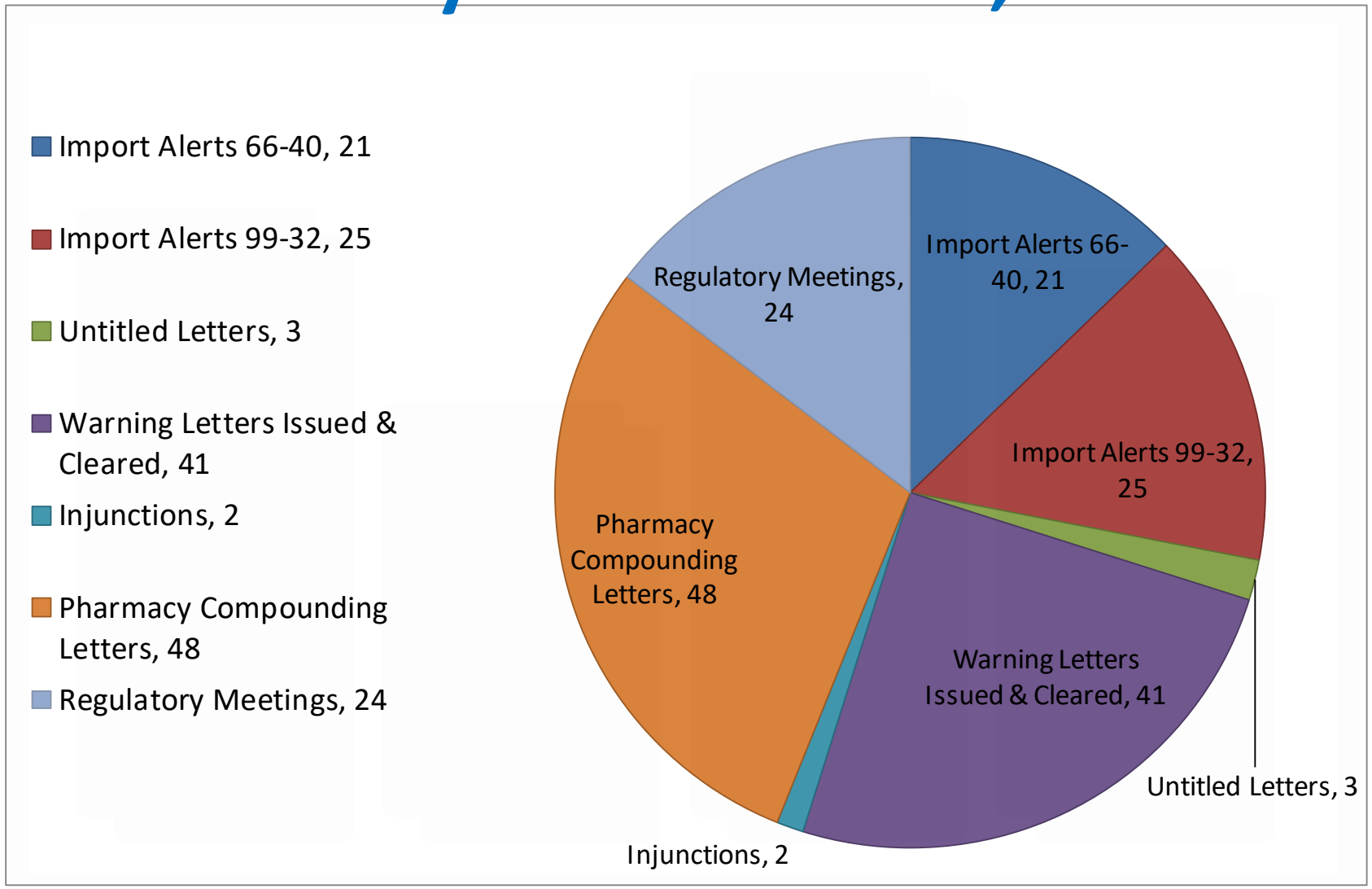
OMQ Actions
January to October 31, 2016



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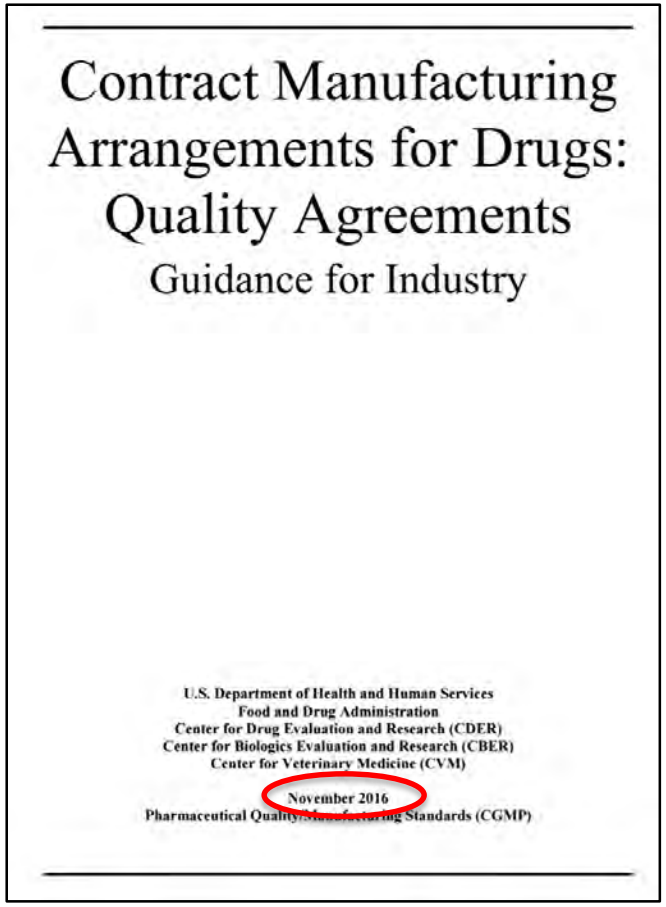
Now Final: FDA Guidance on Quality Agreements


Contract Manufacturing Arrangements for Drugs: Quality Agreements

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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November 2016

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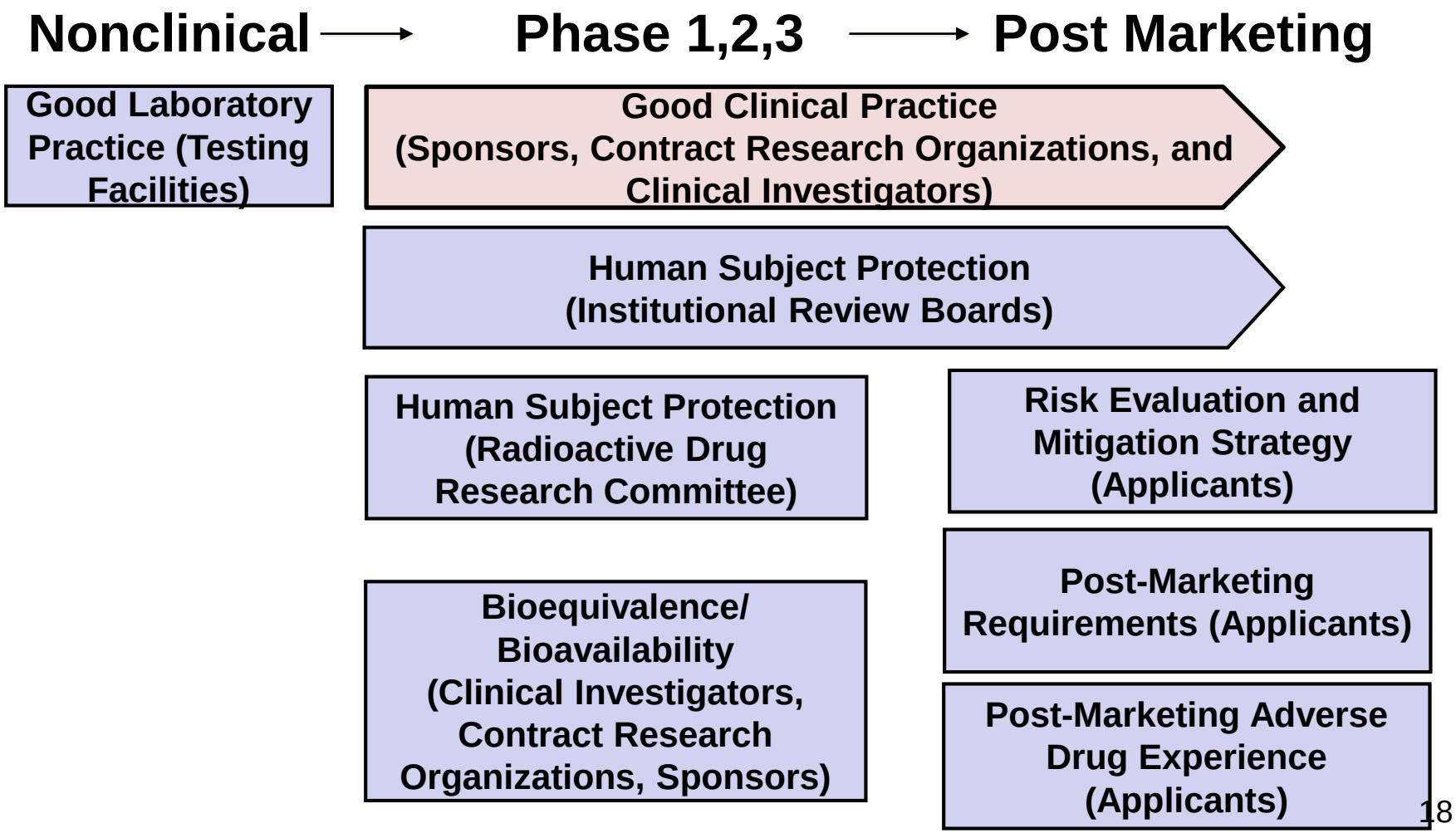
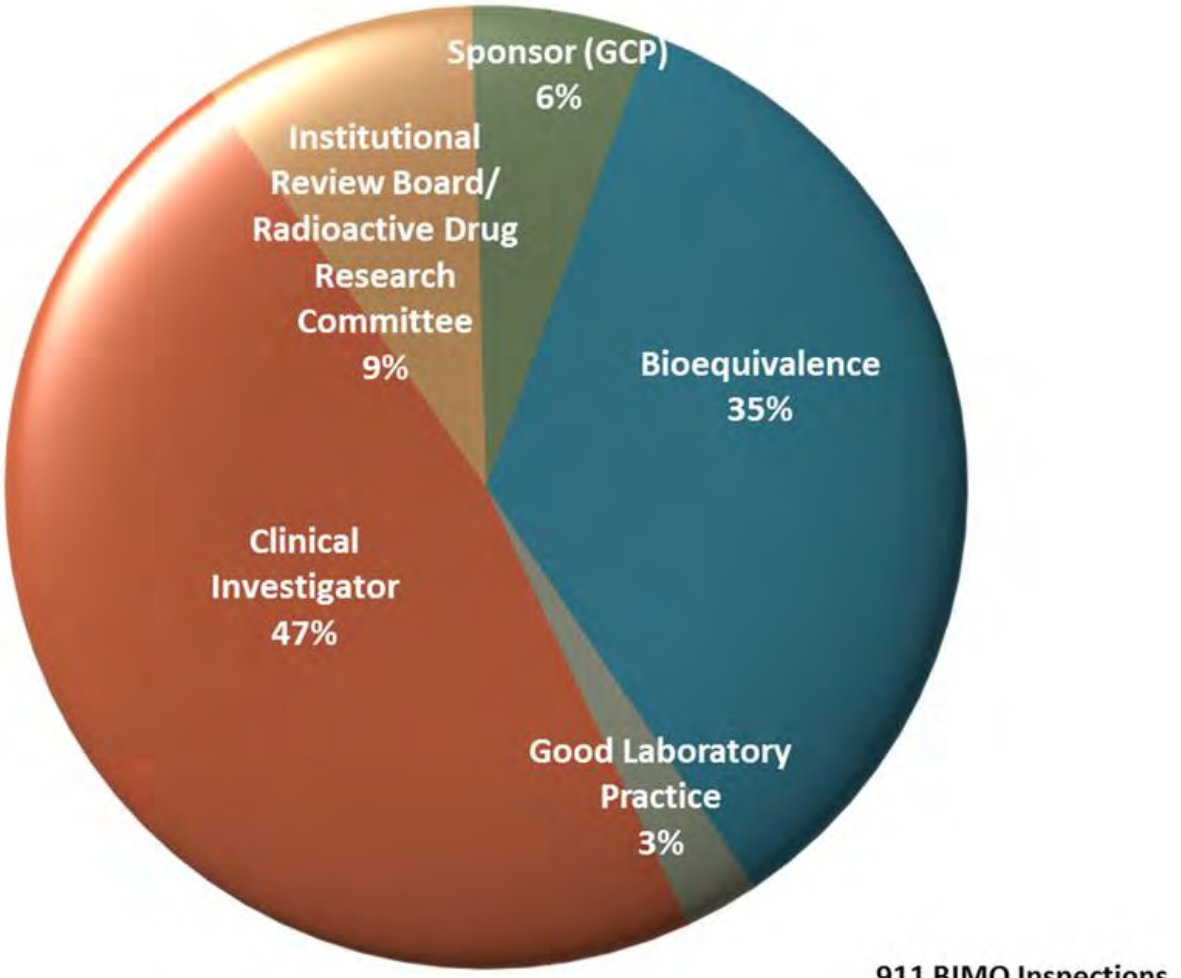


18

Bioresearch Monitoring Program Inspections*

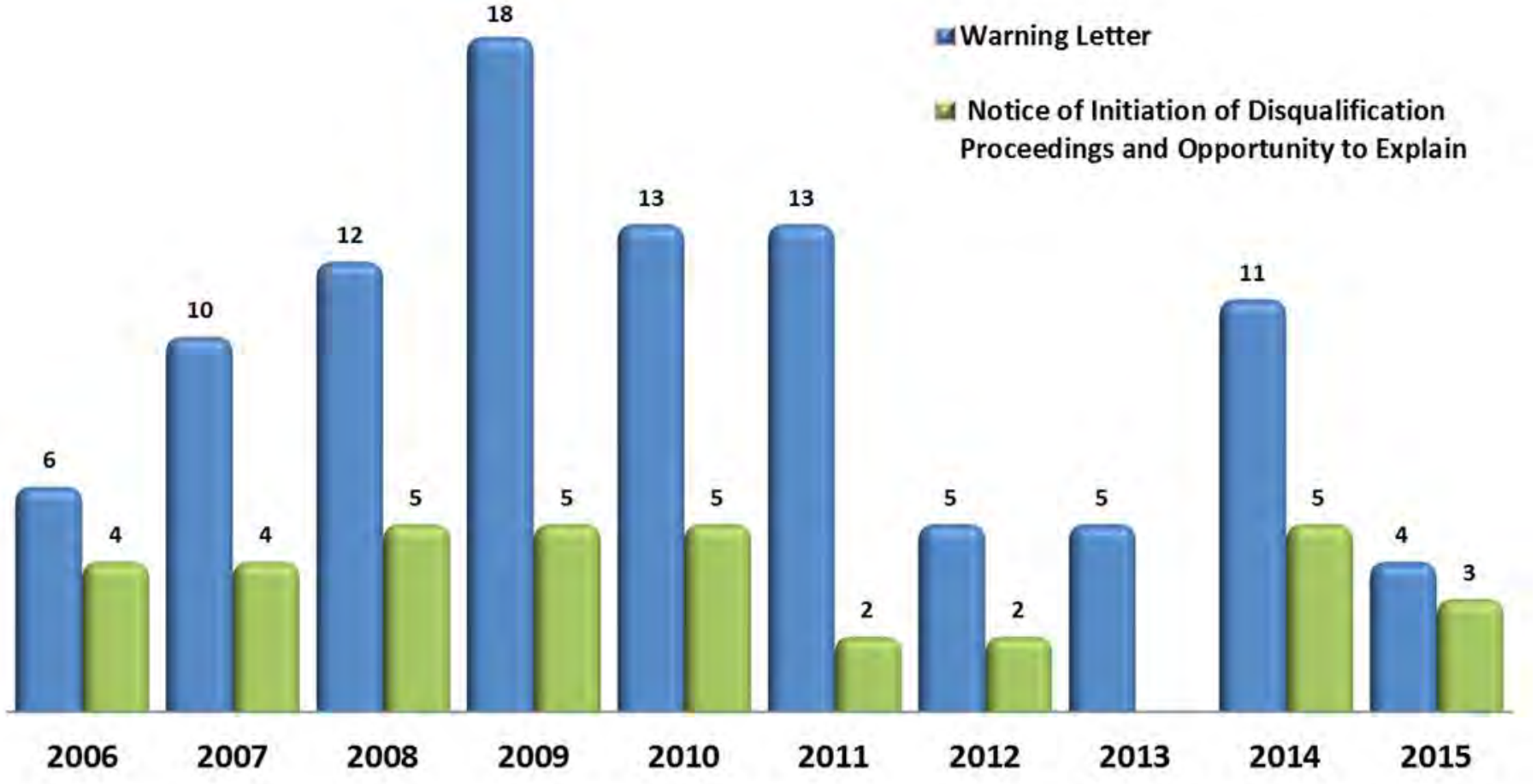
(CDER, FY 2015)



*Based on inspection start date – [Complis database as of January 20, 2016]

Clinical Investigator Warning/NIDPOE Letters*

(CDER, FY 2006 - FY 2015)



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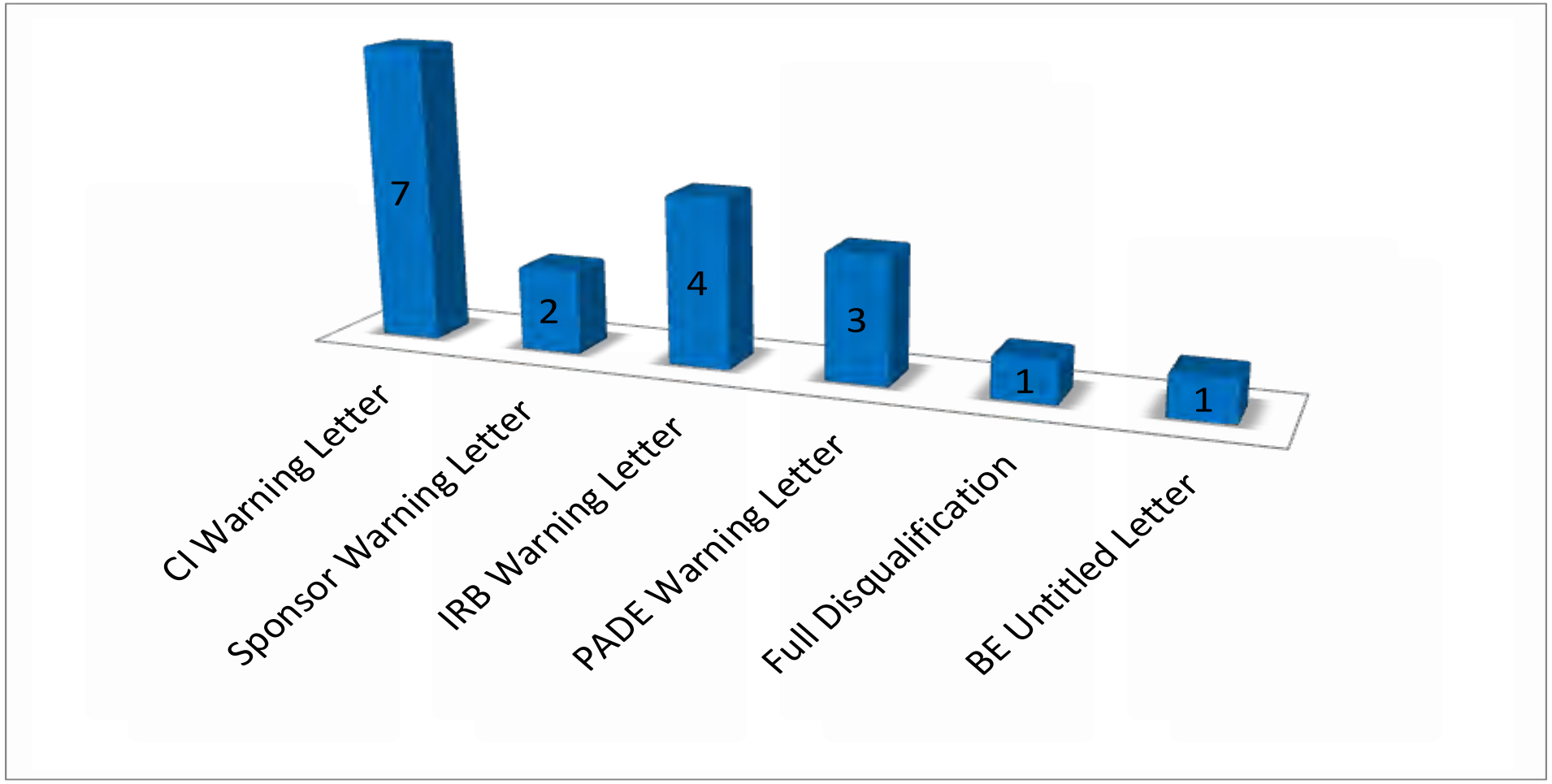
NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

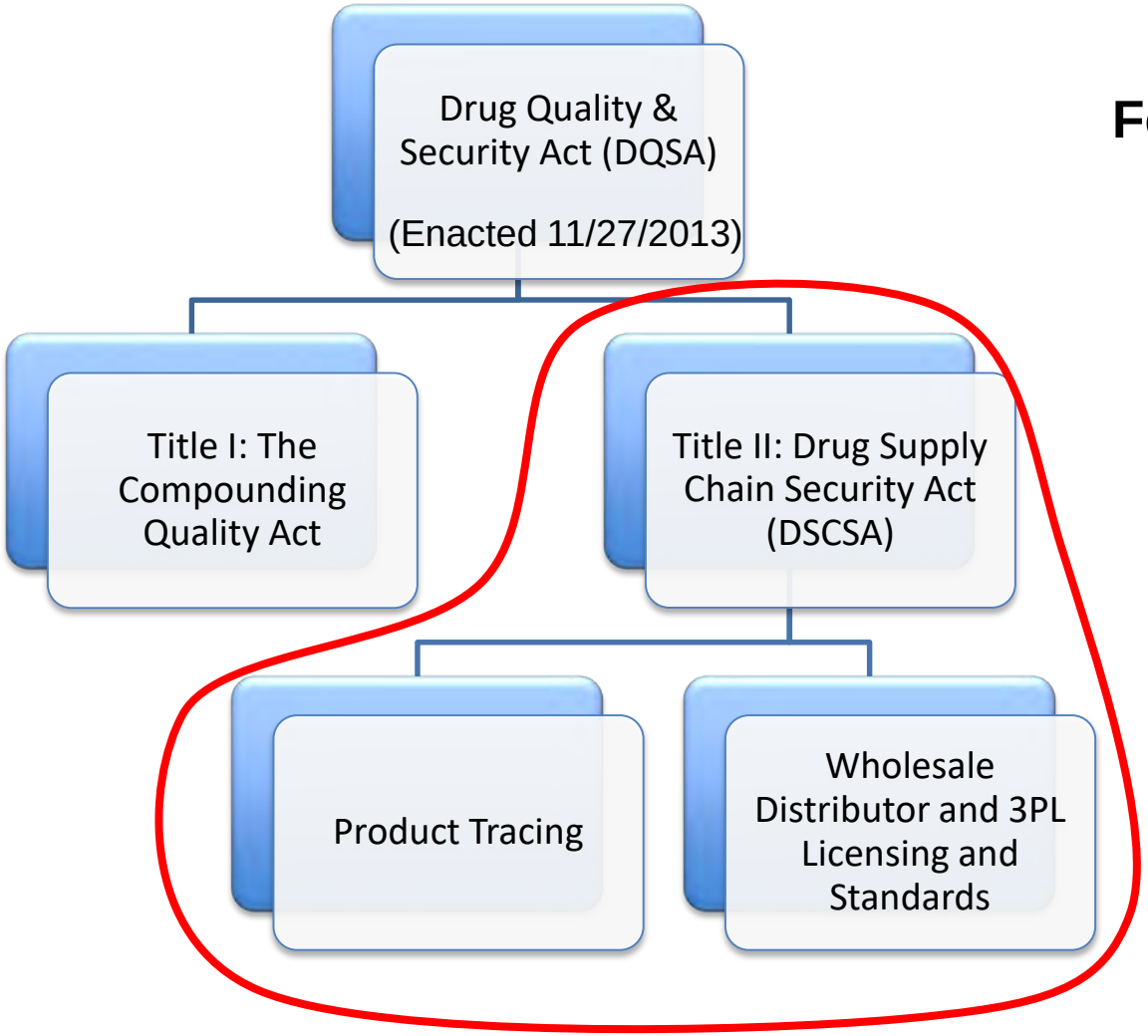
FY 2016 OSI Enforcement



Office of Drug Security, Integrity, and Response (ODSIR): Focus

- Internet pharmacies
- Counterfeit and foreign approved drug actions
  - Indictments/Prosecutions
  - Letters to doctors
- Imports/exports
- Recalls
- Incident response
- International collaborations
- Drug Supply Chain Security Act (DSCSA) implementation ("track and trace law")

The Drug Supply Chain Security Act (DSCSA) of 2013



Federal FD&C Act Sections:

- 581 – Definitions
- 582 – Requirements (product tracing, product identification, verification)
- 583 – Standards for licensure of wholesale distributors
- 584 – Standards for licensure of third-party logistics providers (3PL)
- 585 – Uniform national policy

Goals of the DSCSA

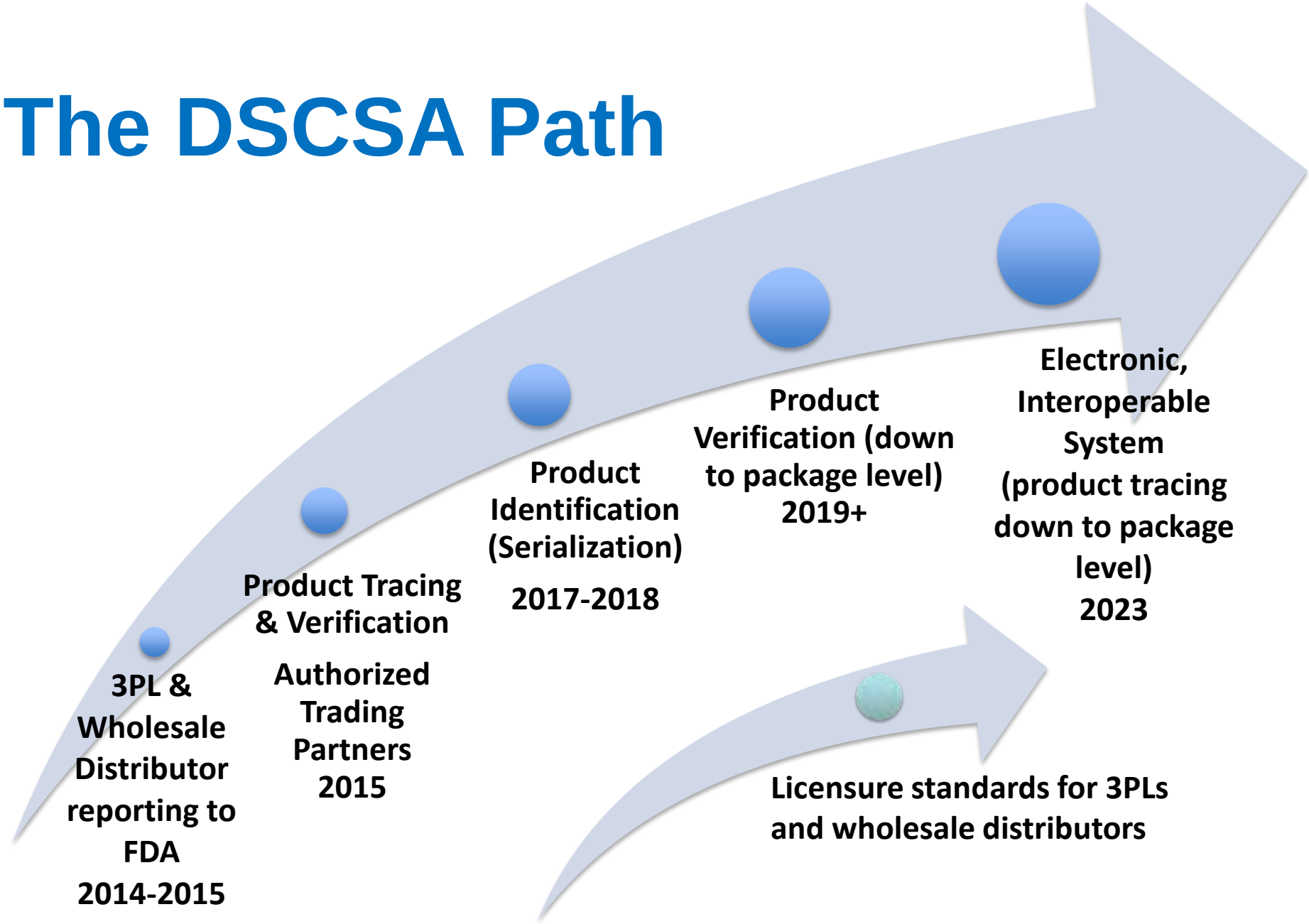
- Develop an electronic, interoperable system by 2023 to identify and trace certain prescription drugs as they move through the U.S. supply chain.

  The new system will:

  - facilitate the exchange of information by trading partners at the individual package level
  - improve efficiency of recalls
  - enable prompt response to suspect and illegitimate products when found
  - create transparency and accountability in the drug supply chain

- Establish national standards for licensure for wholesale distributors and third-party logistics providers.

The DSCSA Path



Compounding Actions

Since enactment of the DQSA on November 27, 2013, FDA has:

- Conducted approximately 425 *inspections* of compounders.
- Overseen over 90 *recall events* by compounders, and requested numerous compounders to cease operations
- Issued over 130 *warning letters*; one addressed violations identified at four facilities
- Issued over 30 *letters* referring findings from inspections of pharmacies that compounded their drugs in accordance with the conditions of section 503A to the states
- Obtained *4 civil consent decrees* of permanent injunction
- Sought several criminal prosecutions

Inspection Observations

- Continue to identify insanitary conditions at many of the compounding facilities inspected
  - Dog beds and hairs in close proximity to sterile compounding room
  - Dead bugs in ceilings
  - Renovations being made without evidence of controls to prevent contamination
  - Compounding by personnel with exposed skin

Other Compounding Actions

- Issued over 20 guidance documents
- Issued final rule and proposed rule describing additions and modifications to the Withdrawn or Removed List (503A and 503B)
- Solicited nominations for 503A and 503B bulks lists and for drugs that are difficult to compound under sections 503A and 503B
- Held 6 meetings of the Pharmacy Compounding Advisory Committee
- Held 4 sets of listening sessions with over 75 stakeholders
- Held 4 intergovernmental working meetings with the states

What's next….

- New legislation…
  - User fee reauthorization
  - 21st Century Cures?
- Continue implementation of DQSA (compounding/track and trace)
- Focus on quality/safety and data integrity
- Guidance and standards for compliance
- Program alignment
- More….

Thank You

Thomas Cosgrove, J.D.
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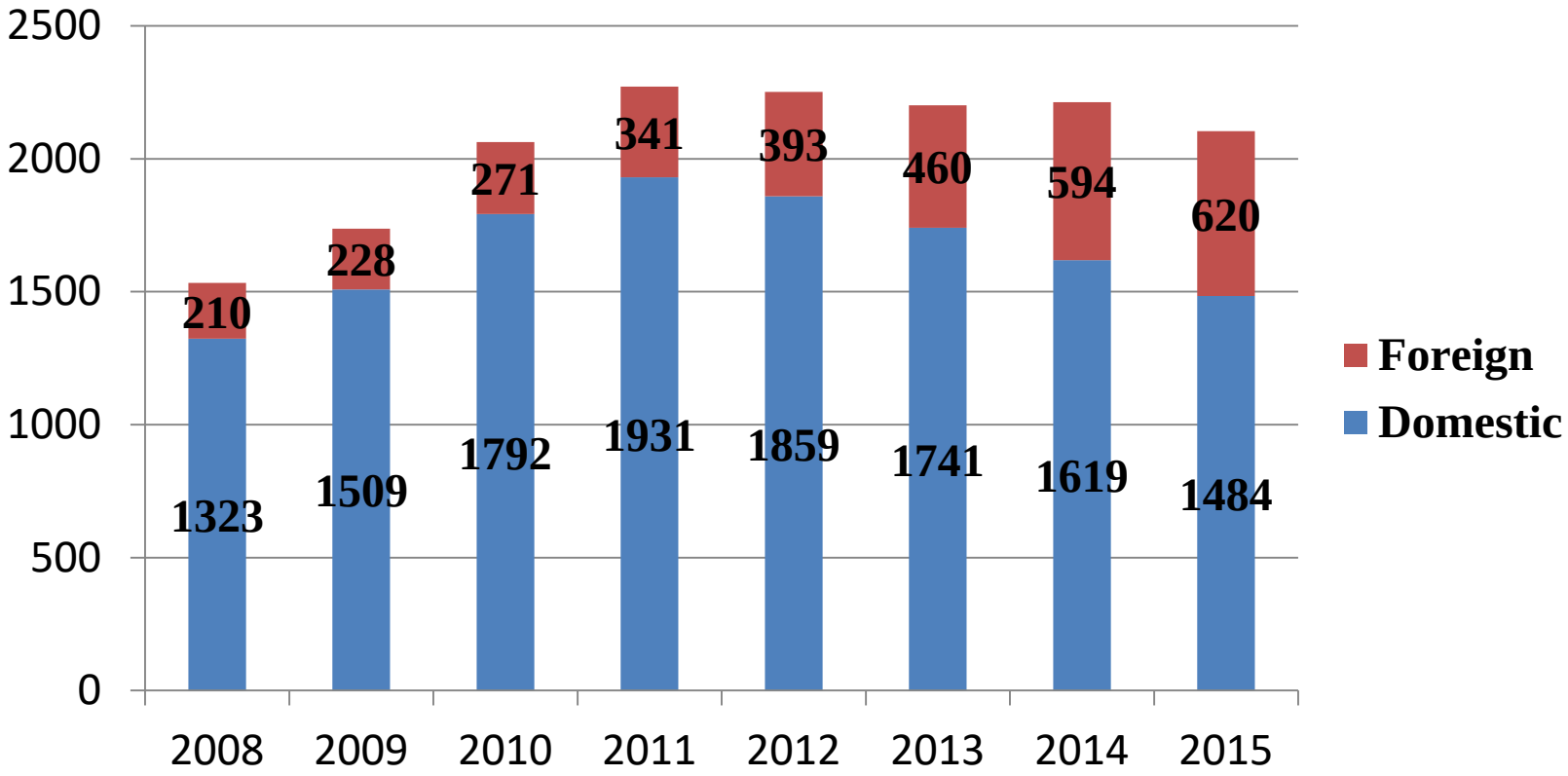
Center for Devices and Radiological Health

Carl Fischer, PhD
Senior Advisor
Office of Compliance
Center for Devices and Radiological Health

Medical Device QS Surveillance Inspections CY2008—CY2015

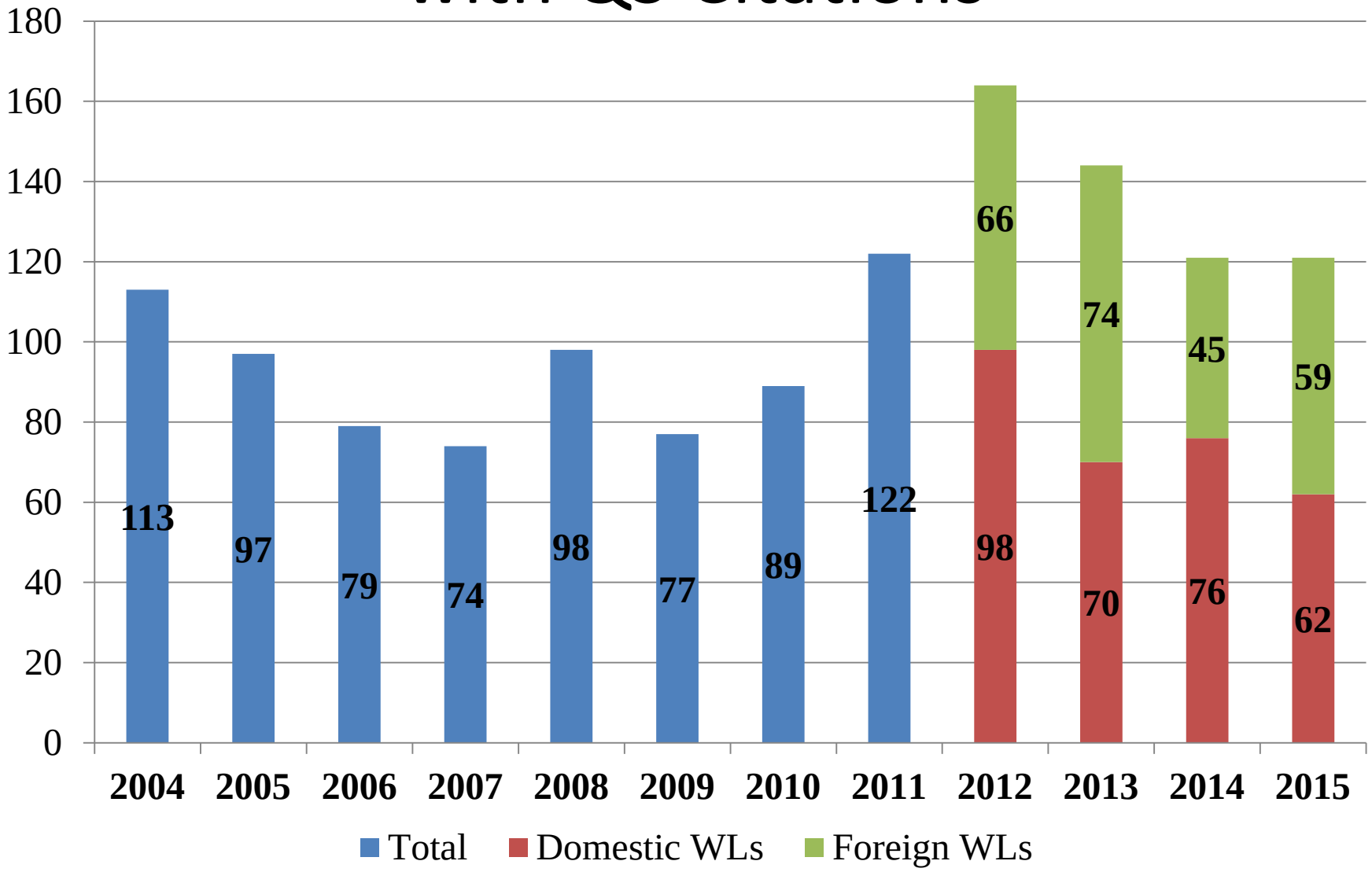


CY2015 QS Medical Device Inspections

Total Domestic Inspections	Total Foreign Inspections
1484	620

Domestic Inspection Outcomes		Foreign Inspection Outcomes	
NAI	49%	NAI	39%
VAI	41%	VAI	46%
OAI	10%	OAI	15%

Foreign and Domestic WLs with QS Citations



User Facility Inspections

- 17 facilities
- Related to contaminated duodenoscopes and morcellators
- Regulatory approach
- Public workshop on improving hospital-based surveillance systems

Medical Device Single Audit Program

- Auditing Organizations – 6 of 13 authorized to conduct MDSAP audits. All 13 working toward recognition
- 152 Participating manufacturing sites
  - 94 domestic locations
  - 58 international locations
- 117 Audit Reports Received to Date
  - 73 – U.S. Audits
  - 44 – International Audits
- Regulatory Exchange Platform – secure

Benefit-Risk Goals

Opportunity to develop and implement a set of principles that…

- Allow CDRH to arrive at the same risk determinations for medical devices
- Weigh the relative benefits and risks of options for pre and post market product quality and safety activities
- Minimize disruption of care and protect the public health

Benefit-Risk -Decision Making

Examples Related to Product Availability Decisions

- Recall and shortage
- Evaluation of a variance petition
- Continued Access to Nonconforming Product

Examples Related to Compliance and Enforcement Decisions

- Evaluation of whether to send an Warning Letter or take an alternative approach
- Evaluation of potential actions following an inspection of a manufacturer with observed Quality System deficiencies

Compliance ≠ Quality

- Quality is *more* than being free from defect and cannot be achieved by complying with a set of rules

- Quality is about products aligned with the needs of providers and patients that are produced in a reliable and trustworthy manner.

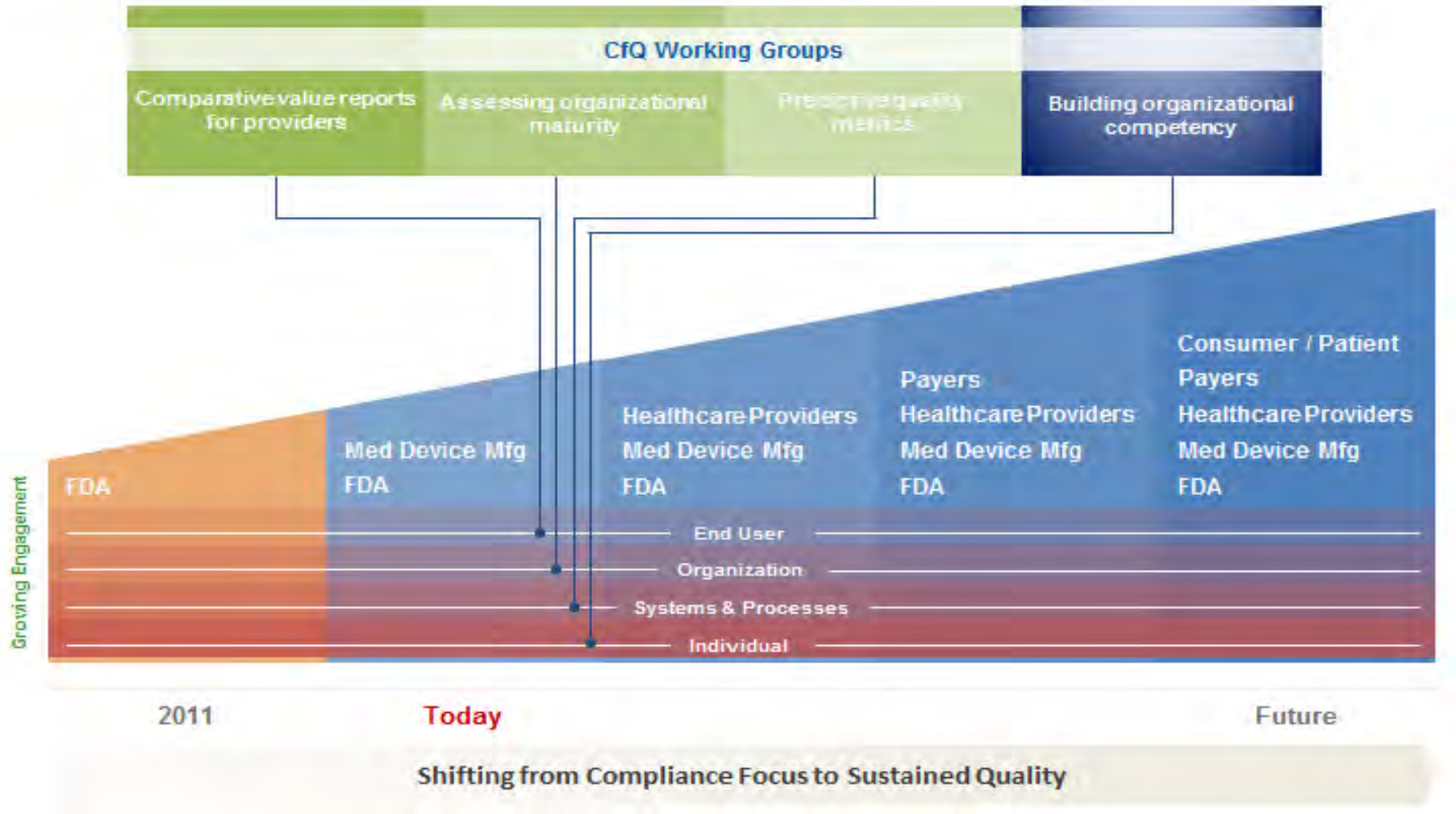
***Compliance to regulations is still important, as it is required—a high quality product is not a substitute for a compliant product under our current statutory situation.

Case for Quality Goals

- Identify new metrics for measuring, monitoring, and controlling device quality
- Collaborate on performance and organizational expectations that result in higher quality
- Explore policies and practices that foster a culture of quality
- Advance solutions for increasingly complex and dynamic ecosystems

Case for Quality Vision

Shift the medical device ecosystem to focus beyond regulatory compliance to sustained device quality for improved patient outcomes.




Real World Evidence
Will build upon and leverage the information created everyday as a part of routine health care or real world evidence.
Patient
Post Market Benefit Risk Initiative
Patient focused, appropriately scoped and informed decisions by manufactures and FDA
Case for Quality
Will identify and promote practices that result in high-quality devices and adapt FDA regulatory approaches to align with those practices

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Compliance Central: CBER Update

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Mary Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research/FDA

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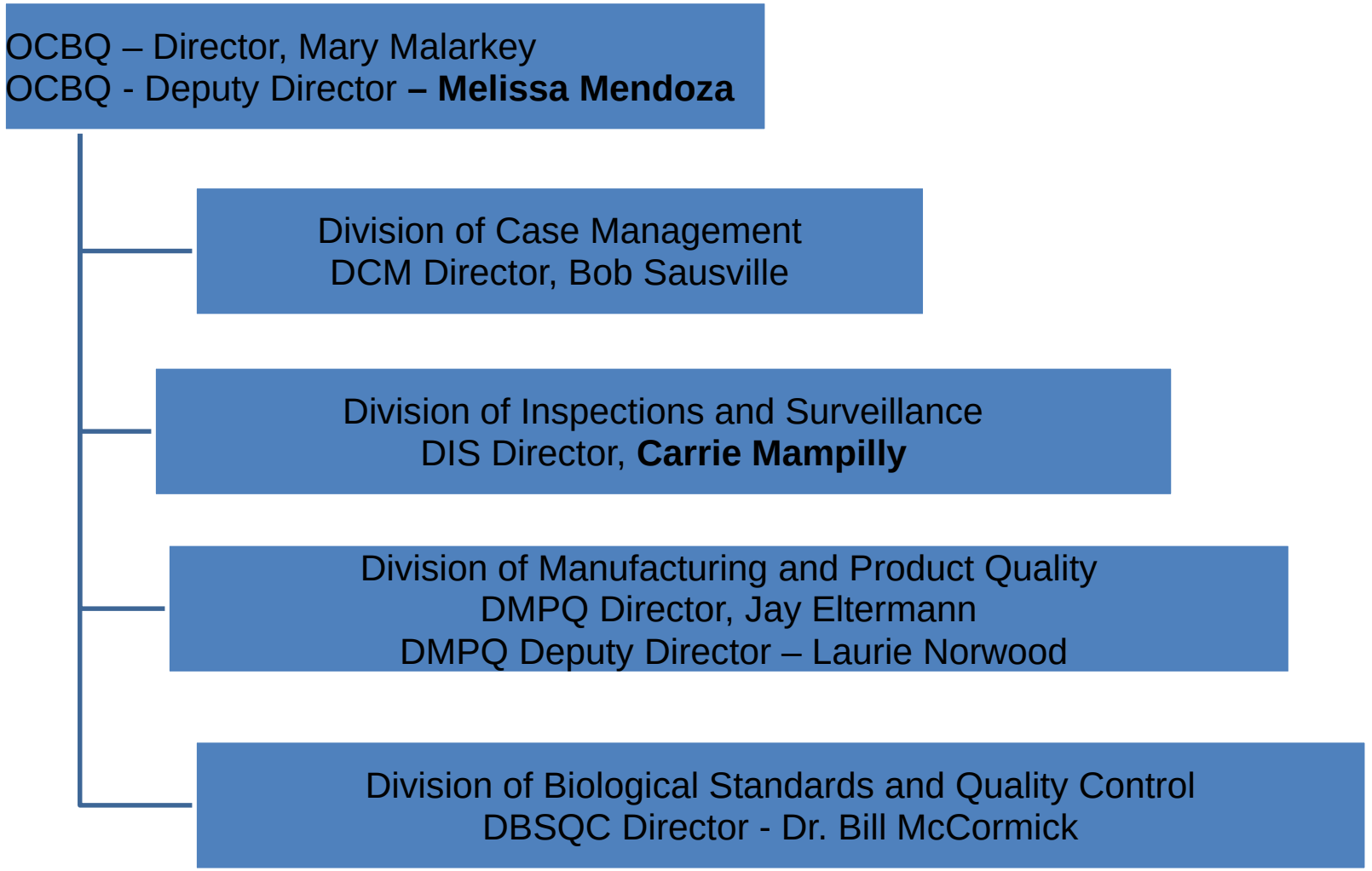
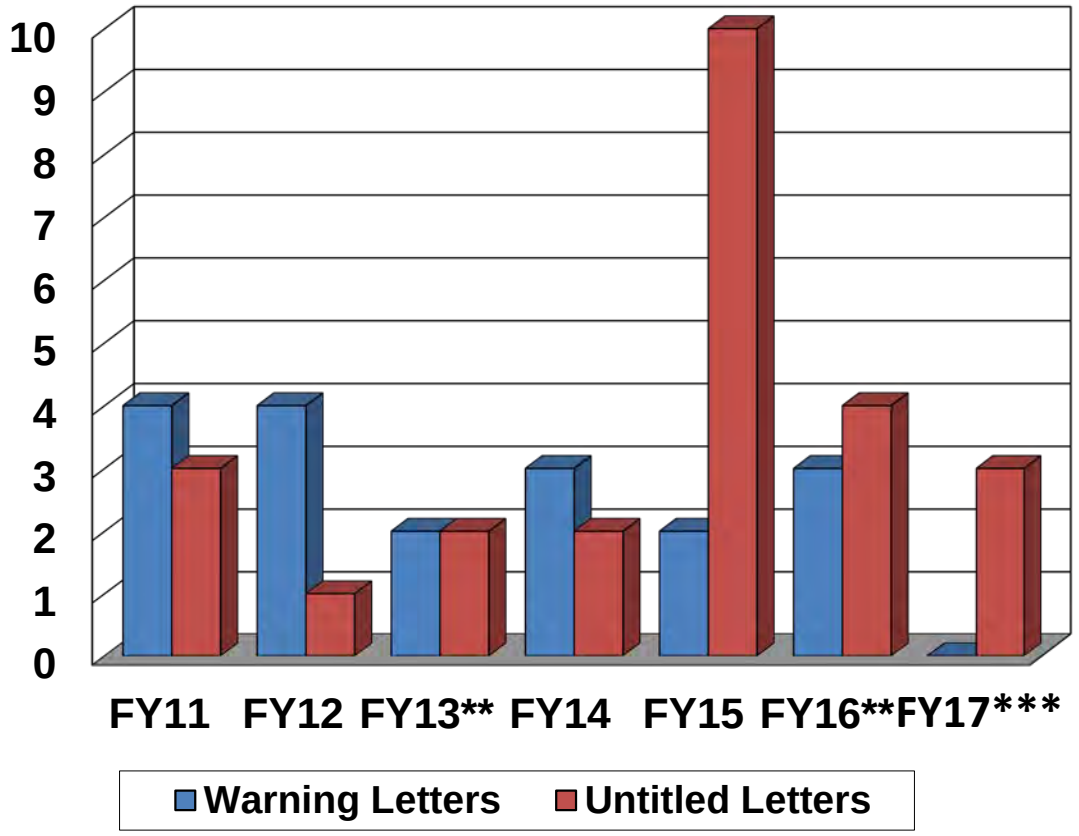


OCBQ's mission is to ensure the quality of products regulated by CBER over their entire lifecycle through pre-market review and inspection, and post-market review, surveillance, inspection, outreach and compliance

U.S. FOOD & DRUG ADMINISTRATION

Compliance Actions

Postmarket/Inspectional: Drugs and Devices



**One Warning Letter based on inspection of multiple facilities ***as of November 30,2016

Biological Drugs and Devices GMP/GTP Compliance Actions – FY15 – FY17*

- Warning Letters
  - CGMP deviations/need for premarket review and approval (1271.10(a))
  - Need for premarket review (device)
- Untitled Letters
  - Unapproved device
  - Unapproved biological drug
  - Need for premarket review and approval (1271.10(a))
  - QS regulation deviations/need for premarket review (device)
  - CGMP deviations

* as of November 30, 2016

Bioresearch Monitoring

- **Disqualification of an IRB.** The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines, per 21 CFR 56.121(b), that:

1. The IRB has refused or repeatedly failed to comply with any of the applicable regulations, and

2. The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

First Order of Disqualification for an IRB

- Order dated February 29, 2016
- Texas Applied Biomedical Services

  dba Texas Applied Biotechnology Research Review Committee IRB

  dba TABS Research Review Committee IRB # 1

http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/complianceenforcement/ucm369514.htm

U.S. FOOD & DRUG ADMINISTRATION

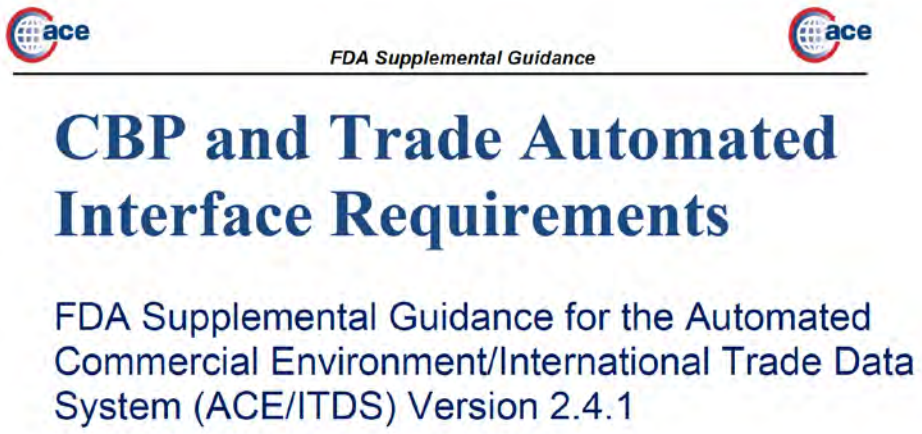
Some Current Priorities

New Technology/Product Initiative

- Prepare staff in CBER and ORA for review and inspection of new products, often breakthrough therapies.
- Develop agile approaches to introduce new technologies/manufacturing processes.
- “Horizon scanning”

Implementation of New Regulations

- Final rule, “Submission of Food and Drug Administration Import Data in the Automated Commercial Environment,” ACE



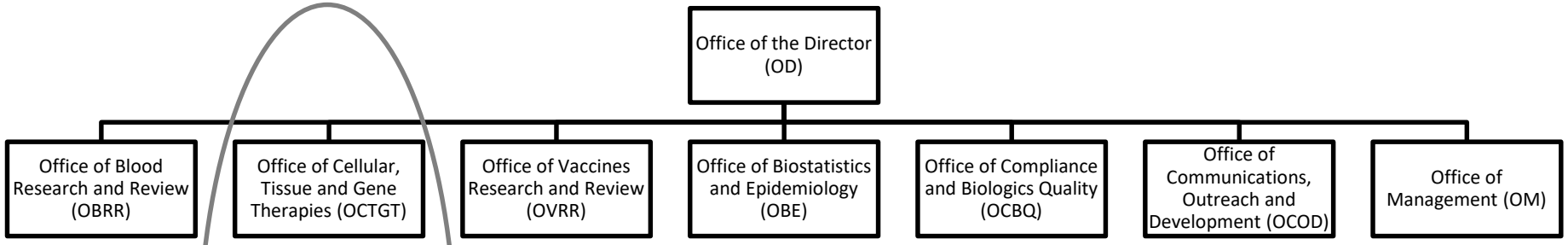
Implementation of Voluntary Reporting Program

- Draft Guidance for Industry – “Submission of Quality Metrics Data”
  - “FDA is initiating a voluntary reporting phase of the FDA quality metrics reporting program.”
  - Lot Acceptance Rate (LAR); Product Quality Complaint Rate (PQCR); Invalidated Out-of-Specification (OOS) Rate.
  - Excludes blood and blood components, vaccines, allergenics and human cells, tissues and cellular and tissue-based products.

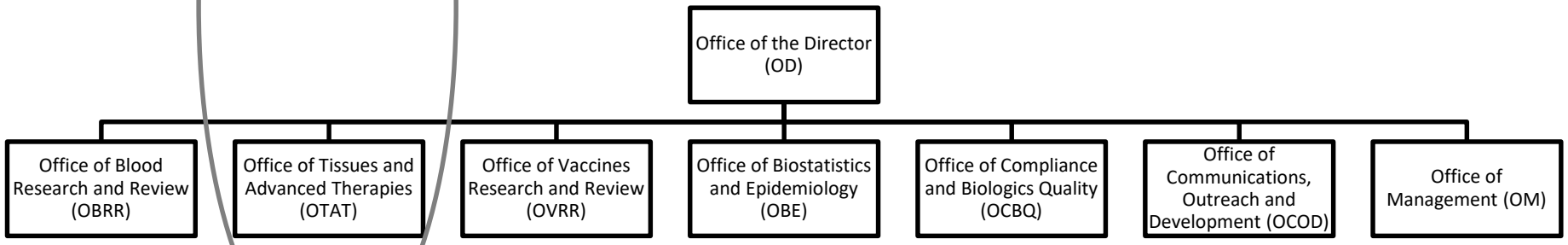
- Facilitating development of donor screening tests and vaccines for Zika – providing guidance to industry.
- Working closely with our colleagues in ORA to provide guidance and support, at present in SJN-DO and FLA-DO.
- Continue to be part of an intergovernmental working group facilitating importation and exportation by providing communication channels between all relevant government components: CBP, HHS/BARDA, FDA, CDC, USDA/APHIS, DOT, FWS, DOC/BIS

Internal CBER Restructuring

Prior to Reorganization



Following Reorganization



Effective Date: October 16, 2016

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov
Phone: 301-827-4081

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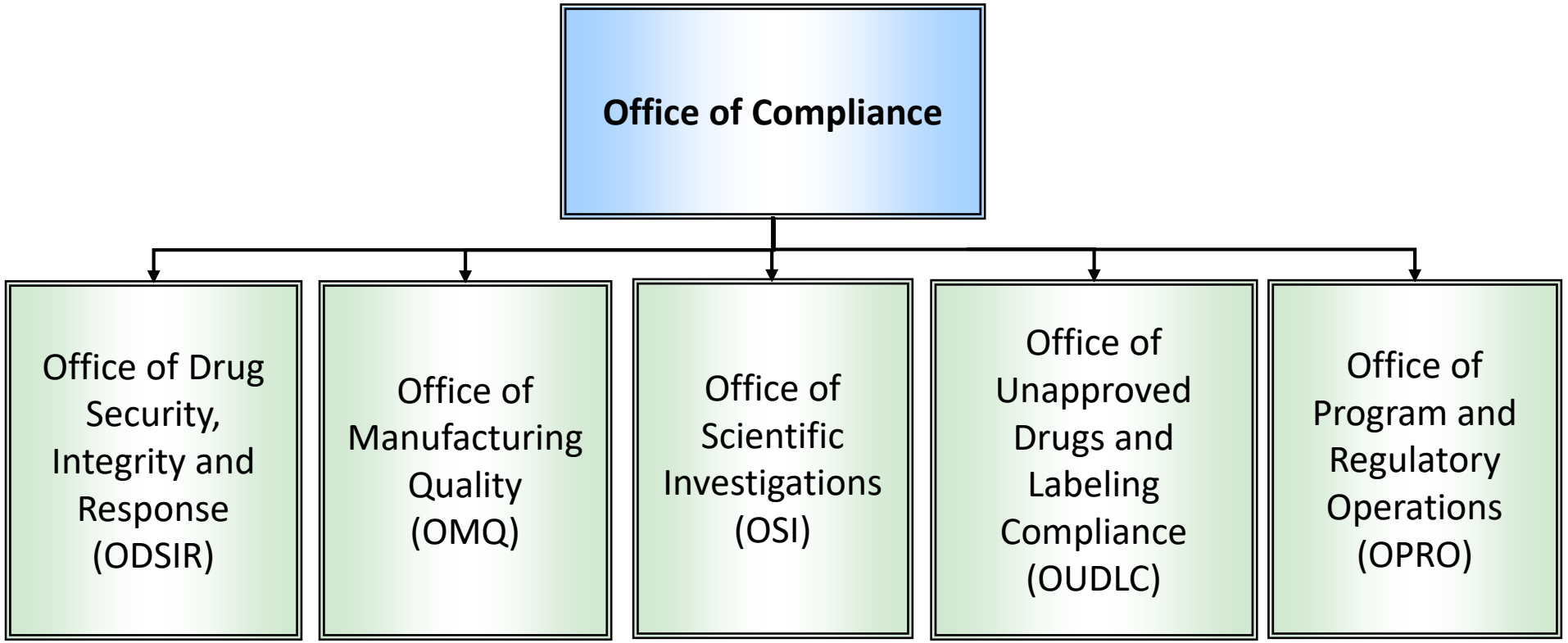

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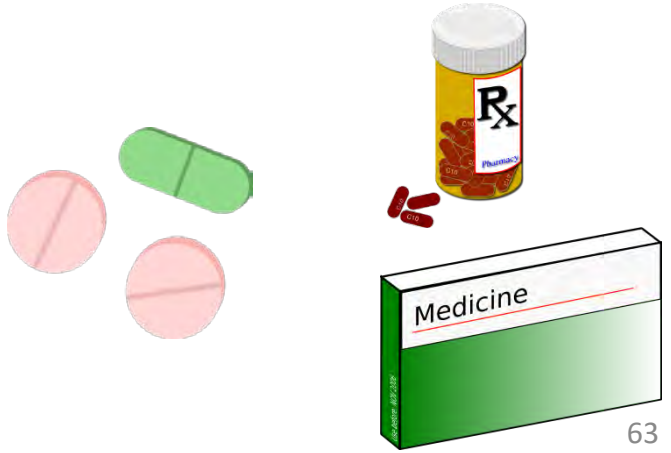

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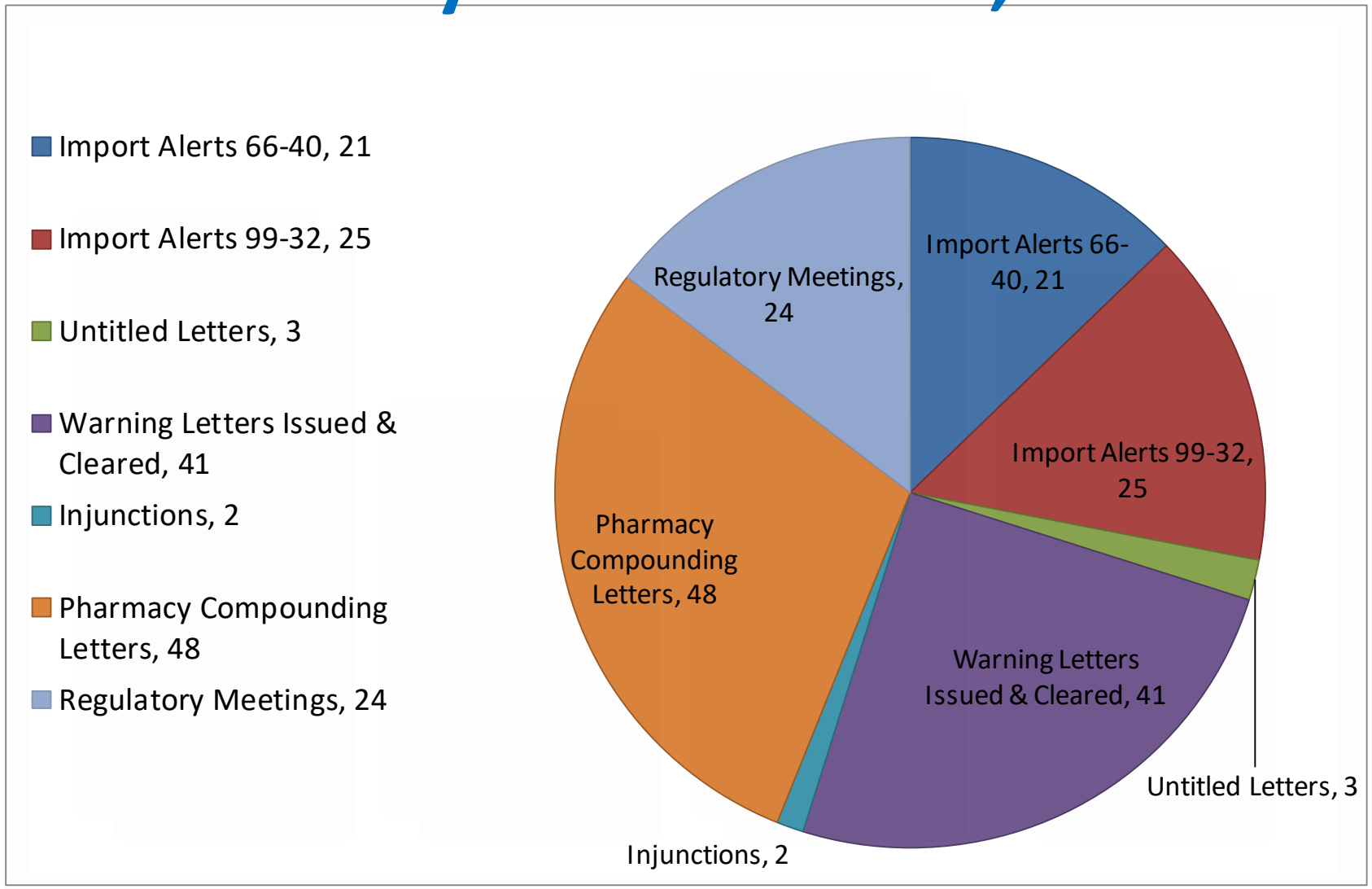

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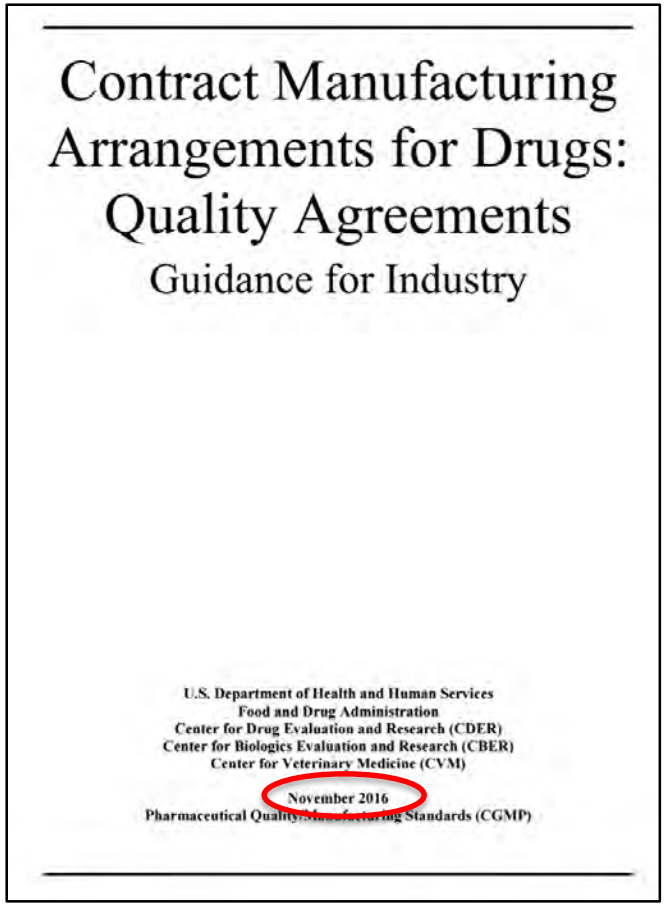
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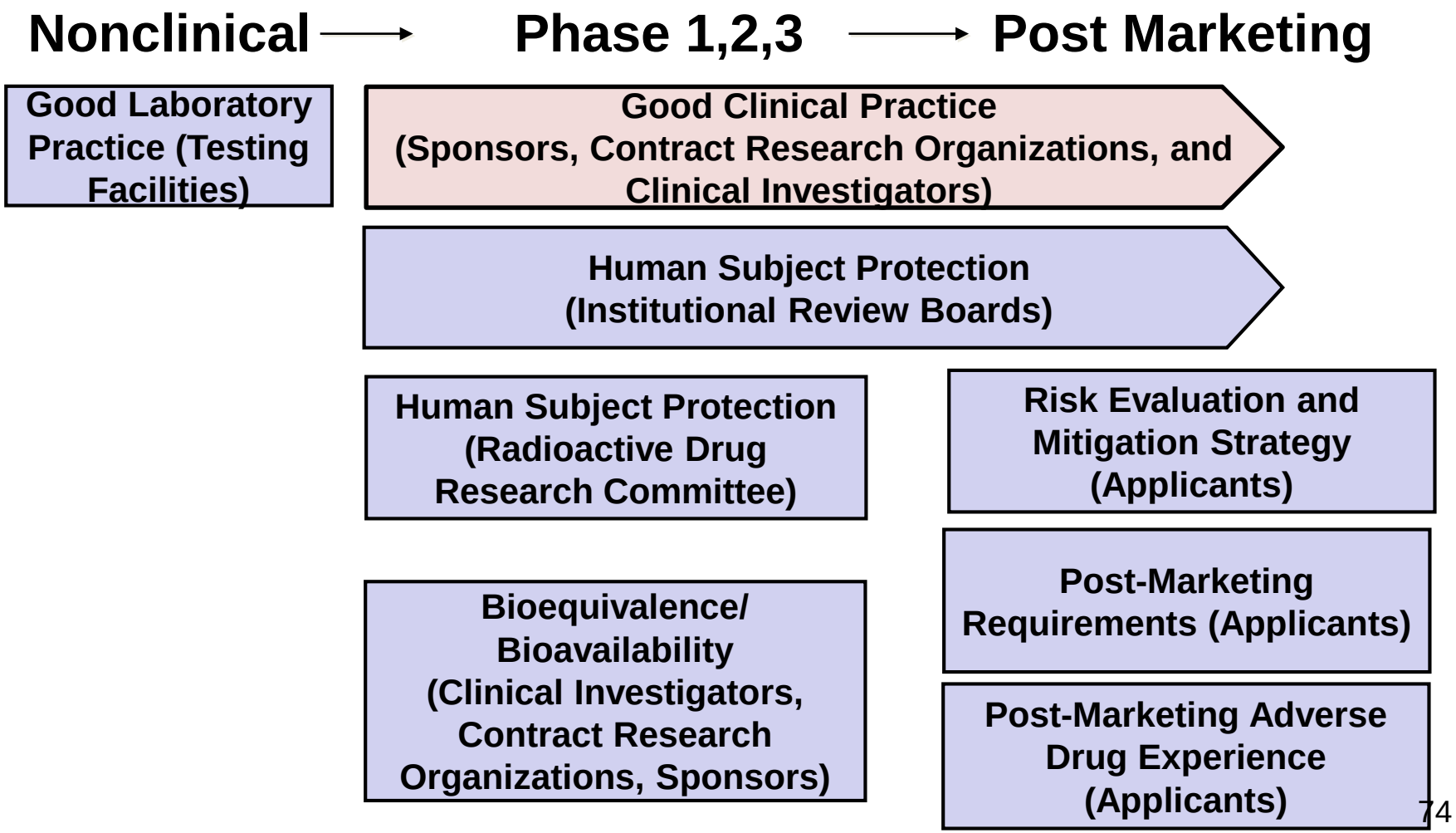
- Maximize operational excellence

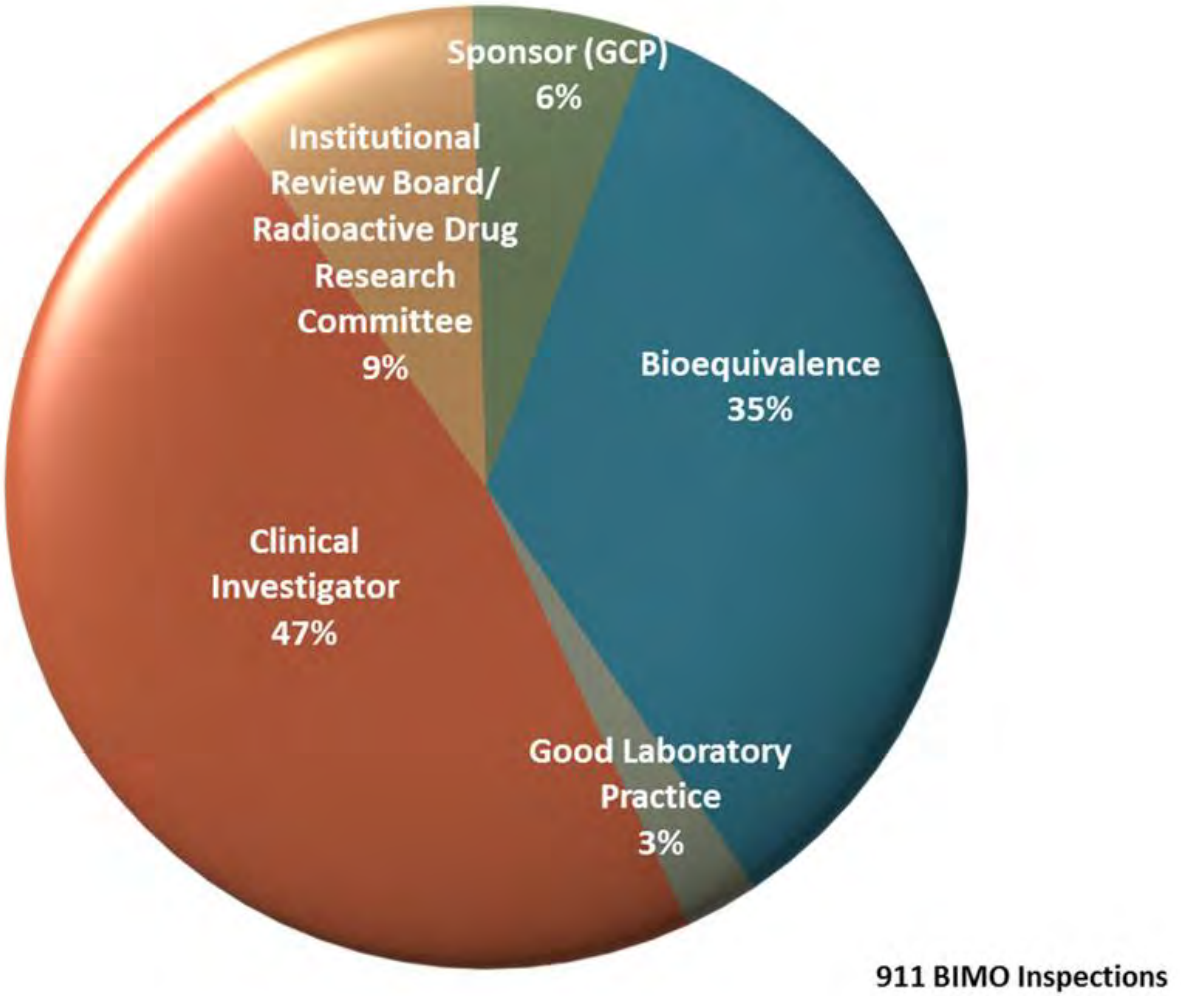
OSI Program Areas (inspected entities)



74

Bioresearch Monitoring Program Inspections*

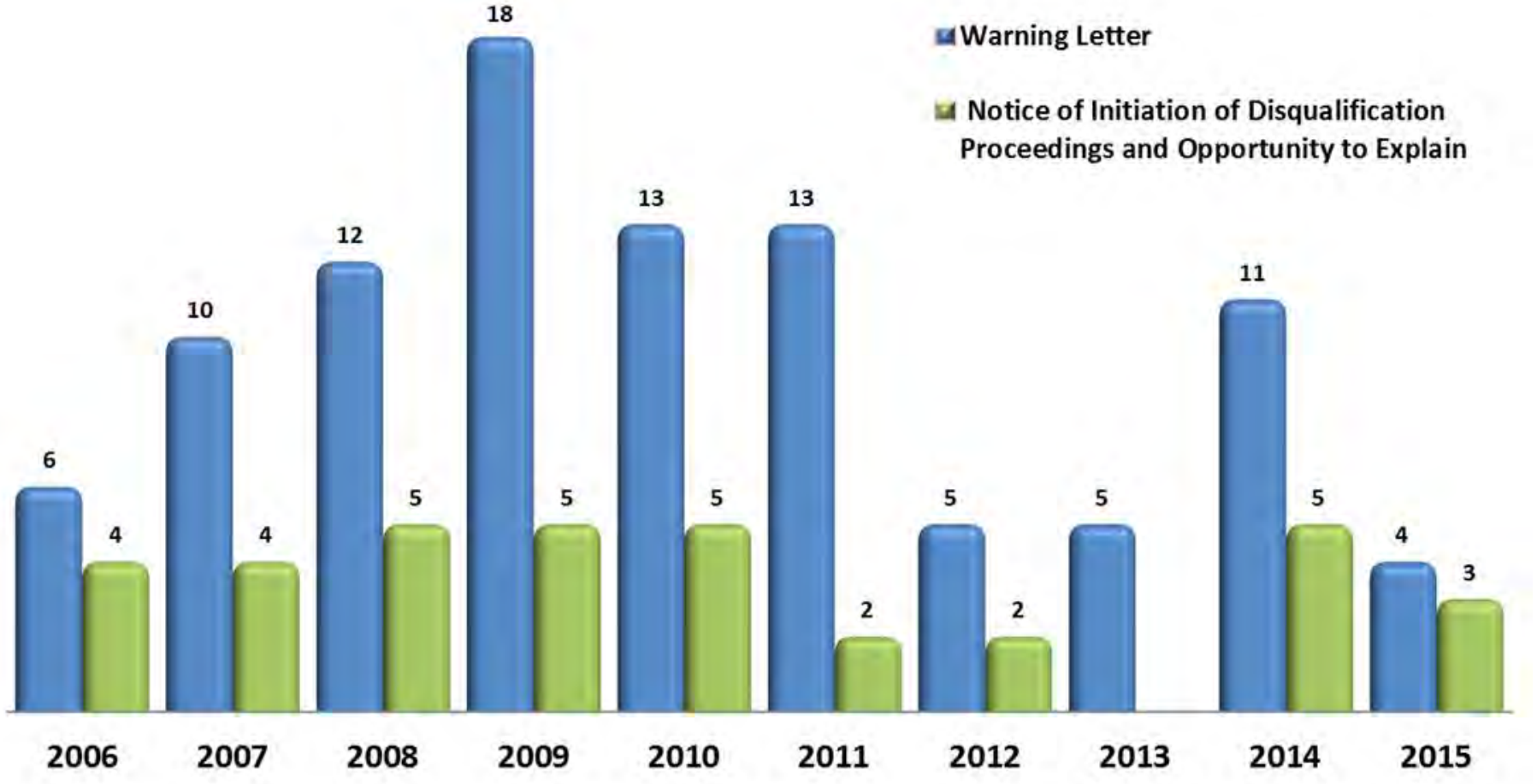
(CDER, FY 2015)



*Based on inspection start date – [Complis database as of January 20, 2016]

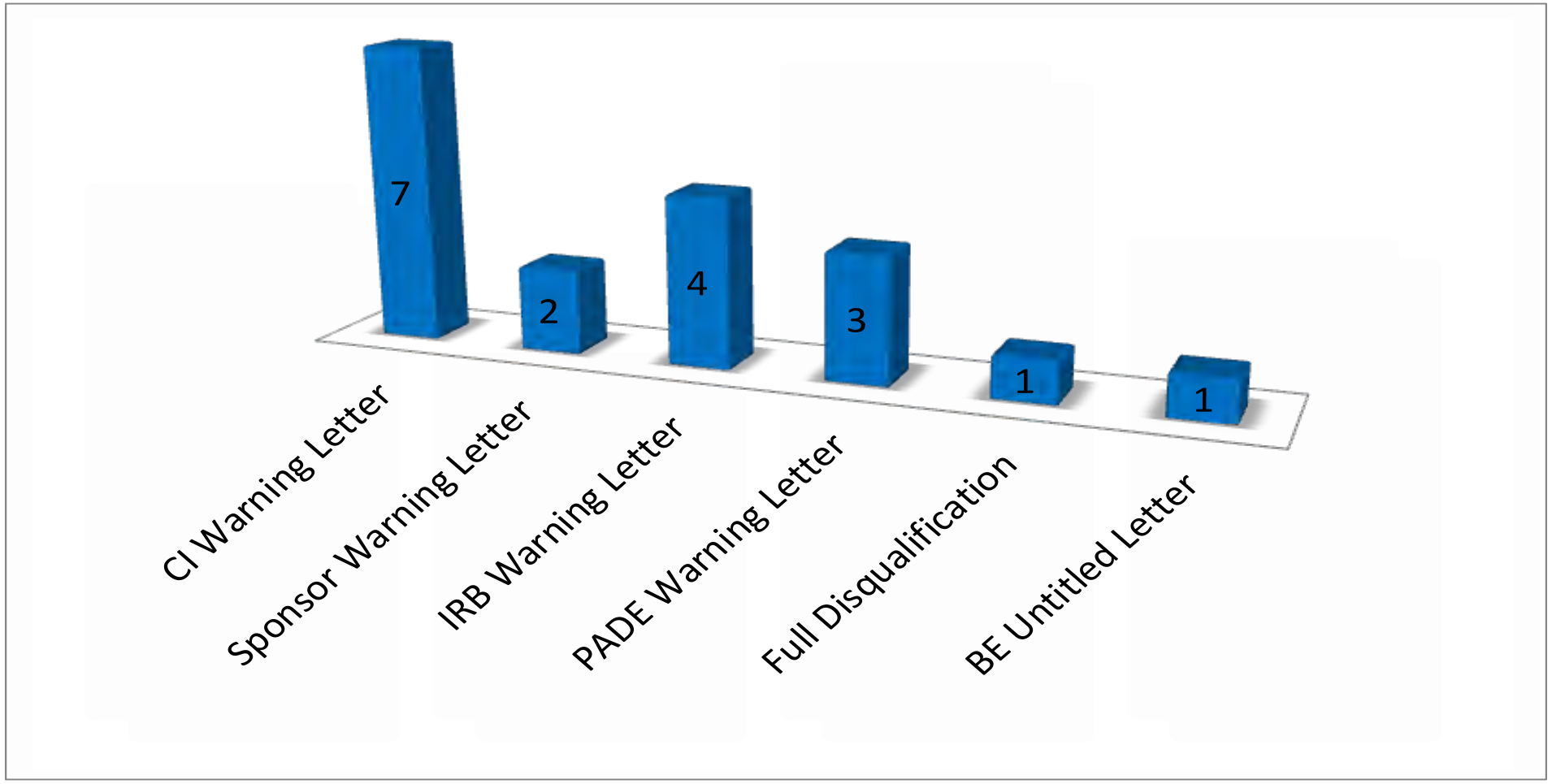
Clinical Investigator Warning/NIDPOE Letters*

(CDER, FY 2006 - FY 2015)



*Based on letter issue date [Complis database as of January 20, 2016]
NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

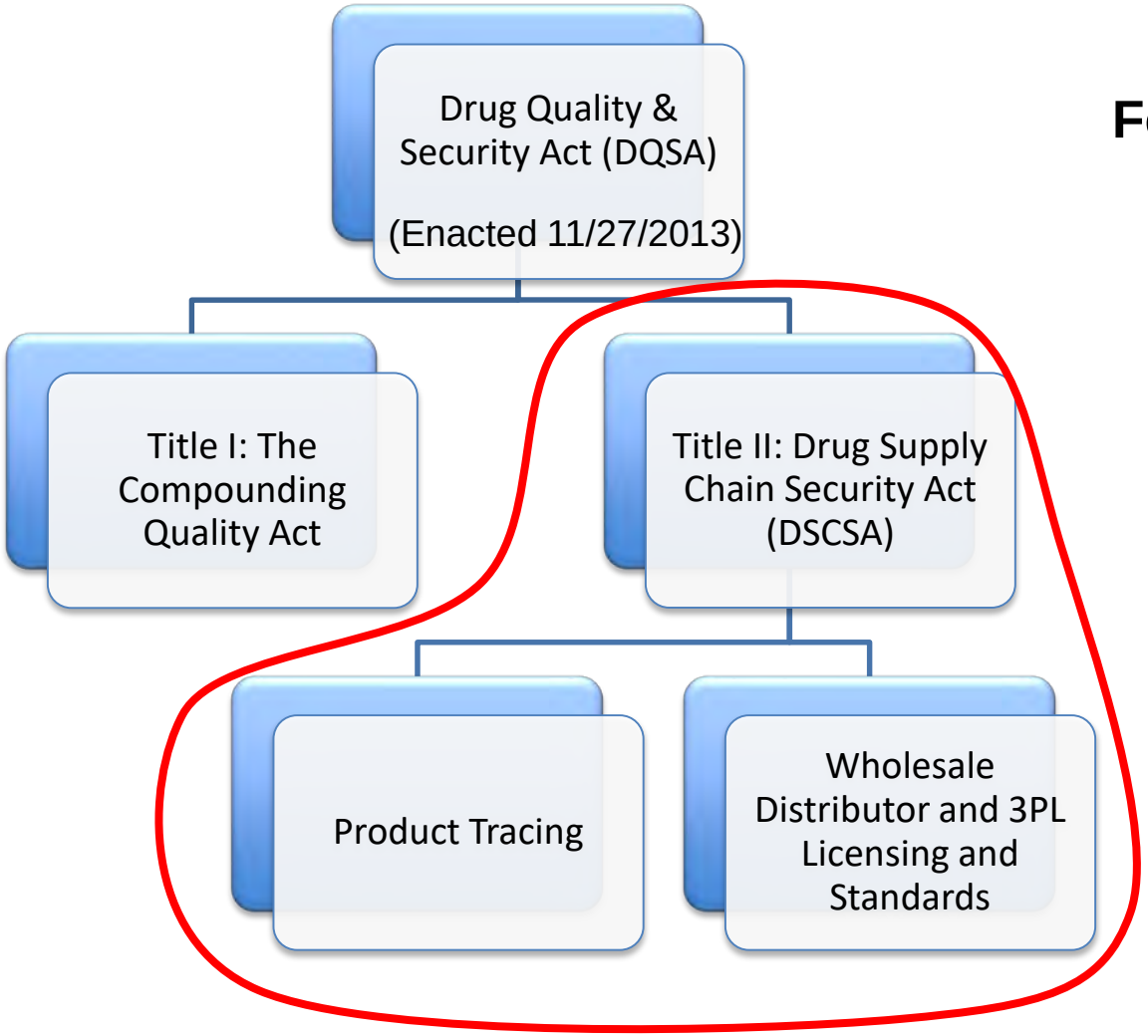
FY 2016 OSI Enforcement



Office of Drug Security, Integrity, and Response (ODSIR): Focus

- Internet pharmacies
- Counterfeit and foreign approved drug actions
  - Indictments/Prosecutions
  - Letters to doctors
- Imports/exports
- Recalls
- Incident response
- International collaborations
- Drug Supply Chain Security Act (DSCSA) implementation ("track and trace law")

The Drug Supply Chain Security Act (DSCSA) of 2013



Federal FD&C Act Sections:

- 581 – Definitions
- 582 – Requirements (product tracing, product identification, verification)
- 583 – Standards for licensure of wholesale distributors
- 584 – Standards for licensure of third-party logistics providers (3PL)
- 585 – Uniform national policy

Goals of the DSCSA

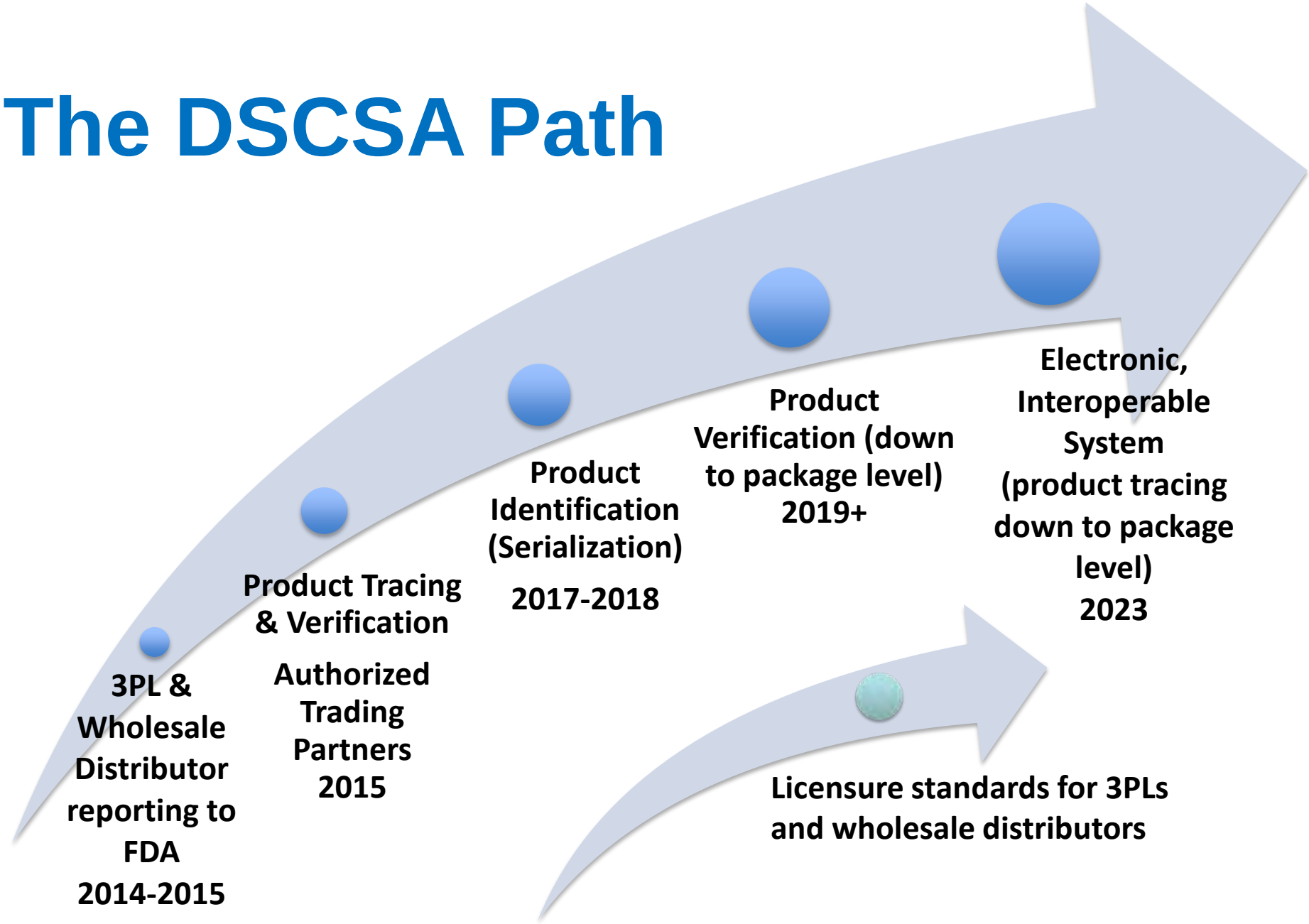
- Develop an electronic, interoperable system by 2023 to identify and trace certain prescription drugs as they move through the U.S. supply chain.

  The new system will:

  - facilitate the exchange of information by trading partners at the individual package level
  - improve efficiency of recalls
  - enable prompt response to suspect and illegitimate products when found
  - create transparency and accountability in the drug supply chain

- Establish national standards for licensure for wholesale distributors and third-party logistics providers.

The DSCSA Path



Compounding Actions

Since enactment of the DQSA on November 27, 2013, FDA has:

- Conducted approximately 425 *inspections* of compounders.
- Overseen over 90 *recall events* by compounders, and requested numerous compounders to cease operations
- Issued over 130 *warning letters*; one addressed violations identified at four facilities
- Issued over 30 *letters* referring findings from inspections of pharmacies that compounded their drugs in accordance with the conditions of section 503A to the states
- Obtained *4 civil consent decrees* of permanent injunction
- Sought several criminal prosecutions

Inspection Observations

- Continue to identify insanitary conditions at many of the compounding facilities inspected
  - Dog beds and hairs in close proximity to sterile compounding room
  - Dead bugs in ceilings
  - Renovations being made without evidence of controls to prevent contamination
  - Compounding by personnel with exposed skin

Other Compounding Actions

- Issued over 20 guidance documents
- Issued final rule and proposed rule describing additions and modifications to the Withdrawn or Removed List (503A and 503B)
- Solicited nominations for 503A and 503B bulks lists and for drugs that are difficult to compound under sections 503A and 503B
- Held 6 meetings of the Pharmacy Compounding Advisory Committee
- Held 4 sets of listening sessions with over 75 stakeholders
- Held 4 intergovernmental working meetings with the states

What's next….

- New legislation…
  - User fee reauthorization
  - 21st Century Cures?
- Continue implementation of DQSA (compounding/track and trace)
- Focus on quality/safety and data integrity
- Guidance and standards for compliance
- Program alignment
- More….

Thank You

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