FDA Drug Quality Regulation

CDER Small Business - Regulatory Education for Industry (REdI)
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Office of Compliance, CDER, FDA

Purpose

The presentation will summarize

1. Overview CDER reorganization: **OPQ**
2. What happens after an inspection; what you should do when FDA finds deviations.
3. The top 5 drug quality violations
4. Importance of the integrity of drug quality information
5. Post-marketing reports: Do’s and Don’ts
6. Current policy initiatives

Agenda

- Office of Pharmaceutical Quality *(proposed)*
- Hosting an inspection
  - before, during, and after
  - do's and don'ts
- Top 5 Quality Problem Areas
- Defect reports
- BLA: What's new?

- Questions

Brief History:
20th Century: Standards for Mfg & Testing

- GMP regulations first published in 1963
- Evolution of CMC filing requirements
- Beginning in 1990s, ICH sought standardization of requirements, including many CMC areas
  - common technical document for regulatory filings
  - quality guidance (API GMPs, testing, etc.)
- On-going reliance on USP and other pharmacopoeias for public standards

Brief History (cont.): Early 2000s: FDA's Pharmaceutical Quality for 21st Century Initiative

- Succeeded at many levels:
  - 'Enabling' of modern technology (e.g., PAT)
  - Updates to GMP regs; revised GMP guidance
  - Multiple ICH documents:
    - Pharmaceutical Development and QbD
    - Quality Risk Management;
    - Quality Systems
  - Formation of Pharmaceutical Inspectorate
  - Risk-based selection of facilities for inspection

Brief History (cont.): Early 2000s: FDA's Pharmaceutical Quality for 21st Century Initiative

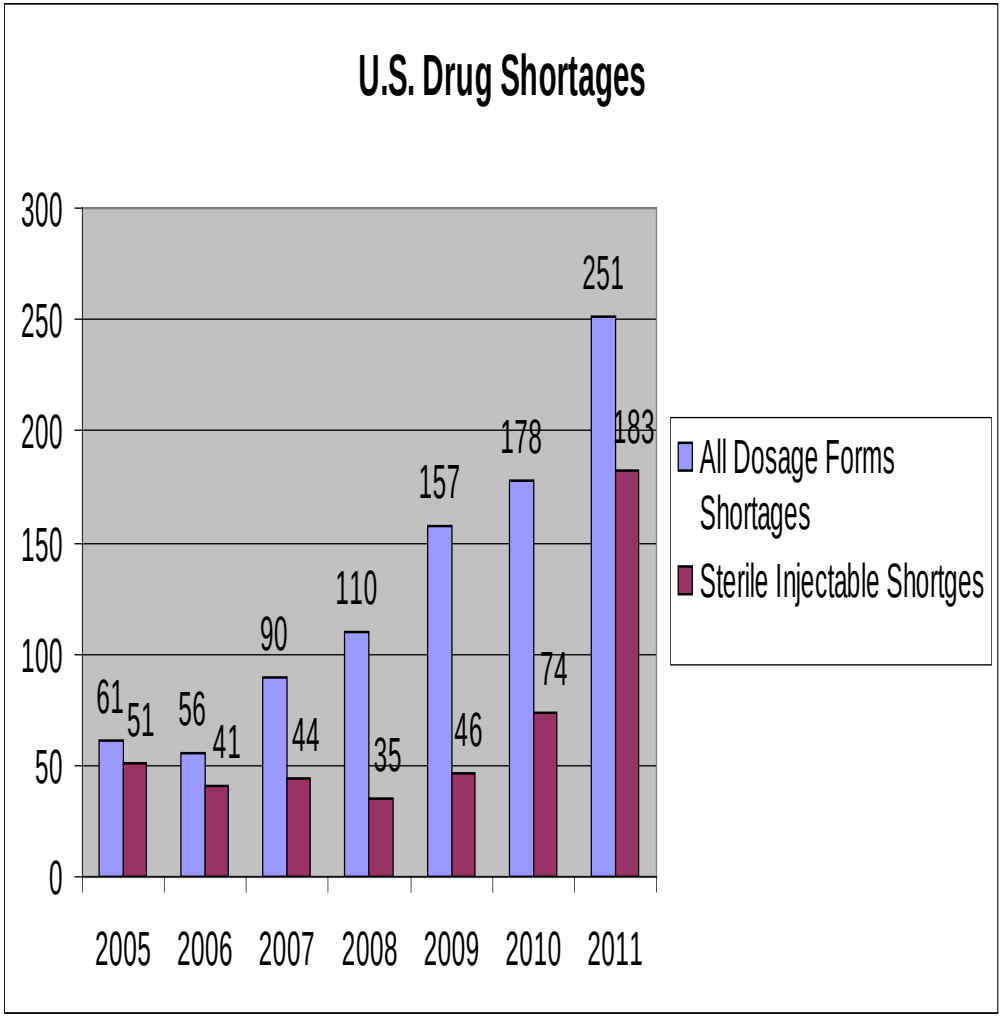
Vision

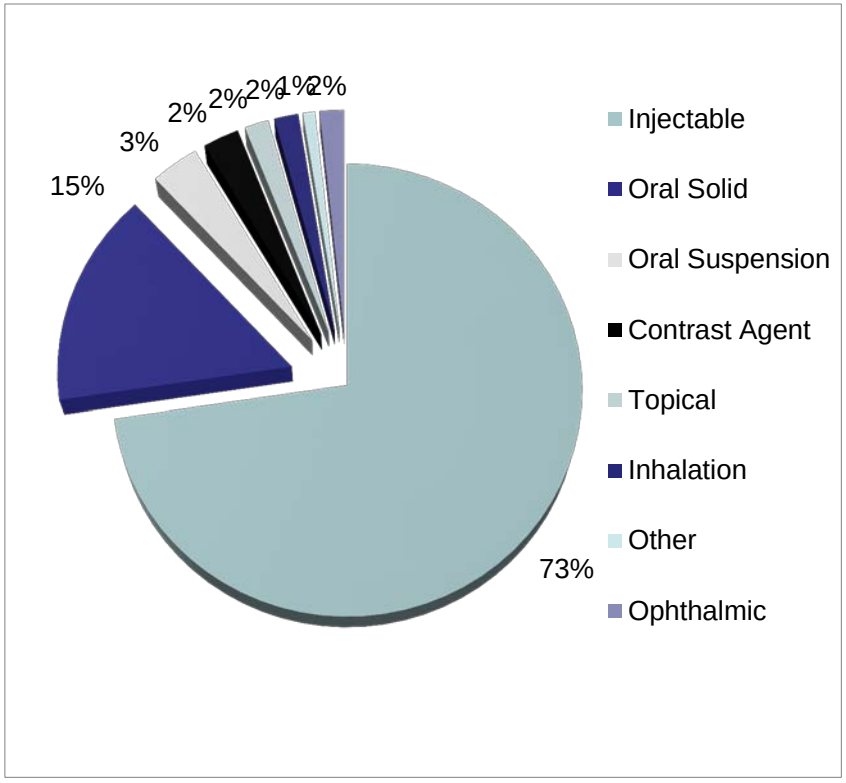
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

Current Challenges

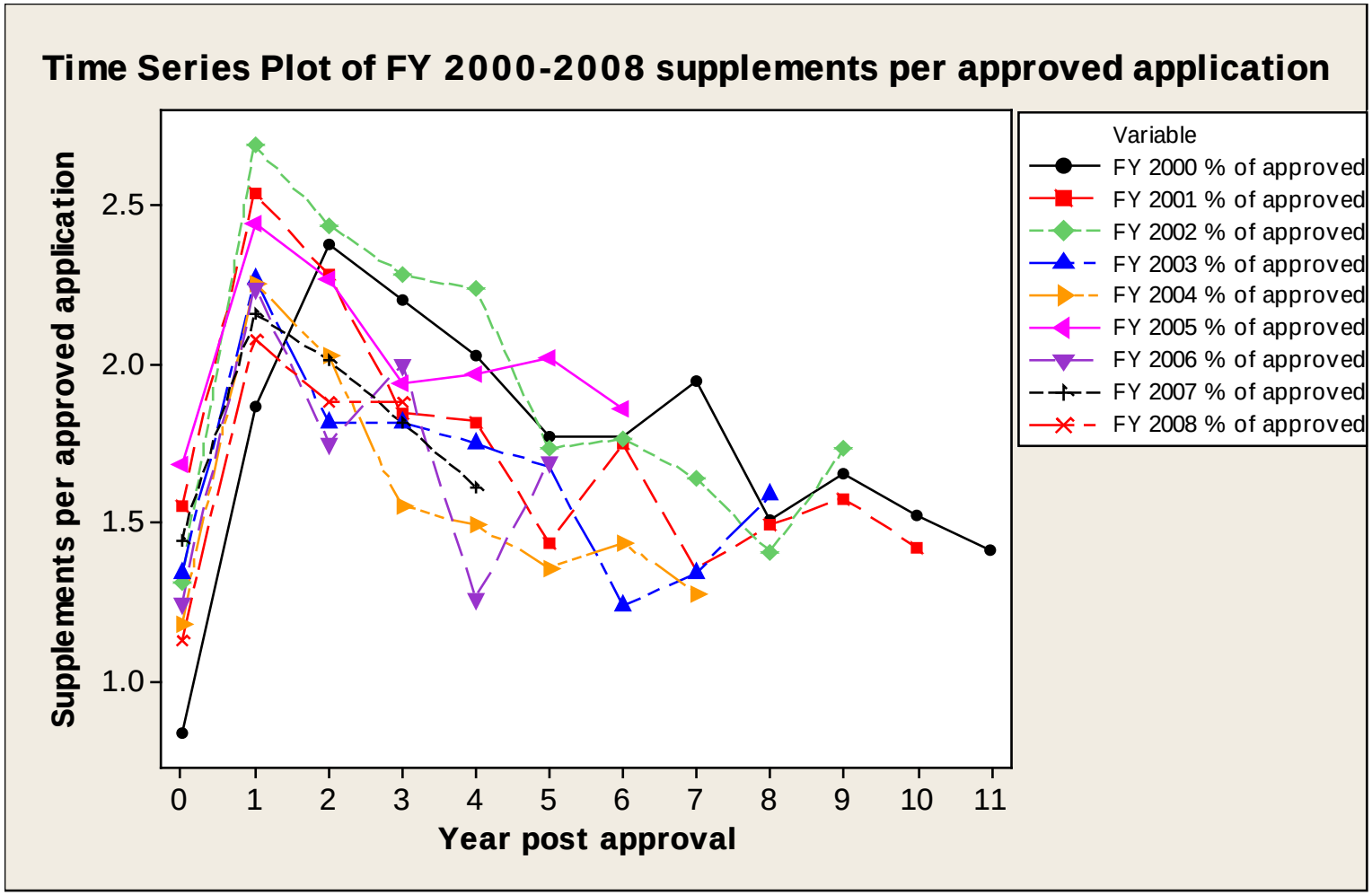
- Generic application review backlog and large number of manufacturing supplements
  - Time required for regulatory approval holds back or blocks facilities improvements, e.g., site changes, major upgrades
  - Manufacturers with robust quality systems should be able to manage such changes without regulatory oversight
- Need for ongoing innovation in manufacturing
  - Regulatory oversight one factor in lack of industry adoption of modern manufacturing technology
- State of drug quality?
  - Lack useful quality indicators across-industry.
  - Can we prevent these problems?

Drug Shortages – State of Quality?

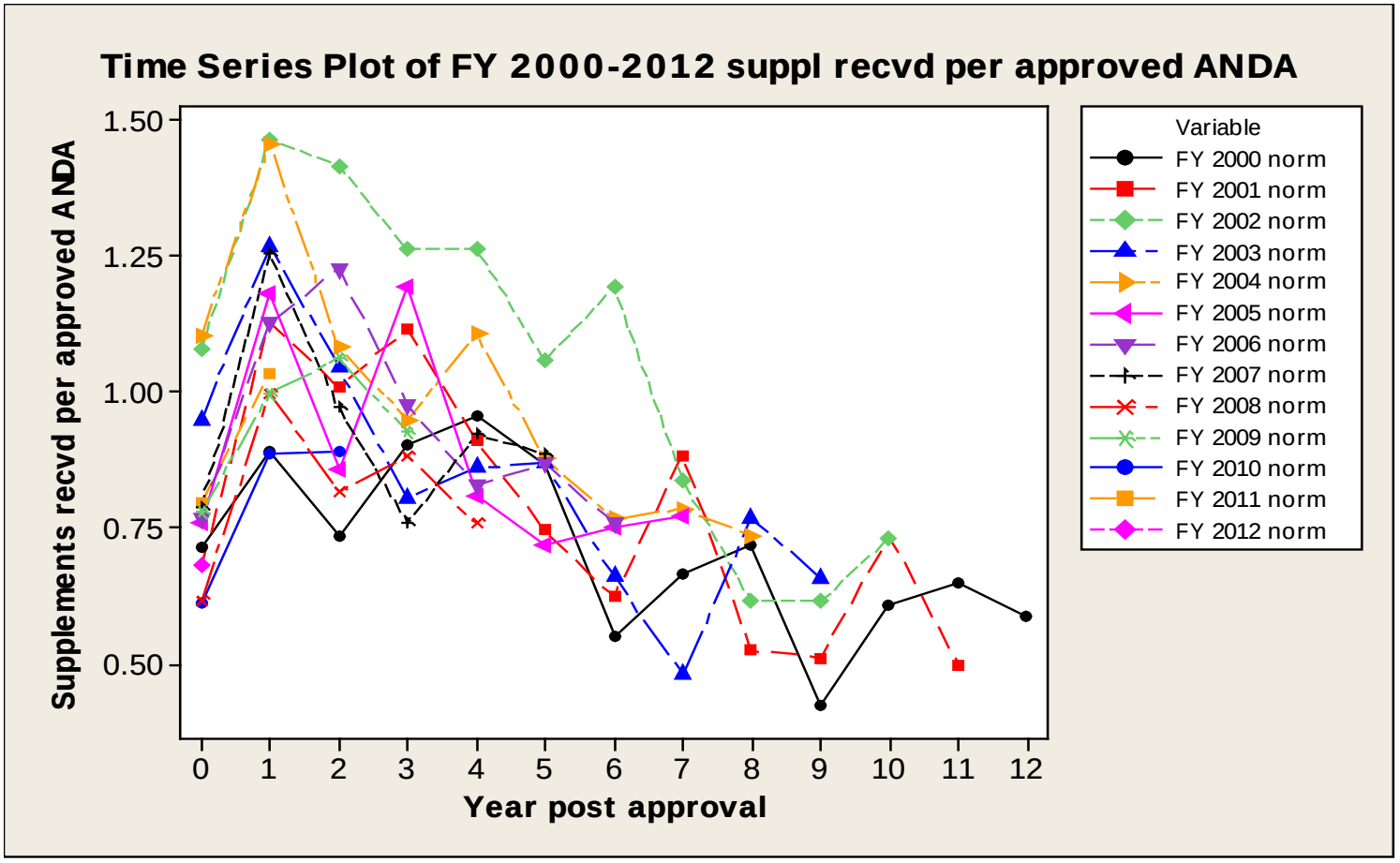




NDA CMC Supplements



ANDA CMC Supplements



Where are we going?

CDER OPQ

Mission

The Office of Pharmaceutical Quality assures that quality medicines are available to the American public.

Vision

The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality.

One Quality Voice

OPQ: Organizing Principles of Change

- Same quality standards for all drugs; **lifecycle approach**
  - Clinically relevant specifications
- Unified **policy and standards** development/analysis
- Establish clear standards for review and inspection
  - Clear enforcement policies
  - Surveillance using quantitative metrics
- Specialization and team review: **integration of review and inspection** for a quality assessment
- Accountability: Overall **QMS** and evaluation system

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Defining Theme: *One Quality Voice*

- **One Quality Voice for Drugs**
  - ***OPQ will centralize quality drug review—creating one quality voice by integrating quality review, quality evaluation, and inspection across the product lifecycle.***
- **One Quality Voice for Patients**
  - ***OPQ will assure that quality medicines are available for the American public.***
- **One Quality Voice for Industry**
  - ***OPQ will establish consistent quality standards and clear expectations for industry.***
- **One Quality Voice for Healthcare Professionals**
  - ***OPQ will anticipate quality problems before they develop and help preven shortages.***
- **One Quality Voice for Healthcare Purchasers**
  - ***OPQ will emphasize quality metrics.***

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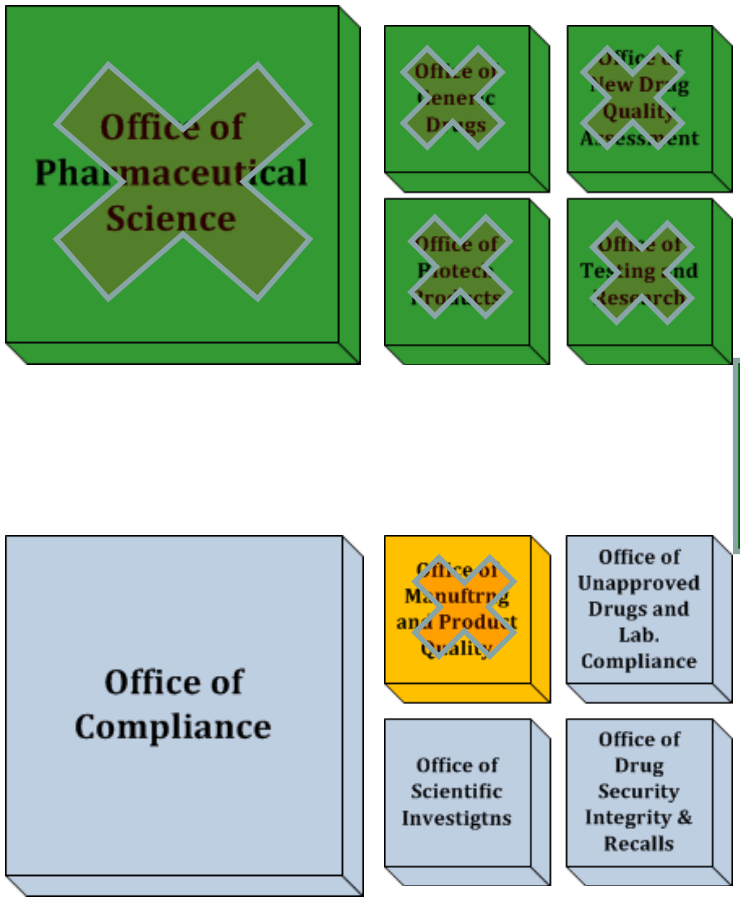
Current State



Future State

OPQ Structure

OPQ Immediate Office

- Office of Operations
- Office of New Drug Products
- Office of Lifecycle Drug Products
- Office of Process and Facilities
- Office of Surveillance
- Office of Testing & Research
- Office of Biotechnology Products
- Office of Policy

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Office of Pharmaceutical Quality (OPQ)

- Directs overall regulation of pharmaceutical quality
  - submission review, manufacturing facility assessment, and surveillance of the quality of marketed pharmaceutical products
- Plans, develops, and directs the office strategy
  - research, new technology, policy, and regulatory support for the various functions of subsidiary offices
- Encourage creative thinking, collaboration, and transparency
- Leads and coordinates partnerships between offices, centers, and agencies
  - includes international harmonization and collaboration

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OPQ/Office of Operations

Manages the business processes, internal quality management system, and training and development system:

- Develops and implements internal processes to support the drug quality reviews and inspections
- Monitors, reports, and leads corrective and preventive actions relating to the performance of internal processes, as defined by standard procedures
- Designs, develops, and implements OPQ-specific training and developmental programs to ensure the skill sets and competencies of staff are maintained and continually improved.

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OPQ/Office of New Drug Products

Evaluates and assesses product quality aspects of IND and NDA submissions, and API information supporting Abbreviated New Drug Applications (ANDAs)

- Conducts team-based reviews that include cross-OPQ collaboration and participation in inspection where necessary.
- Conveys risk-informed recommendations on approvability
- Responsible for the communication of product-specific residual risk identified in the pre-marketing arena.
- Serve as a liaison to CDER's Office of New Drugs.
- Assessment of the CMC information in an application, including but not only:
  - Drug substance/API information supporting INDs, NDAs, and ANDAs
  - Product quality standards, including:
    - Formulation/product design
    - Product characterization
    - Clinically-relevant specifications, including those related to biopharmaceutics
    - Container/closure system
    - Stability
  - Product-related post-marketing requirements/commitments

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OPQ/Office of Lifecycle Drug Products

Evaluates and assesses product quality aspects of Abbreviated New Drug Applications (ANDAs), and makes risk-informed recommendations on the approvability of such products to appropriate stakeholders

- Conducts team-based reviews that include cross-OPQ collaboration and participation in inspection where necessary.
- Serves as the liaison to CDER's Office of Generic Drugs
- Evaluates and assesses post-marketing activities for both the approved brand and generic drug products to ensure that, over time, the generic version adequately mirrors the innovator drug product as lifecycle changes are made in either
- Assessment of the CMC information in an application, including but not only:
  - Identifying potential failure modes
  - Quality standards, including
    - Formulation/product design
    - Clinically-relevant specifications, including those related to biopharmaceutics
    - Product characterization
    - Container/closure system
    - Stability
  - Post-approval change management

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OPQ/Office of Process and Facilities

Performs the review of NDAs, ANDAs, and BLAs and as appropriate, post-approval supplements, investigational drug applications (INDs)

- Evaluates manufacturing processes and sites to determine if the facilities, process design, and control strategies provide appropriate assurance that the applicant can manufacture quality products
- Utilizes risk-based approaches for efficient assessment of the following application-related aspects:
  - Facilities, processes, and controls for
    - select DS and intermediates and all drug products
    - microbiological aspects for drug substances and drug products
    - facility and manufacturing process suitability for commercial manufacturing and consistency with the principles of CGMP
- Manages the pre-approval (PAI) and pre-license inspection (PLI) programs
- Continued evaluation, through a Post-Approval Inspection program, of application-specific coverage of recently approved applications
- Partners with other offices internal and external to OPQ to establish standards for OPF-related review and inspectional activities, including novel and complex manufacturing technologies.

OPQ/Office of Surveillance

Conducts continual monitoring, assessment, and reporting on the state of quality across the inventory of drug products and facilities regulated by FDA.

- Serve as the business owner of quality data systems and the pharmaceutical quality platform.
- Develops, implements, and manages an analytic and potentially predictive program to assess and report on the state of the inventory of regulated industry manufacturers at a product and site level using all available data sources.
- Develops, implements, and manages a new inspection program focusing on the surveillance of quality, which is distinct but complementary to traditional inspections for compliance with CGMPs, or inspection conducted as part of a marketing application review.

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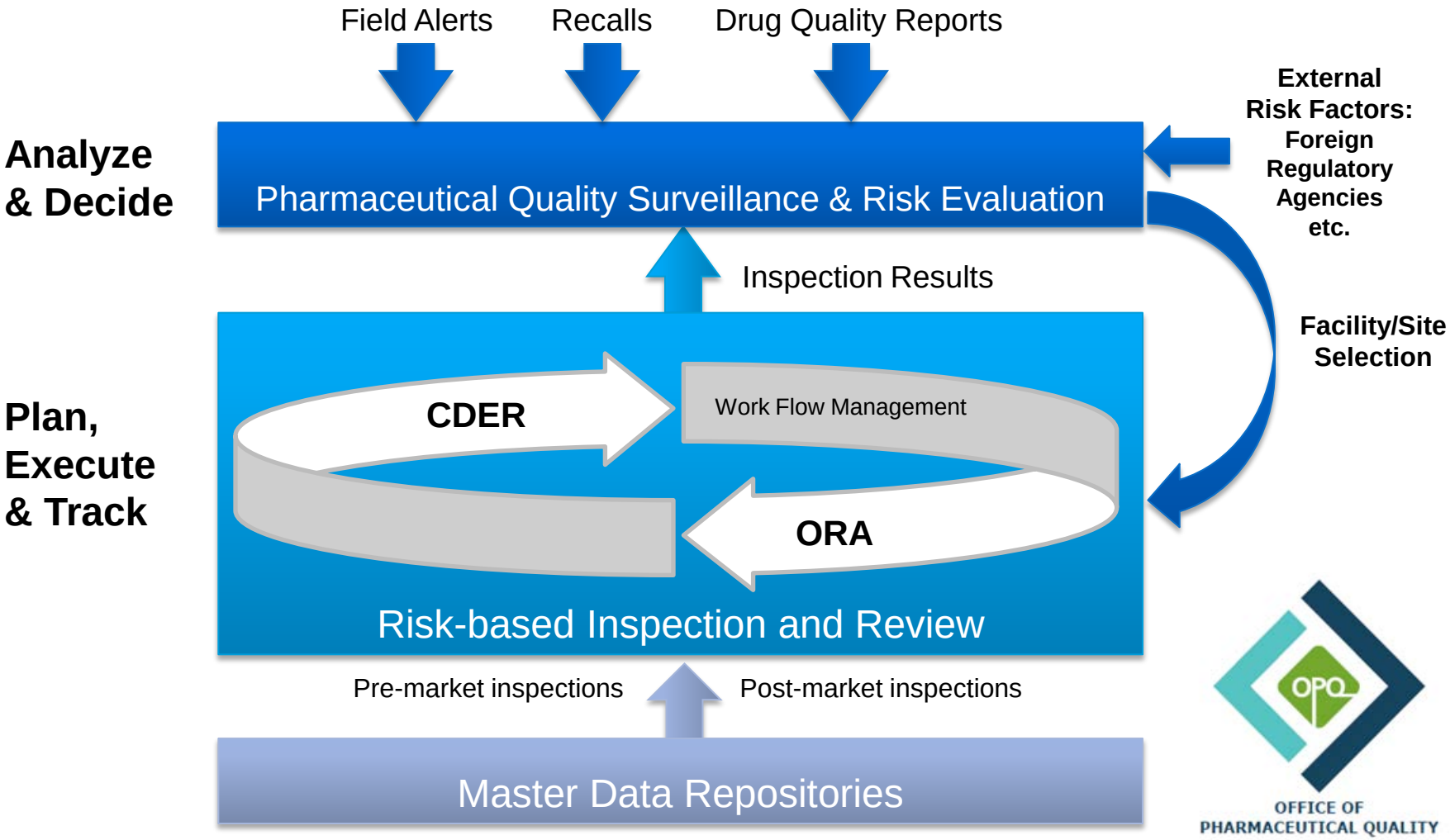
Pharmaceutical Quality Platform



OPQ/Office of Testing & Research

Conducts research to support the development of scientific standards on the composition, quality, safety, and effectiveness of human drug products, including research to understand new technologies, to modernize current regulatory pathways or to indicate new regulatory pathways.

- Provides advice, collaborative research opportunities, and scientific training for review staff on pharmaceutical quality and bioavailability/bioequivalence issues including manufacturing, formulation, analytical testing and modeling

- Directs drug quality surveillance testing and laboratory-based investigational activities for the Center as needed for public health emergencies

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OPQ/Office of Biotechnology Products

Protects and advances the public health through review, regulation, and research of biological products and biosimilar biological products as specified by the Public Health Service (PHS) Act and applicable provisions of the Federal Food, Drug, & Cosmetic (FD&C) Act.

- Provides risk-based product quality assessments of the manufacturer's assurance that the quality of a biologic product fully anticipates the clinical outcomes of the label claim and through characterization of both product and associated manufacturing processes
  - Reviews, evaluates, and takes appropriate action on investigational new drug applications (INDs)
  - Participates in inspections of manufacturing facilities for compliance with applicable standards.
- Plans and conducts mission-related research on the development, manufacture, testing, and molecular actions of therapeutic biological, including emerging technologies
- Performs the investigational device exemption (IDE) review process for devices related to biological therapeutic products regulated by the office, and develops related policy.
- Tests and partners with other Center units in the testing of products submitted for release by manufacturers.

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OPQ/Office of Policy

Coordinates the development of regulations, guidance, policies, and CDER MAPPs

- Over-the-counter and prescription drugs, application-based and non-application-based drugs; pre-approval; post-approval
- Ensures that regulatory policies and standards incorporate benefit-risk considerations
- Manages CDER interactions with external standard-setting organizations
- Coordinates with other product centers and ORA through FDA's Council of Pharmaceutical Quality to address strategic policy objectives
- Collaborates with OPQ laboratories to prioritize research to support policy development and regulatory decision-making

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Risks Associated with Initiative

- Changing FDA approach to drug quality requires sustained management attention and coordination
- Internal and external stakeholders may be concerned with direction: it represents a change in approach
- Magnitude of effort required for GDUFA requires major focus on accomplishing those goals

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Role of Industry

- FDA plans to be transparent and engage external stakeholders as we initiate changes
- Technical experts in industry and professional societies have been and will continue to be consulted
- This will be a multi-year process; there will be ample opportunity for input
- Now only in early stages

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Next Steps

- Finalizing a proposed organizational structure over the next months
- In parallel, will develop relevant procedures and processes
- Also, will be developing some changes in approaches concurrently
- At the same time, working to implement GDUFA
- and...

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Summary

- FDA has made some improvements to regulating pharmaceutical quality, but major challenges remain
- Re-organization and re-alignment to achieve a "**One Quality Voice**" approach
  - Coordinated organizational, process, and policy changes that will move us more towards our articulated vision

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Program Alignment across FDA

- Transition to distinct commodity-based and vertically-integrated regulatory programs with:
  - Well-defined leads
  - Coherent compliance policy and enforcement strategy development
  - Well-designed and coordinated implementation
  - De-layered management structure
  - Investigators, compliance officers , import reviewers, laboratory personnel, and managers to become more specialized in a particular regulatory program

Integrity and Trust

Why is Data Integrity Important?

- Lack of integrity undermines the assurance and confidence in a drug's safety, efficacy and quality
- Data integrity problems break trust
- Data integrity problems can severely impact your business

Legal Framework

- Retention of complete and accurate data is a CGMP requirement:
  - 211.180(d): “true copies” such as microfilm, photocopies or other “accurate reproductions” are OK in lieu of original records
  - “true copies” can still be considered raw data

- Submitting false data to the FDA is a criminal violation under
  - FD&C Act (CGMP /adulteration provisions)
  - Title 18 U.S. Code - various sections

Legal framework

FD&C Act 505(e):

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section, if the Secretary finds…"

"…(5) that the application contains any untrue statement of a material fact"

Definition: Data & Application Integrity

- Presence of accurate & reliable data and information in an application submitted to the FDA for scientific review and approval
- All records submitted to FDA & supporting documents in the possession of the applicant are accurate & true representations of:
  - Actual tests performed & the actual test results
  - Actual manufacturing & quality control steps & procedures associated with the development and manufacture of the submission batch (clinical/pilot or biobatch)
  - Any other actions and conditions associated with the application

Definition

- Data and application integrity also means the absence of a pattern of unexplainable discrepancies between data in records submitted to the FDA and data in the original records maintained by the applicant.

Data that lacks integrity is….

- Unreliable
  - Omission of significant data from the submission that is determined to be material to the review process.
  - Data that is not submitted, but should have been.
- Inaccurate
  - e.g., first data failed specs, retest data passes specs, lab investigations are inadequate or non-existent, but retest data is submitted to the application, anyway.

Features of the Application Integrity Policy

- An “administrative action”
- Once AIP is invoked, FDA suspends review of the application or applications until the provisions of the AIP are met by the applicant holder
- Intended to assure the accuracy and reliability of data & information in applications submitted to FDA for scientific review and approval
- No statute of limitations

Data Integrity – What We See

- Not recording activities contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data
- Re-running samples
- Discarding data

Example: No, really. We promise. The raw data is back here *somewhere.*

No raw data for:

- Standard preparation
- Sample weights
- Sample solution preparation and sample dilutions
- This type of missing raw data has been observed at least five unrelated sites.
- Without this information, assays cannot be calculated.
- In one case, sample weights were made up and backdated, and there were and handful of passwords shared by 40 analysts.

Example: Audit trail? What audit trail?

Are the analytical methods well-defined *and* followed?

- HPLC integration parameters were changed and re-run until passing results were obtained
- Audit trail function was disabled

- Chemist recorded false data in the logbook under direction of a senior colleague

Example: Too good to be true

- Quality control data
  - Test results for one batch were used to release other batches
  - Occurred for at least 3 batches
  - This happened at three unrelated firms
  - Think about how long it should take to complete the tests; would it be possible to complete the tests in the time purported in the records?

Example: Transcription Conniption

- Sample and reagent weights are written on small pieces of paper and transcribed onto analytical worksheets
- Then, small pieces of paper were discarded
- Transcribing data increases the risk of transcription errors.
- The first recorded data is considered the raw data. In this case, discarding the small pieces of paper means discarding the raw data. Additionally, transcription errors would never be detected in the event the firm needed to conduct an investigation.

Example: An Inconvenient Truth

- Unofficial testing of samples with file names like test, trial, or demo
  - Some failed specification
  - All were saved on personal computers instead of a network
  - Employee admitted doing this in order to blend failing and passing batches that resulted in passing batches.

Defect Reports

Field Alert Reports (FARs) = Quality Defects

21 CFR and FD&C Act basis for requirement

- *21 CFR 314.81 Other Postmarketing Reports*
- *21 CFR 314.98 (c) Postmarketing reports*
- FD&C Act, Sec. 505(k)

- NDA and ANDA holders are responsible for filing FARs.
- Foreign application holders are required to have a US agent registered in the US per ***21 CFR 314.50(a)(5).*** The US agent will report FARs.

- GMP-required investigation SOP (see 211.198; 211.192) should identify FAR threshold

What is Reported?

- Application holders are required to report to the FDA
  - "any incident that causes the distributed drug product or its labeling to be mistaken for, or applied to, another article".
  - Bacteriological contamination
  - Significant chemical, physical or other change
  - Product deterioration
  - Out-of-specification result
- If firm cannot invalidate problem within 3 days, Field Alert must be reported

Examples of Reports

- Mislabeling, missing label, obscured label
- OOS results obtained during stability testing, or from examination of reserve samples (e.g., appearance, particulates)
  - If cannot confirm OOS within 3 days, still report
  - If product is at expiry, still need to report
- Complaints for distributed products which are deemed significant, i.e.:
  - Not necessarily all complaints
  - Reflect pattern or related to other info
  - Obviously a batch defect problem

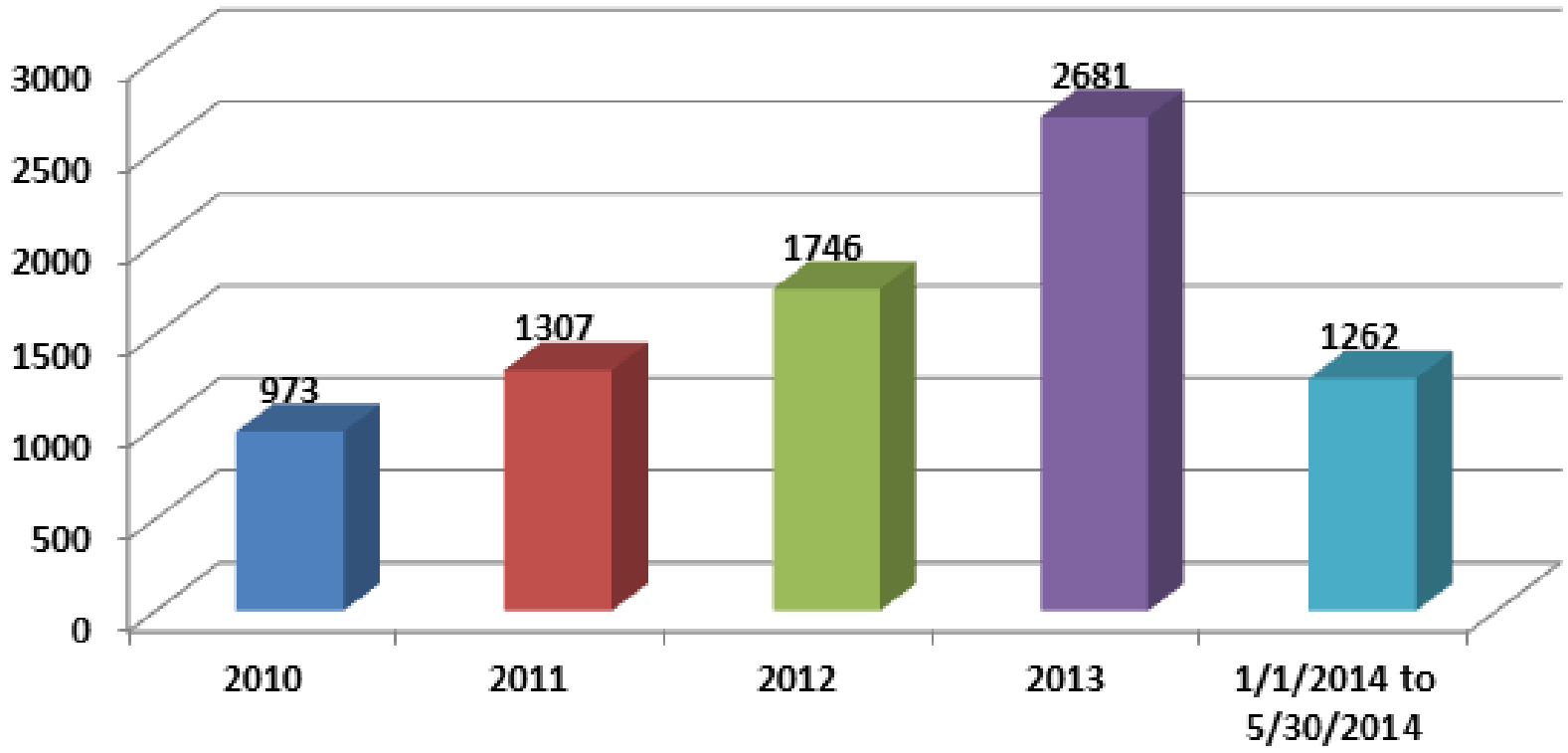
How to report a FAR

- Use voluntary e-submission
- Submit initial report within three working days
- Submit f/u report when new, significant info uncovered
  - Do not submit a new report when, e.g.:
    - identify new batch affected for same A/NDA and defect type and date of discovery
- Final FAR should summarize investigation, including
  - cause and hazard assessment; if recall, report through recall notification
  - identify affected lots and status; corrective action plan
    - how it happened and why it won't recur

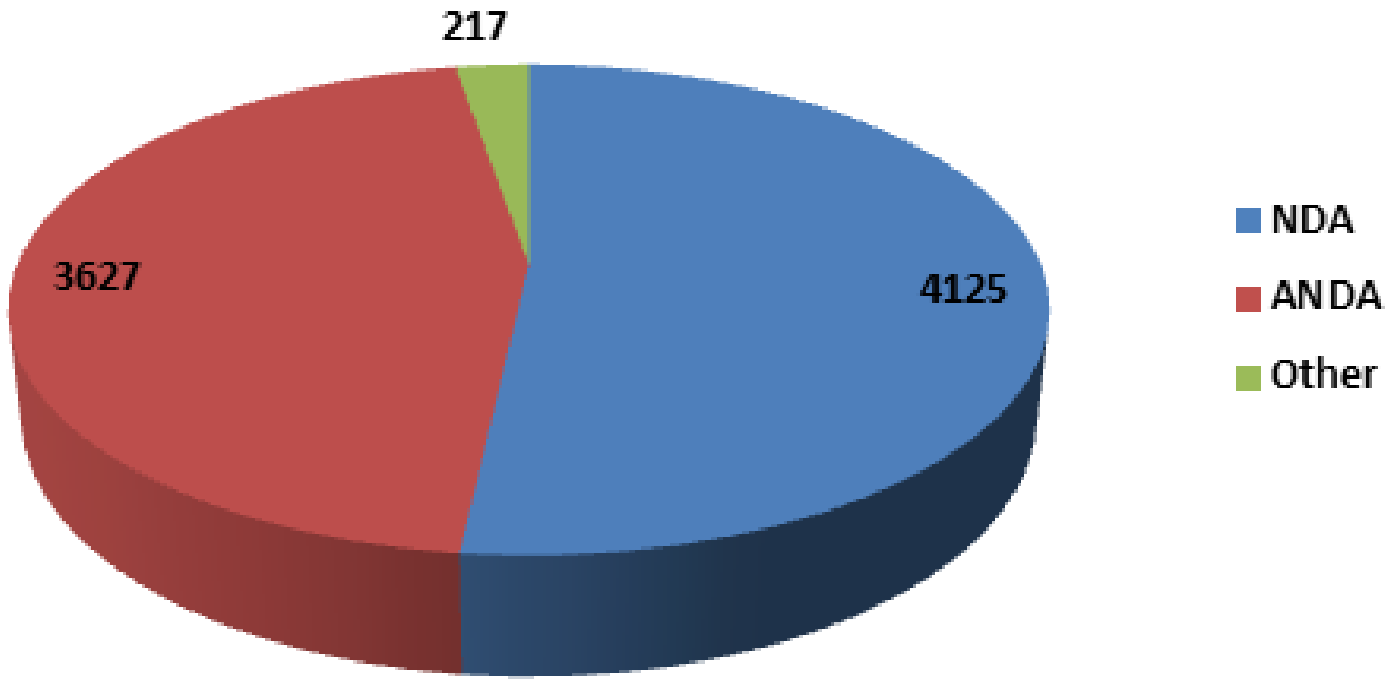
Processing of FARs by FDA

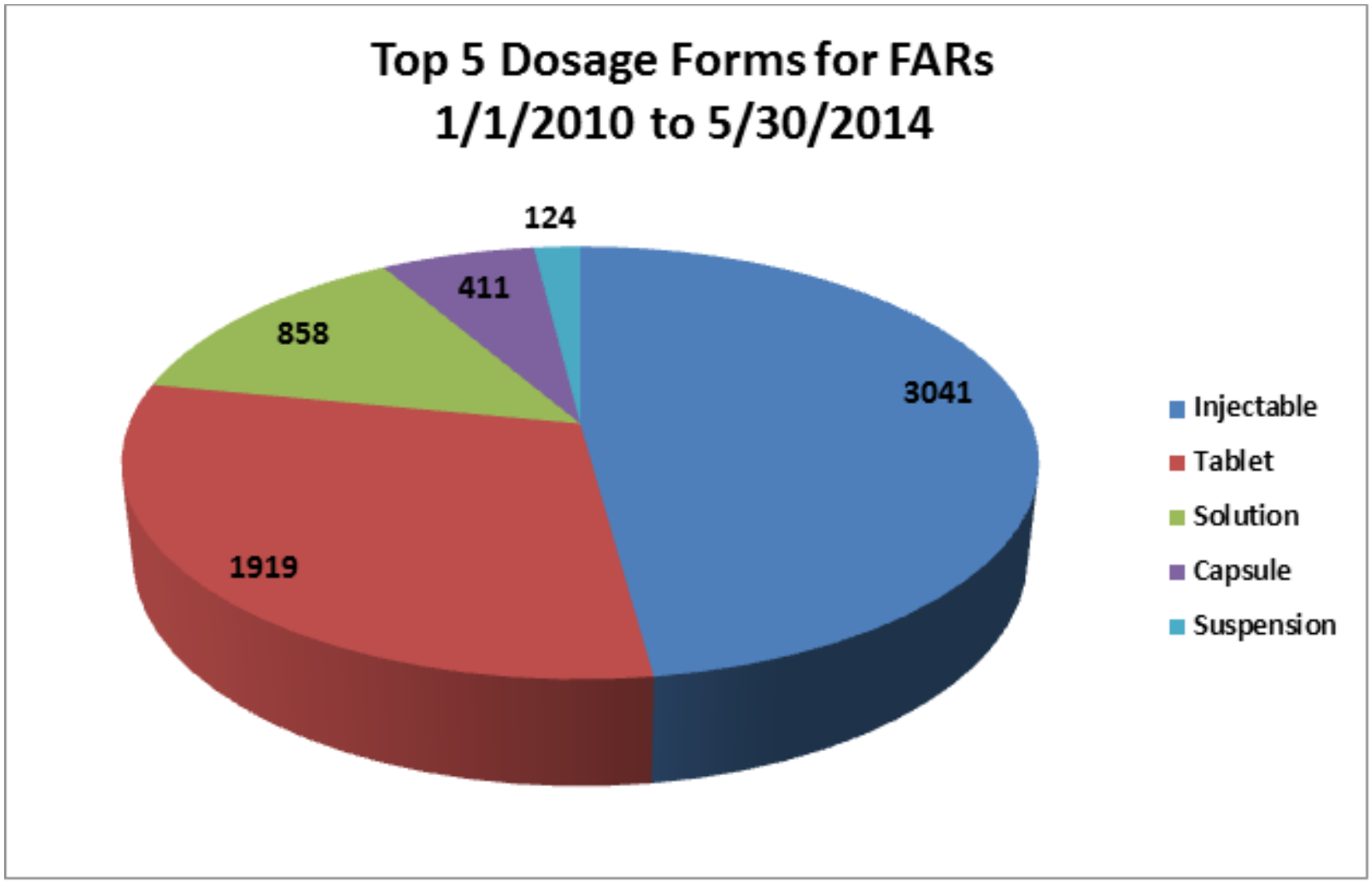
- Firms submit quality defects through "rapid means" to the FDA District Office or where the US agent resides
  - **Please use e-submission option**
- The District Office forwards it to CDER
  - within 5 days of receipt
- CDER enters data into a database
- FAR is evaluated by both field and CDER
  - CDER may request field inspection or with field office request more information
  - Need for recall and/or public notification is considered
  - CDER evaluates for compliance with FAR requirements
- Data are evaluated for patterns/trends
  - additional info may be considered such as MedWatch

Total Inital FARs by Calendar Year 1/1/2010 to 5/30/2014

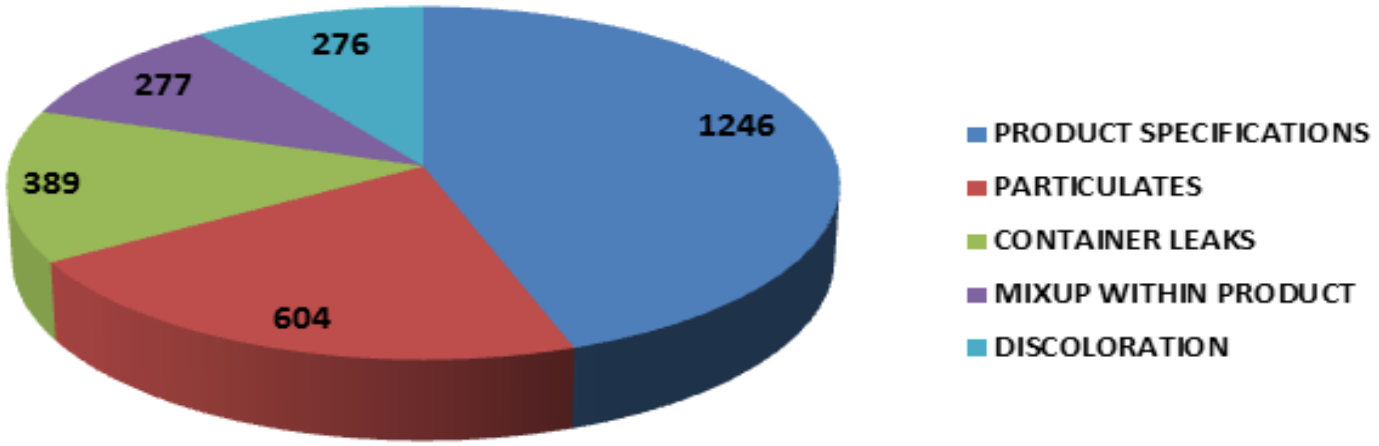


FARs by Application Type
1/1/2010 to 5/30/2014




Top 5 Dosage Forms for FARs
1/1/2010 to 5/30/2014
124
411
858
3041
1919
Injectable
Tablet
Solution
Capsule
Suspension

Top 5 Primary Defects for FARs 1/1/2010 to 5/30/2014

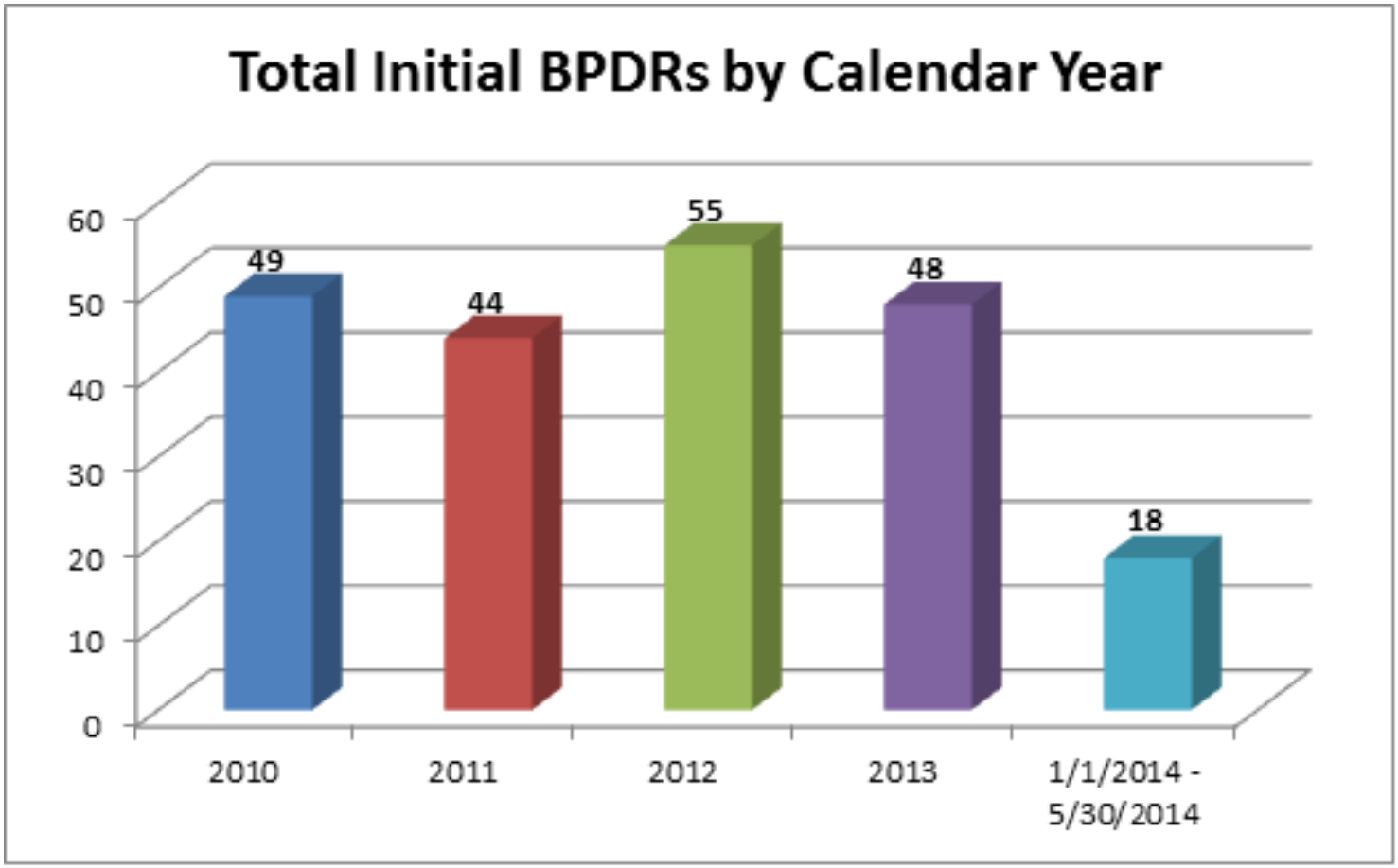


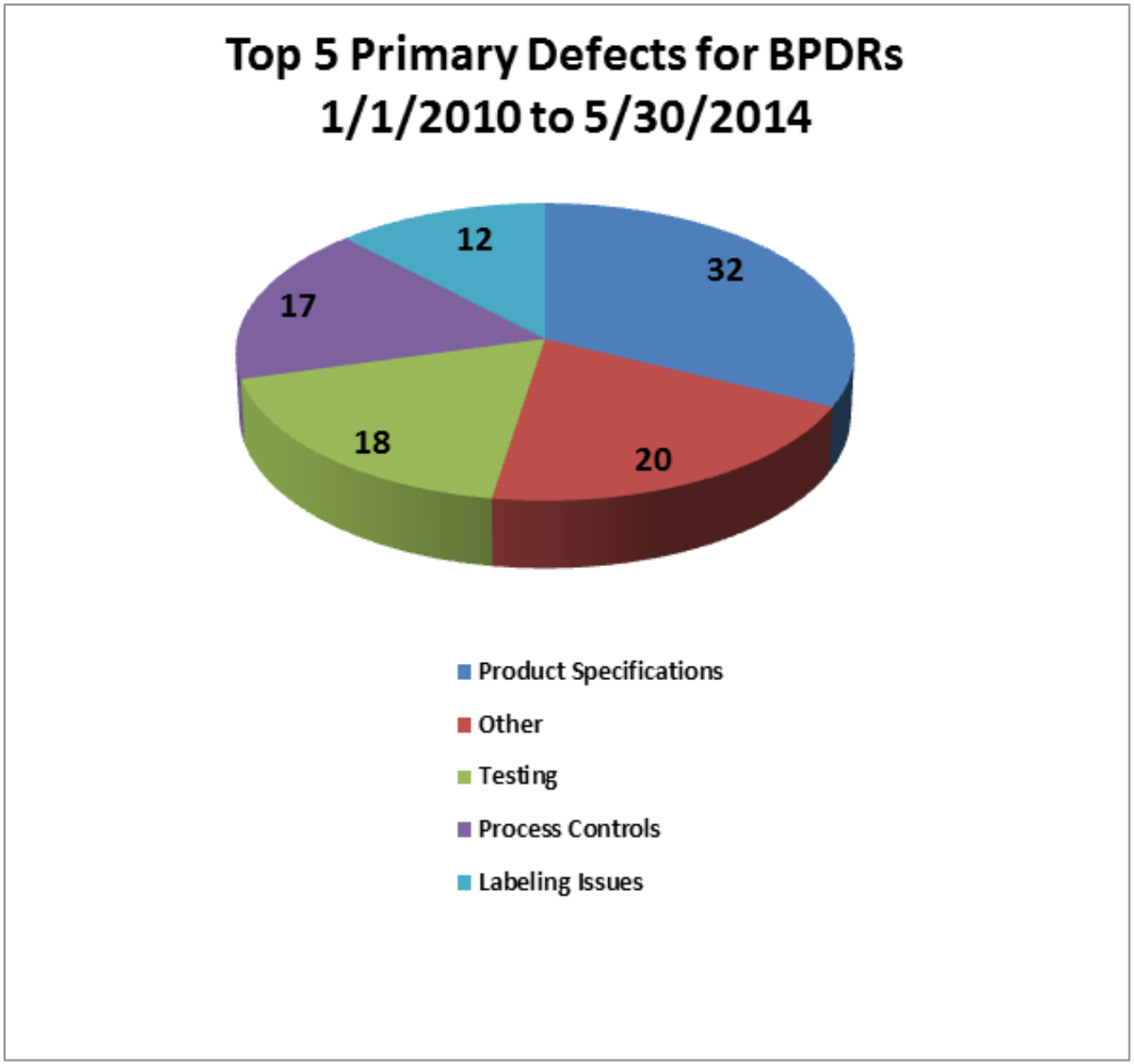
BPDRs

- BDPR Regulation **21 CFR 600.14: Reporting of biological product deviations by licensed manufacturers**
  - Applicant holder must report ASAP but NTE 45 days from date of discovery
  - Required to report any information that may affect the product's safety, purity or potency including:
    - Manufacturing, including Processing, Packaging, Labeling, Testing, Storage/ Holding
    - Distribution
- Use Form FDA 3486

Processing of BPDRs by FDA

- Hardcopy BPDR is received by CDER
  - scanned and archived
- BPDR info is entered into CDER database
- BPDR is initially assessed and assigned for review by CDER/OC and/or CDER/OBP
  - If questions arise from the reviewers, the district office is often asked to contact the firm directly
  - All corresponding emails and final reviews are maintained with original submission


Total Initial BPDRs by Calendar Year
60
50
40
30
20
10
0
49
44
55
48
18
2010
2011
2012
2013
1/1/2014 - 5/30/2014


Top 5 Primary Defects for BPDRs
1/1/2010 to 5/30/2014
32
20
18
17
12
Product Specifications
Other
Testing
Process Controls
Labeling Issues

BLA Issues

Surveillance (CGMP) Inspections of CDER BLA/Biotech Products

- Conducted under the guidance of Compliance Program Guidance Manual 7356.002M
- Current version – implemented October 2003 – largely unchanged from CBER program 7341.001
- Program is presently undergoing a major revision:
  - Will cover biotech DS manufacturing operations only
  - Will emphasize a risk based-approach, drawing on an additional decade of CDER and ORA knowledge, including inspectional observations
  - Will include question-based coverage, with more specific guidance for each of the manufacturing systems
  - Will cover BLA products and NDA products for which the Biologics Price Competition and Innovation Act requires the submission of a BLA by March 23, 2020

BLA/Biotech Manufacturing Areas of Concern

- Failure to use scientific rationale when reaching product impact conclusions for deviation investigations
- Failure to provide adequate quality oversight of manufacturing operations (including CMOs – “We just do what the product sponsor tells us”)
- Failure to subject lots to stability testing following major manufacturing deviations
- Failure to close CAPAs and Change Controls after significant time has passed (without having QA rationale and signoff)
- Failure to report, as required by 21 CFR 601.12, manufacturing changes with moderate or substantial potential to have an adverse effect on product safety or effectiveness
- Failure to handle cell banks as necessary to ensure adequate supply of quality product

Emerging Policies

Recent and Emerging Drug Quality Policies

- Inspection programs recently revised (*Compliance Program Guidance Manuals*)
  - 7356.002A – Aseptic Processing; 7356.002P – PET Drugs
- Enforcement policies (*Compliance Policy Guides*)
  - Parametric Release - Terminally Moist Heat Sterilized Products
  - Interference with Compendial Tests
- Guidance for Industry
  - Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination (final)
  - Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality (final)
  - Contract Manufacturing Arrangements for Drugs: Quality Agreements **(finalize soon)**

Protecting Consumers, Promoting Public Health

U.S. Food and Drug Administration

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