FDA Drug Quality Regulations: Current Topics

CDER Small Business - Regulatory Education for Industry (REdI)
September 19, 2014

LCDR Tara Gooen Bizjak
Senior Science Policy Advisor
Office of Pharmaceutical Science, Immediate Office
CDER, FDA

Agenda

- Current Good Manufacturing Practices
- Inspection Process
- Data Integrity
- Defect reports
- Biotech Surveillance Inspections
- Office of Pharmaceutical Quality *(proposed)*

- Questions

Legal Bases for CGMP

Section 501(a)(2)(B):

"A *drug*... shall be *deemed* to be *adulterated* if the *methods* used in, or the *facilities* or *controls* used for, its *manufacture*, *processing*, *packing*, or *holding* do not conform to or are not operated or administered in conformity with *current good manufacturing practice* to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented* to *possess*."

Legal Bases for CGMP

FDASIA 2012 amendment to section 501:

CGMP "includes the implementation of *oversight* and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the *safety of raw materials*, materials used in the manufacturing of drugs, and finished drug products."

"Current" in CGMP means...

Dynamic and evolves over time

Who decides?

we do; process

Based on what?

risk; cost/benefit; response to problems

Practice need not be prevalent

both "feasible and valuable" in assuring quality

flexible enough to accommodate innovation

Regulations – the CGMP History

1962: Authorizing legislation passed

1963: Initial version; several minor changes followed

1978: Major revision; most remains in current version

1979 – 2008: Many revisions, incl. tamper-evident packaging, label control, reserve samples

3-phased major revision underway:

- 2009 – Finalized Phase 1 ('easier') revisions;
- 2014 – ?

21 CFR 210: CGMPs in manufacturing, processing, packing, or holding of drugs; General

210.1 –**Minimum standard** for **methods** used in, and **facilities or controls** to be used for the **manufacture, processing, packing or holding** of a drug to ensure that such drug meets **requirements of the act** as to safety, and has the identity and strength and meets the quality and purity it purports

210.2

INDs – Phase II and III; guidance for Phase I

Definitions

Establishments Routinely Inspected

- manufacturers of drugs, including
  - dosage form
  - active pharmaceutical ingredient
  - excipient
  - clinical trial material
  - “biotech” (e.g., MaB; therapeutic proteins)
  - medical gas processors and transfillers
- independent packagers/labelers
- independent sterilizers
- independent laboratories
- ‘export-only’ involved in any of above checked establishments

Types of CGMP Drug Inspections

- Surveillance Inspections
  - Risk-based frequency
  - Sites selected by risk model and local judgment
- For-Cause (Compliance) Inspections
  - Local/HQ/Center initiated, e.g., f/u past violations
  - External complaint/allegation
- Pre-Approval and Post-Approval Inspections
  - Center established criteria (product-specific)
  - Center or local office initiated for-cause

Inspection Process

Manufacturer's Role: Before

- Register facility and accurately list all drugs
- If associated with an application
  - keep DMF current; aligned with application role
  - be ready to justify any changes since approval
- Know and follow the quality regulations and guidance
- Be confident in your staff and your operation
  - cultivate honesty and integrity
  - be ready to explain why you do what you do

Inspection Beginning

Knock, knock... then

1. Ask for the most responsible person
2. Show their credentials
3. Issue a written “Notice of Inspection” (FDA 482)
4. Briefly explain purpose of the inspection
5. Observe facility (walk-through)

Manufacturer's Role: During

- Allow access to all areas of manufacturing
- Provide all info requested
  - clarify request if unclear
  - indicate how long it will take
  - can redact financial info
- Make staff available to answer questions
  - don't answer if unsure; check

Investigator Role: During

- Conducts inspection in accordance with CPGM and other guidance and direction.
- Contacts CDER if potential application issues are identified (e.g., problems with specifications)
  - Manufacturer's key contact is District Pre-Approval Monitor* (PAM)
- It is not the investigator's job to advise the firm regarding what specifications or technology are appropriate for drug products during the pre-approval inspection
- Notifies PAM of significant GMP and/or data integrity issues that may likely result in a withhold recommendation

* Investigation Operations Manual (Directory, Drug Pre-Approval Monitors): http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM123522.pdf

Inspection Close-Out

- There will be a close-out meeting
  - No surprises (daily close-out meeting)
  - FDA-483 (Inspectional Observations)
    - **may or may not be issued**
- You can disagree and respond to the inspection findings
  - verbally during the inspection and/or in writing to the District after
  - **15 days to respond to be considered in further action**
- If physical samples were collected, FDA-484 (Receipt for Samples) will be issued.

Investigator Role: After

- Writes Establishment Inspection Report (EIR)
- Provides PAM with pertinent information needed for District recommendation (e.g. FDA 483, EI dates, proposed classification) upon completion of inspection
- Determine if the firm is operating under a **State of Control**
  - Is there an adequate level of assurance of quality, strength, identity and purity for finished drug products?
  - If any **one system** out of control, the firm is out of control and thus all profile classes are unacceptable

After the Inspection

- Inspections are generally classified into one of three categories
  - **NAI**-No Action Indicated
  - **VAI**-Voluntary Action Indicated
  - **OAI**-Official Action Indicated
- Initial outcome:
  - PAI: Investigator informs firm management at the conclusion of the inspection of his/her initial recommendation
  - Post-Approval: Investigator will not provide recommendation at the conclusion of inspection
- Expect a copy of FDA inspection report

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 & Application Integrity

- 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

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 a 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

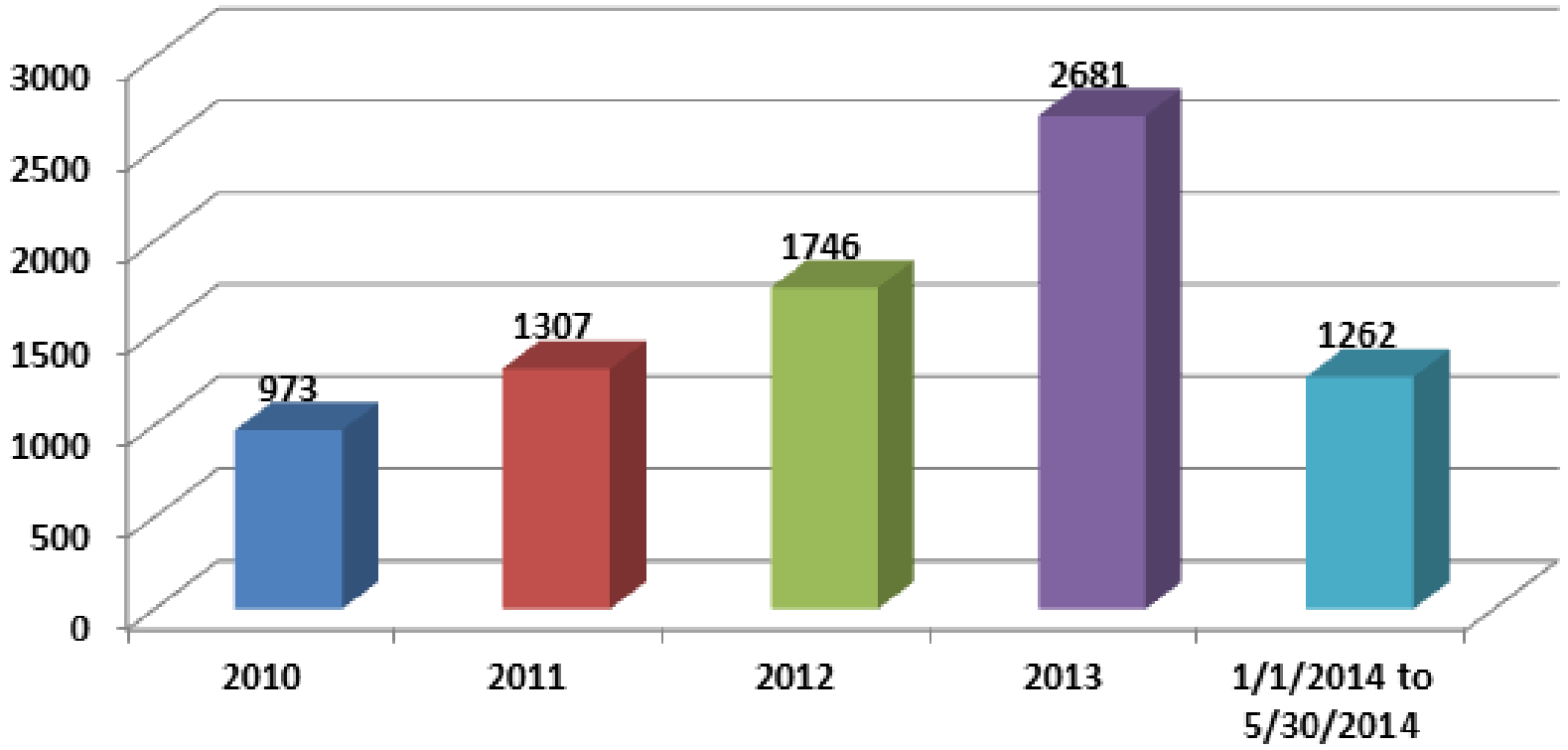
How to report a FAR

- 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

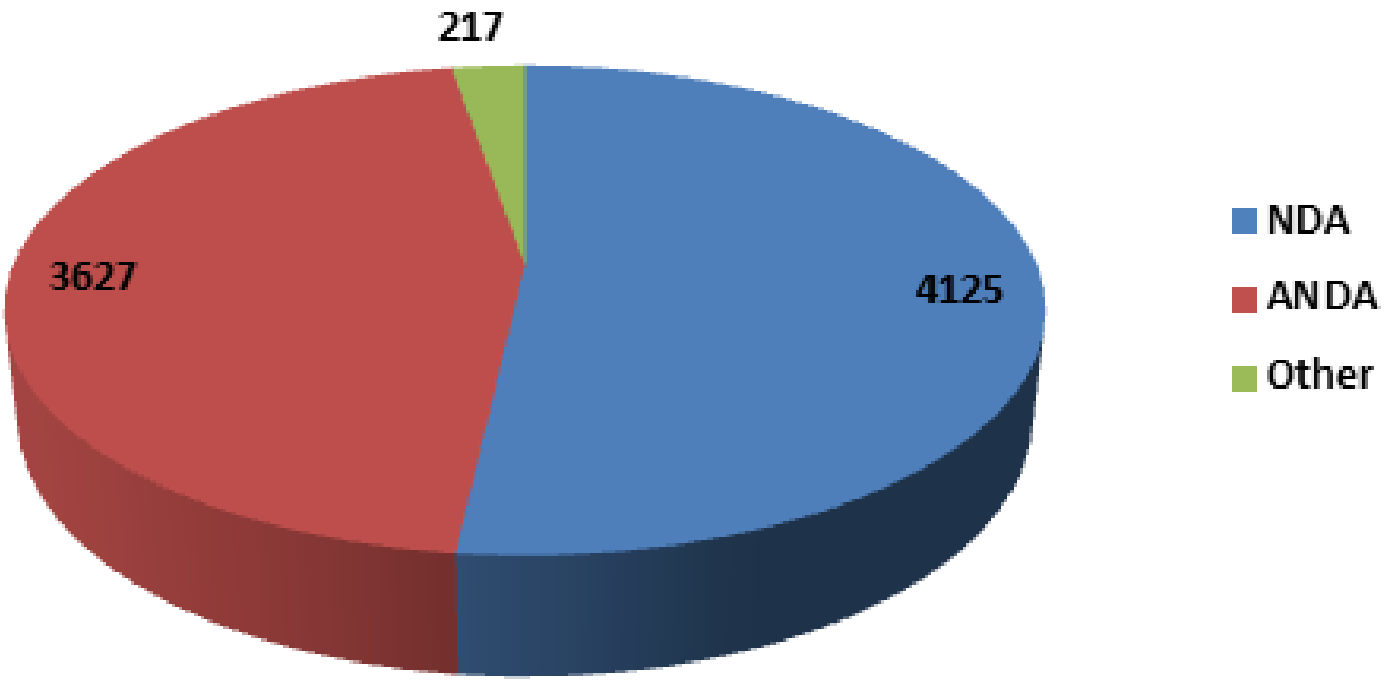
Processing of FARs by FDA

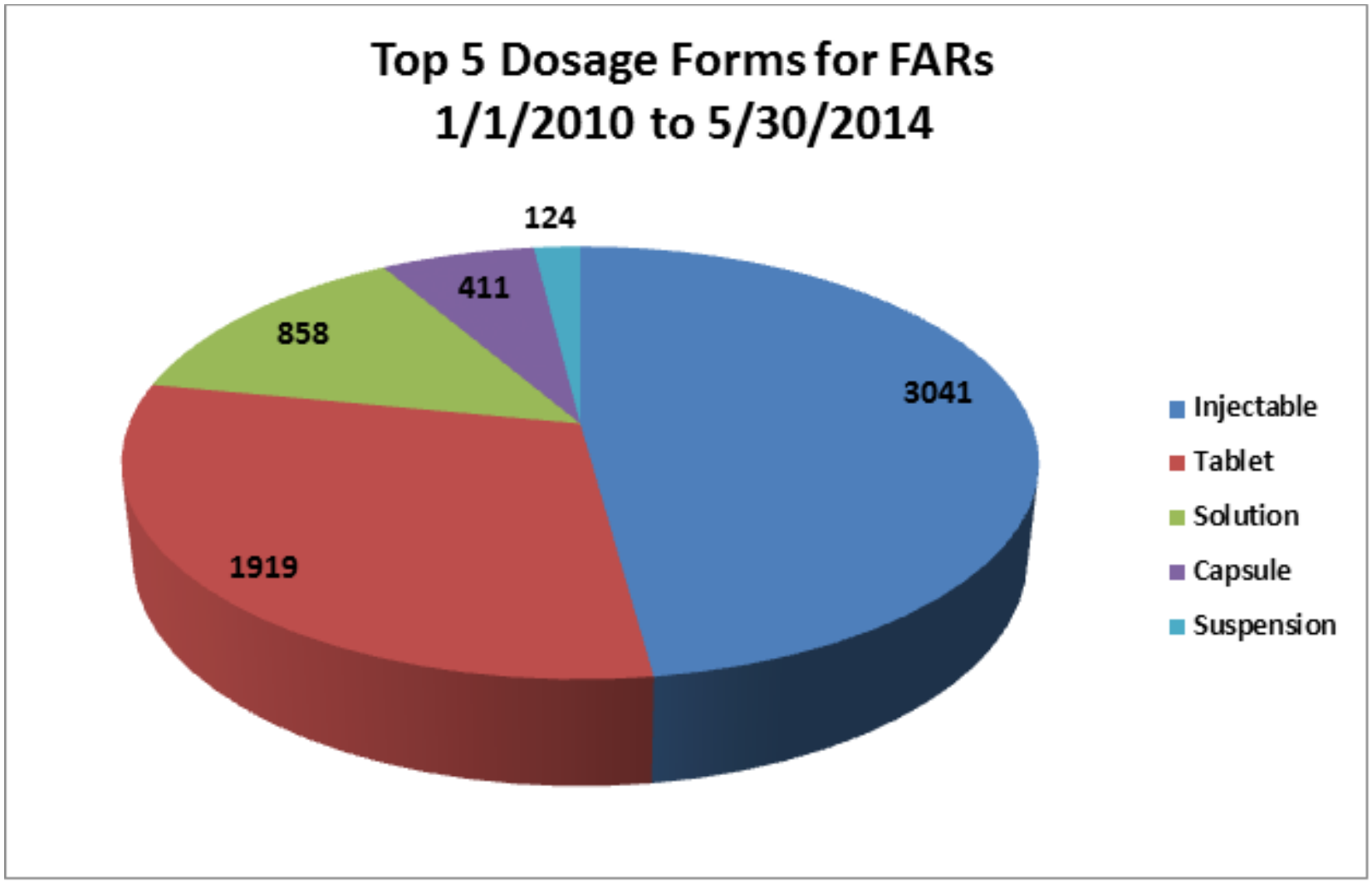
- Firms submit quality defects through "rapid means" to the FDA District Office or where the US agent resides
  - **Please use e-submission option**
- The District Office forwards it to CDER
  - within 5 days of receipt
- CDER enters data into a database
- FAR is evaluated by both field and CDER
  - 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

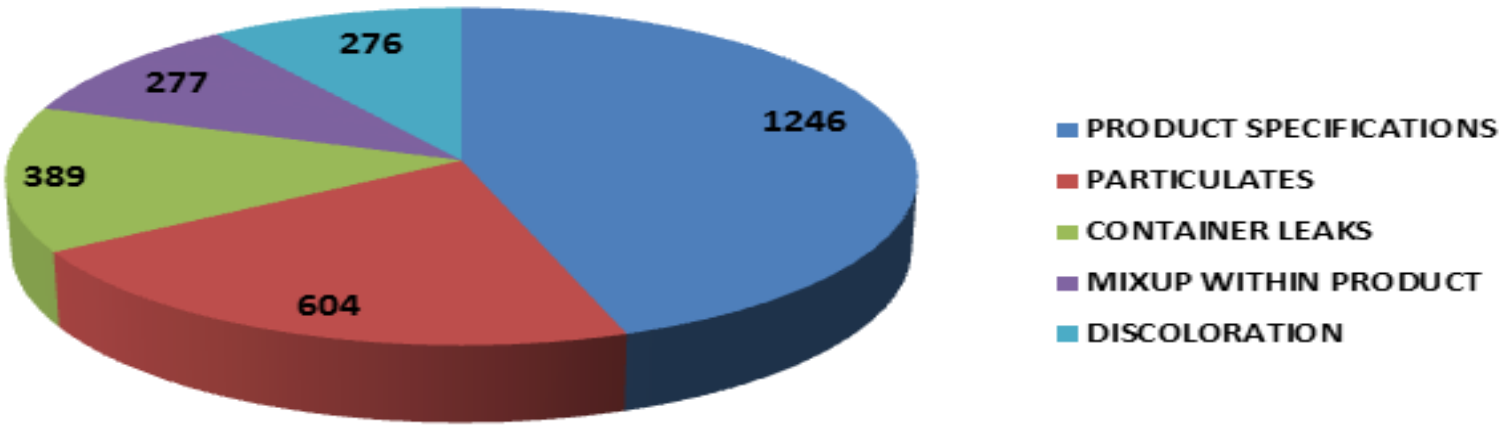


FARs by Application Type
1/1/2010 to 5/30/2014




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

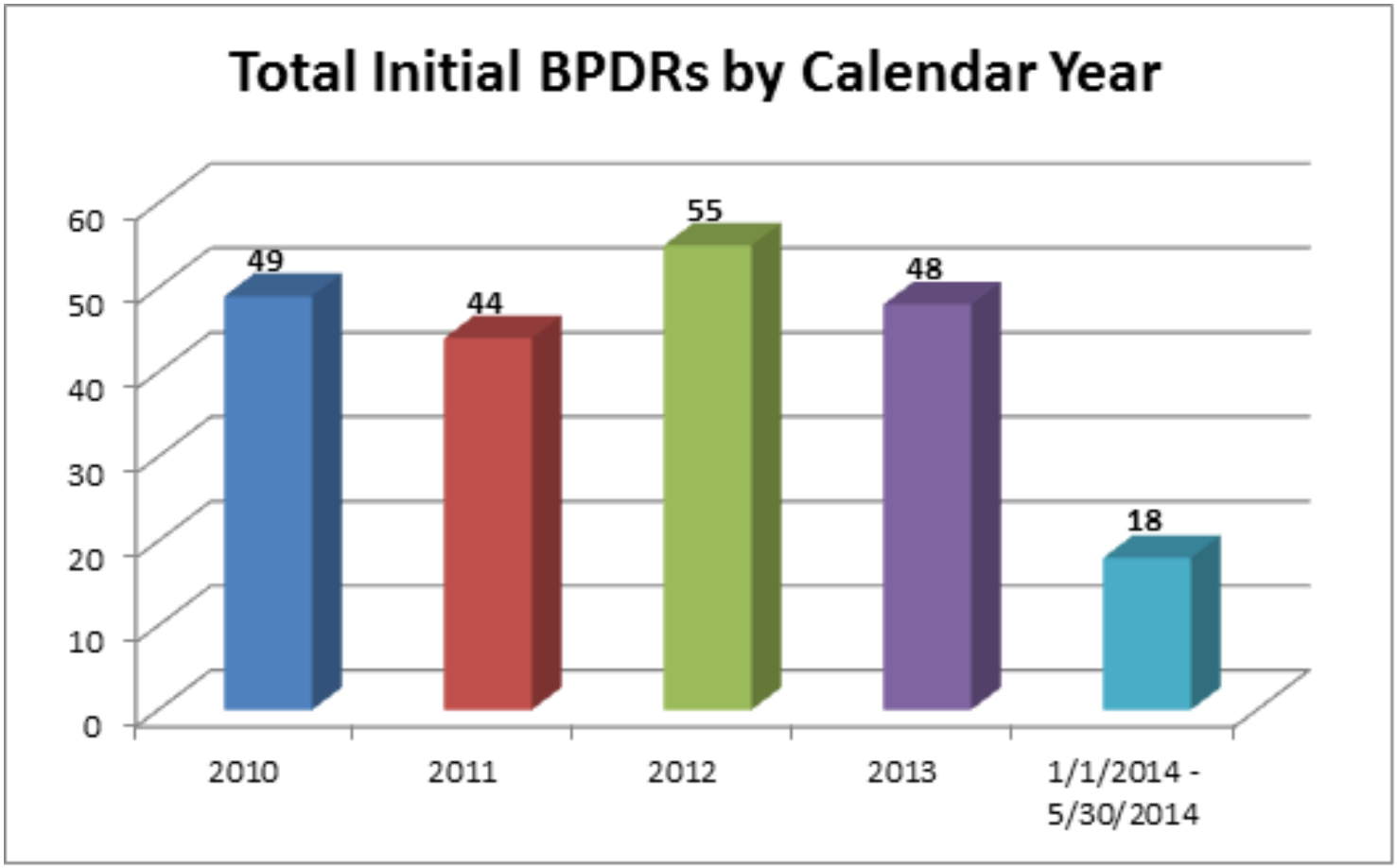


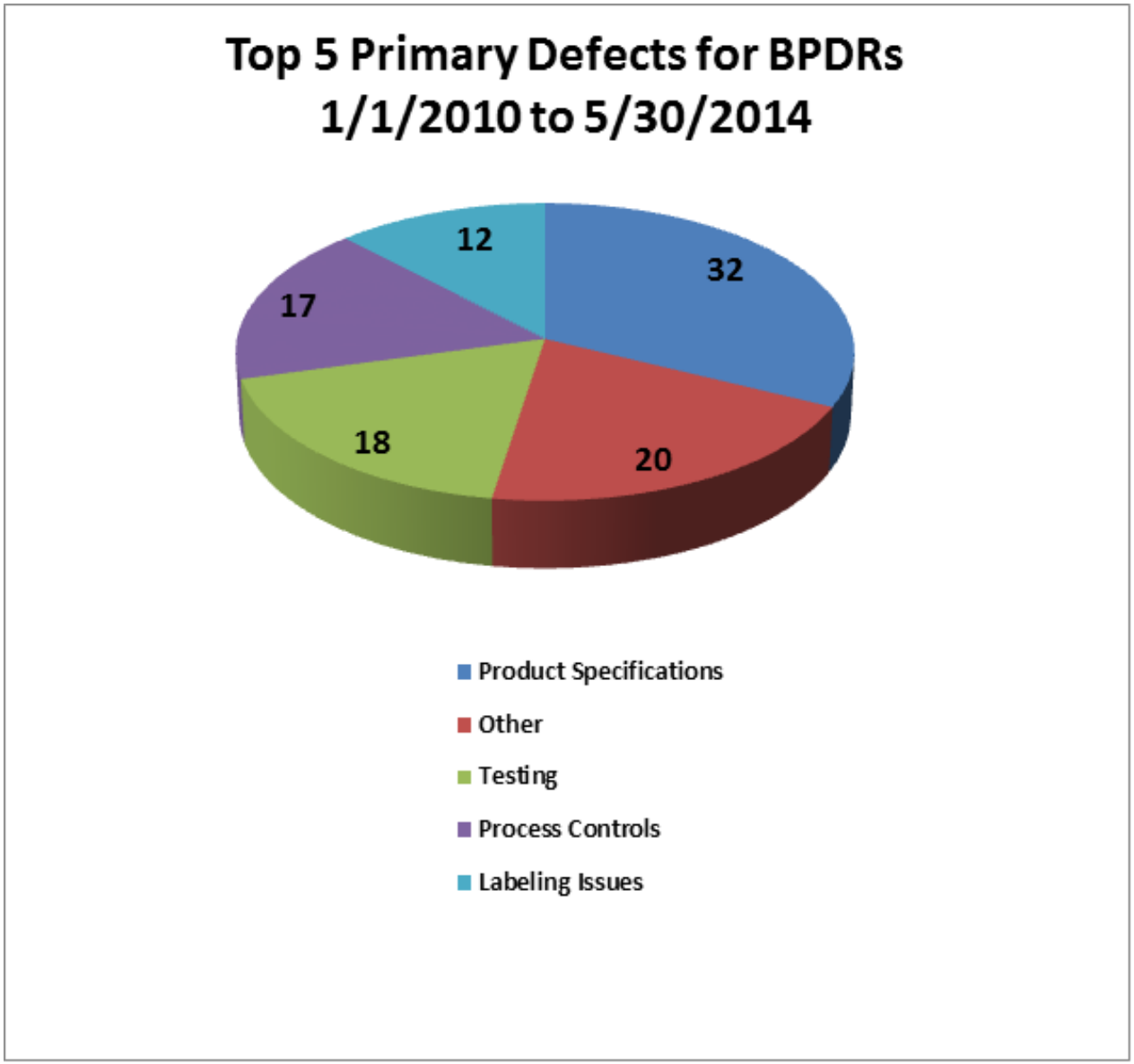
BPDRs

- 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 handle cell banks as necessary to ensure adequate supply of quality product
- 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

Where are we (CDER/FDA) going?

Brief History :
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 potentially 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 quality problems?

Drug Shortages – State of Quality?

Figure 1. Number of New and Prevented Shortages by Dosage Form, 2005-2012

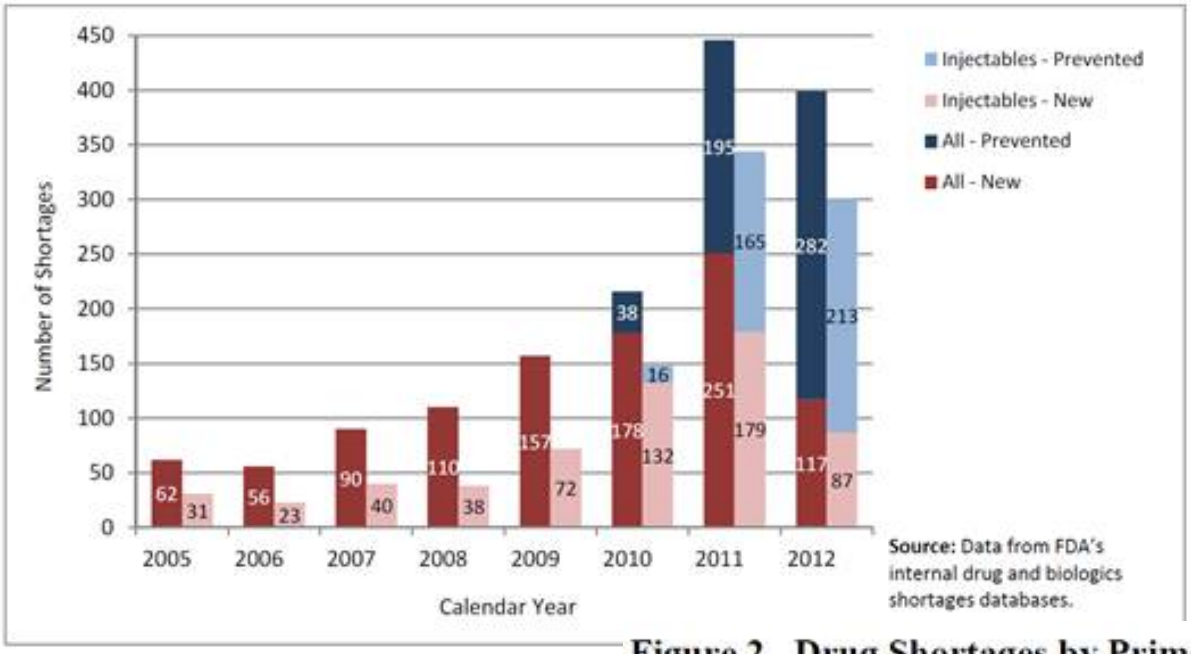
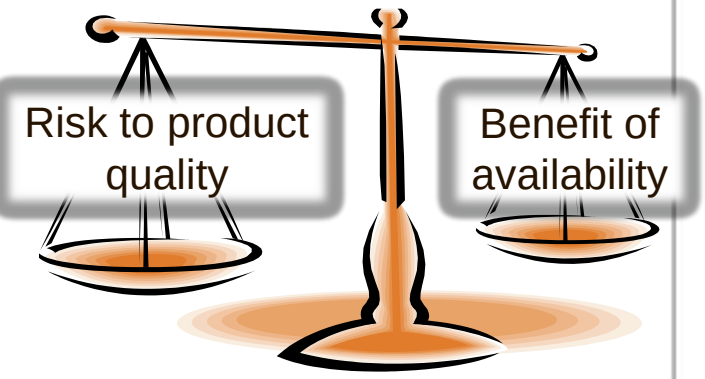
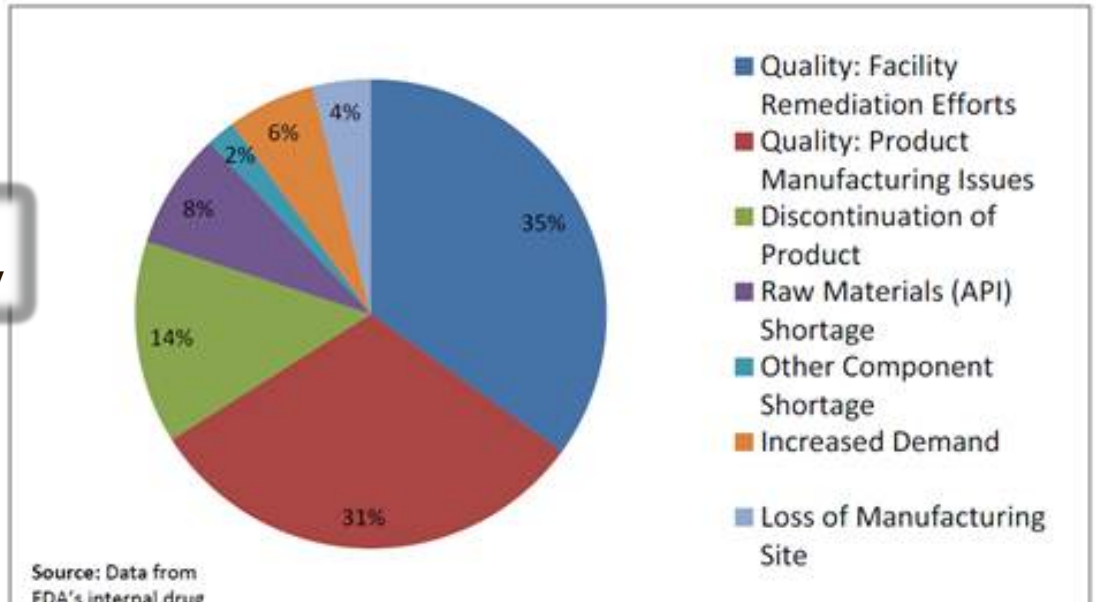
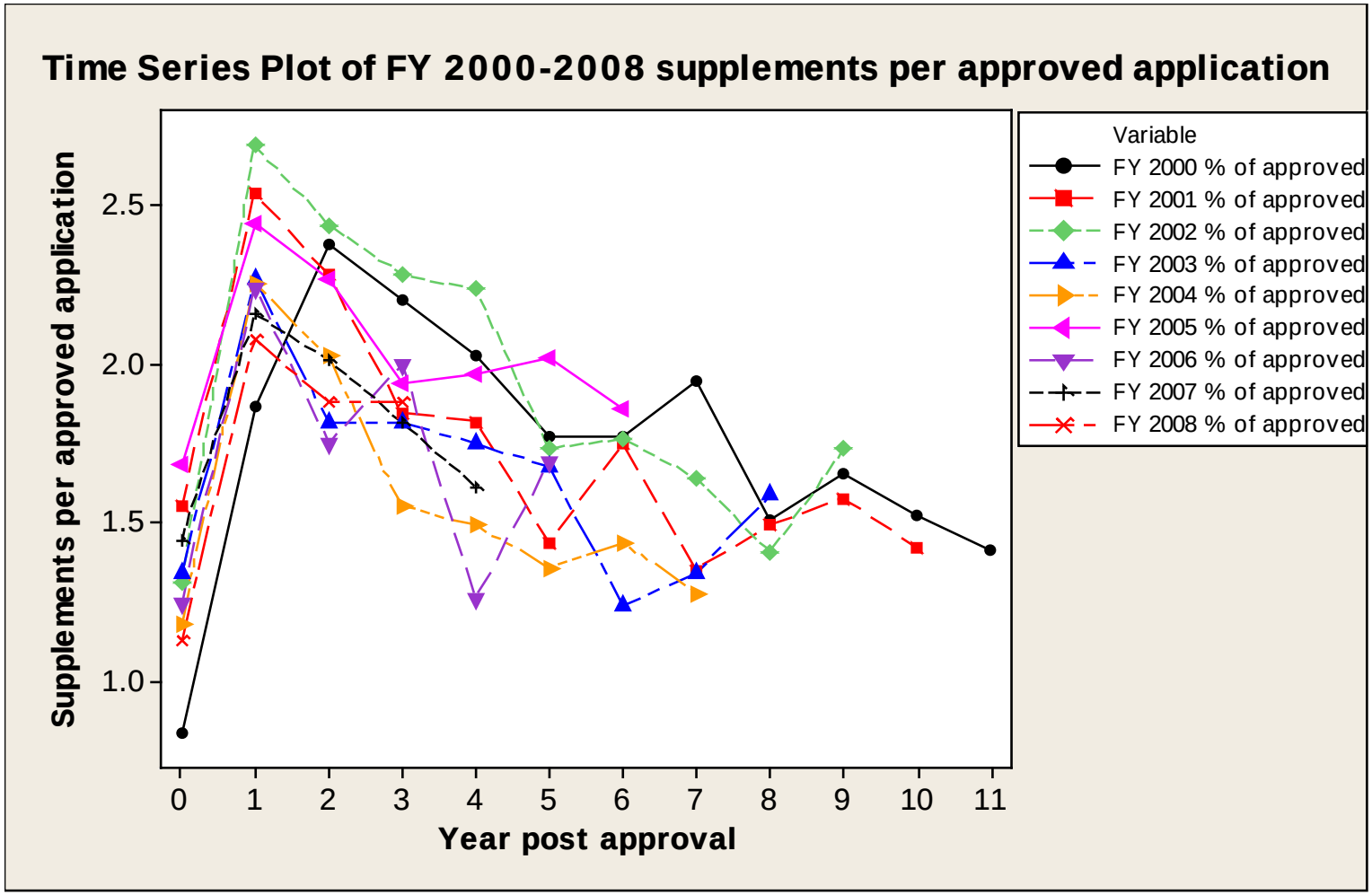


Figure 2. Drug Shortages by Primary Reason for Disruption in Supply in 2012

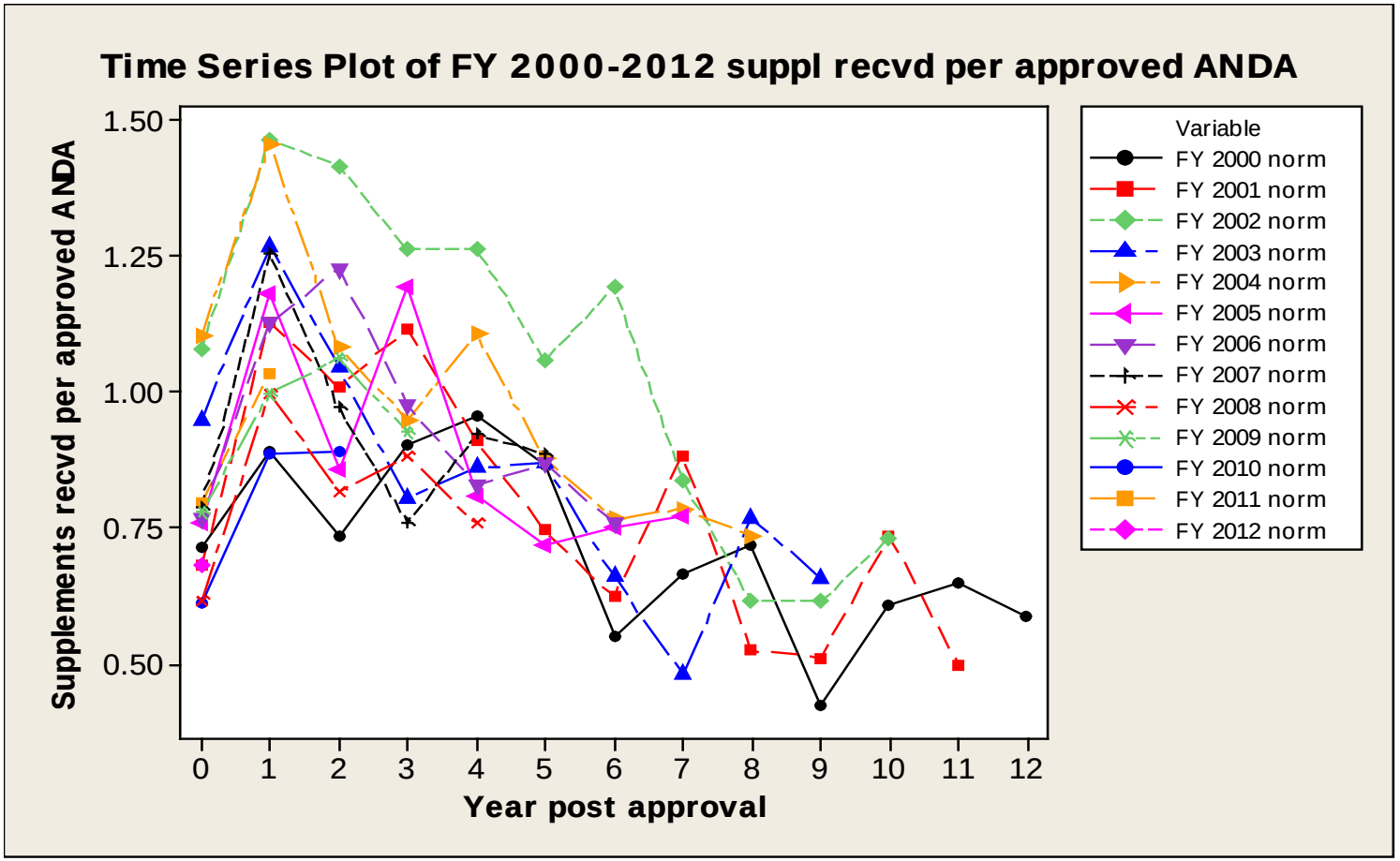




NDA CMC Supplements



ANDA CMC Supplements



CDER OPQ (proposed)

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

OFFICE OF
PHARMACEUTICAL QUALITY

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 including quantitative metrics
- Specialization and team review: **integration of review and inspection** for a quality assessment
- Accountability: Overall **QMS** and evaluation system

OFFICE OF
PHARMACEUTICAL QUALITY

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.*

OFFICE OF
PHARMACEUTICAL QUALITY

What is the Emerging Technology Team (ETT)?

- A small cross functional team with representation from all relevant CDER review and inspection programs
- Vision: Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience. Includes:
  - Innovative or novel product, manufacturing process, or analytical technology subject to CMC review
  - Existing or planned submission(s)

The ETT Charter

- Provides a forum for knowledge sharing and scientific discussion
- Provides consistency, continuity and predictability
  - Facilitates establishment of review and inspection standards and policy
- Supports GMP manufacture of quality product over the lifecycle
- Long term goals:
  - Engage international regulatory agencies to share learnings and approaches
  - Modernizing pharmaceutical development and manufacturing

Role of ETT

- Provides perspective on quality review and inspections
  - ETT members serve to lead/co-lead cross-functional team during review process
  - Participates or supports relevant inspection(s) and/or pre-operational visits
  - Identify and capture decisions that may inform future FDA approaches and decisions
- Serve as advocates for innovative technology while balancing risk vs. benefit
- Identify and evaluate roadblocks relating to existing guidance, policy, or practice
- Early applicant engagement with the ETT is recommended
- Contact us: **CDER-ETT@fda.hhs.gov**

New CDER Policy

Recent and Emerging Drug Quality Topics

- Inspection programs recently revised (*Compliance Program Guidance Manuals*)
  - 7356.002A – Aseptic Processing; 7356.002P – PET Drugs
  - Expect to see more question-based formats for CPGMs
- FDASIA and managing risk and knowledge through a product lifecycle
- Guidance for Industry
  - Preventing Contamination from Beta Lactam Drugs (final)
  - Crude Heparin Quality (final)
  - FAR Reporting (out for notice & comment)
  - Quality Agreements: Contract Manufacturing (published for comment)
  - Cloud computing (in development)

Protecting Consumers, Promoting Public Health

U.S. Food and Drug Administration

www.fda.gov