



# Recalls

**CASA**

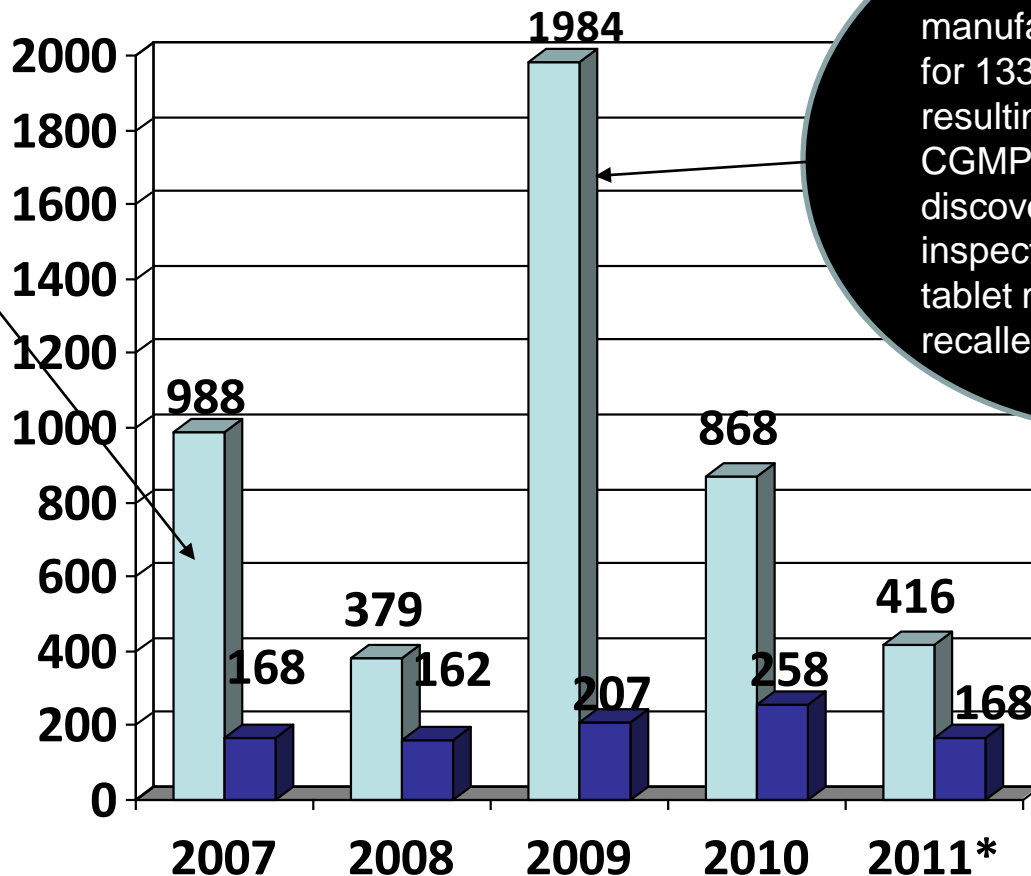
**May 20, 2011**

**Baltimore, MD**

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Chief, Recalls and Shortages  
FDA / CDER / Office of Compliance  
Division of Manufacturing and Product Quality

# Total Number of Recall Events and Product Recalls FY 2007 to 2nd QT 2011

One contract packaging site caused packaging mix-ups accounting for approximately 670 recalls.

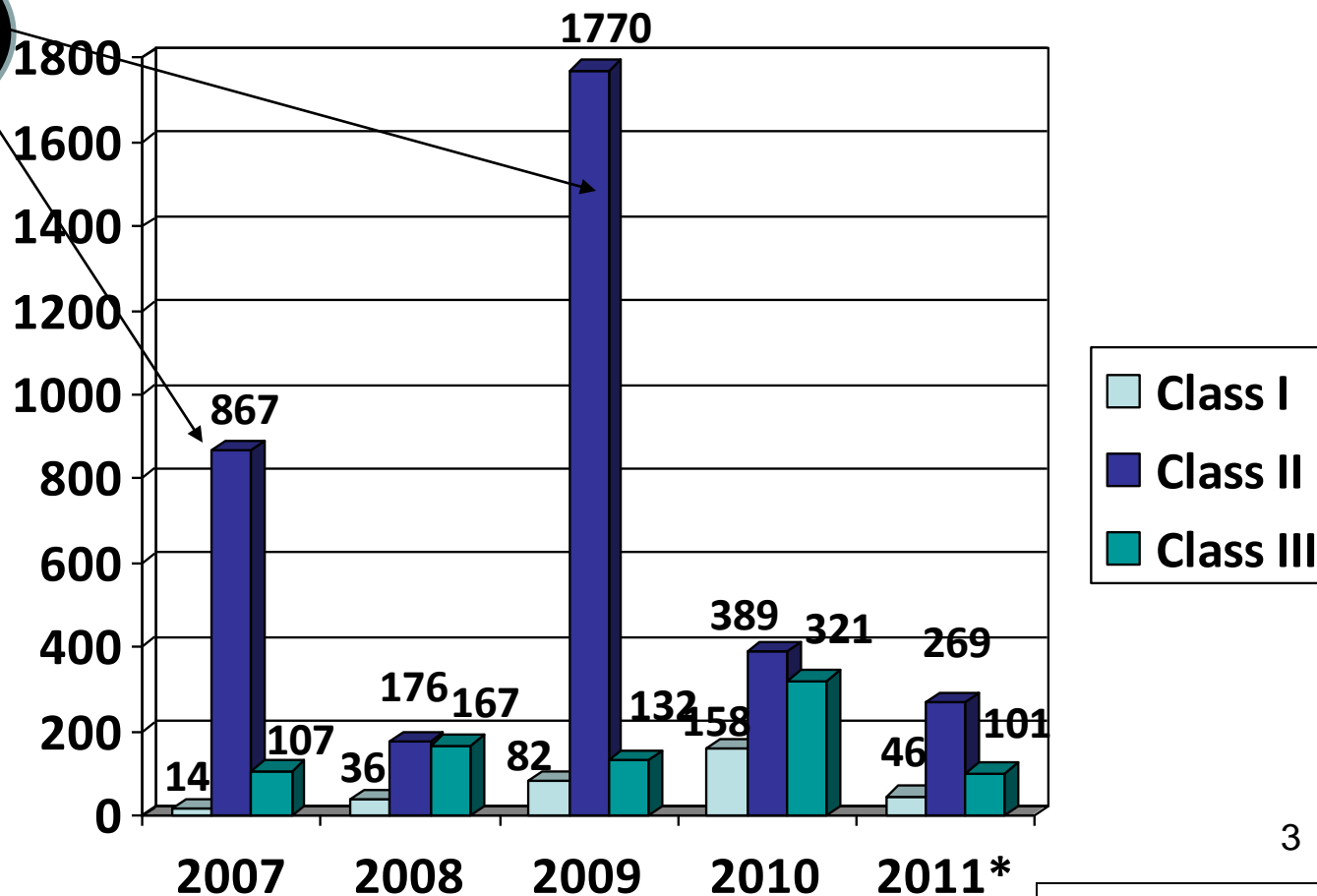


One contract manufacturer accounted for 1335 product recalls resulting from various CGMP violations discovered during an inspection. Also, one tablet manufacturer recalled 190 Rx products.

Products  
Events

# Total Number of Class I, II and III Product Recalls During FY 2007 to 2nd QT 2011

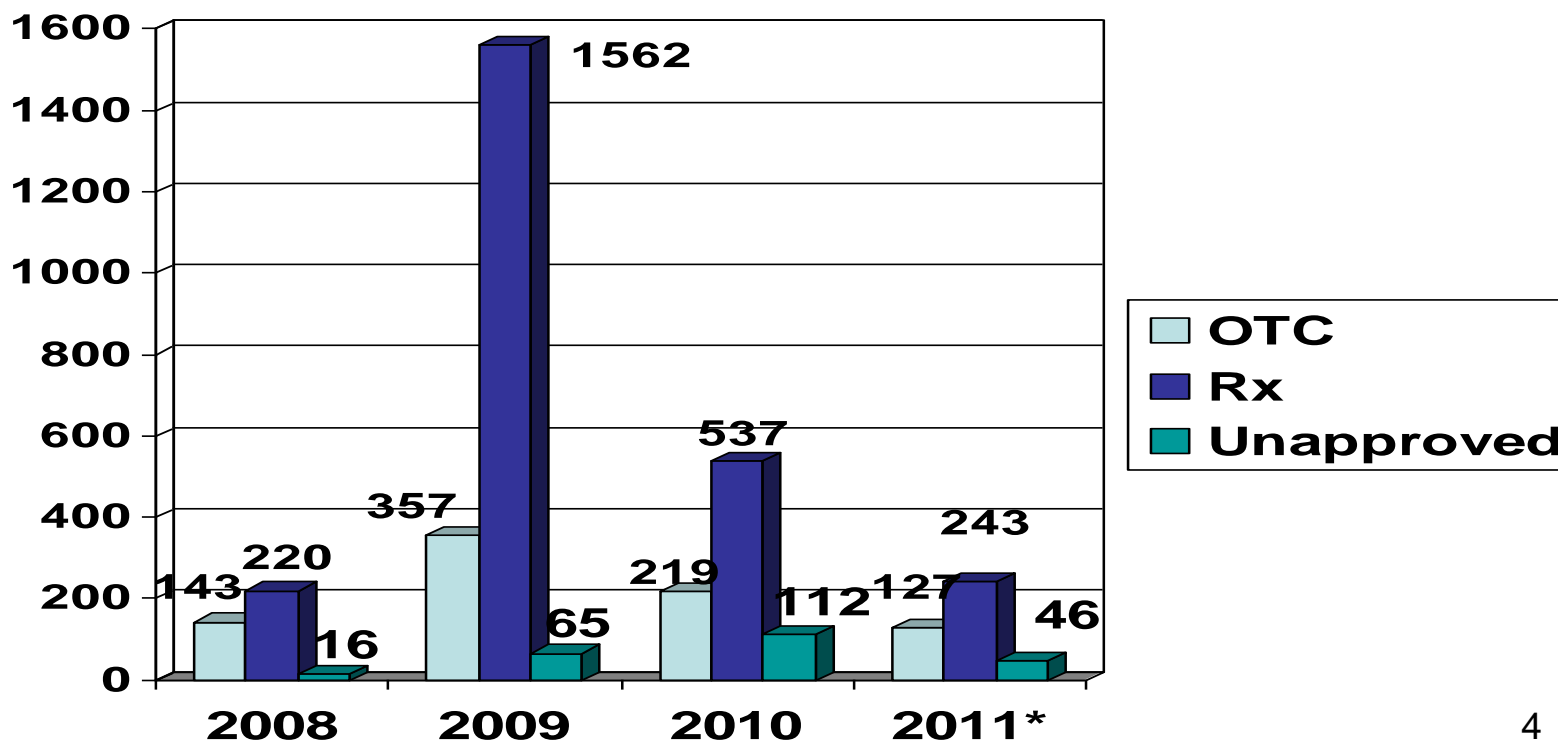
3 major product recall events contributed to majority of Class II recalls



\* End of 2nd QTR 2011

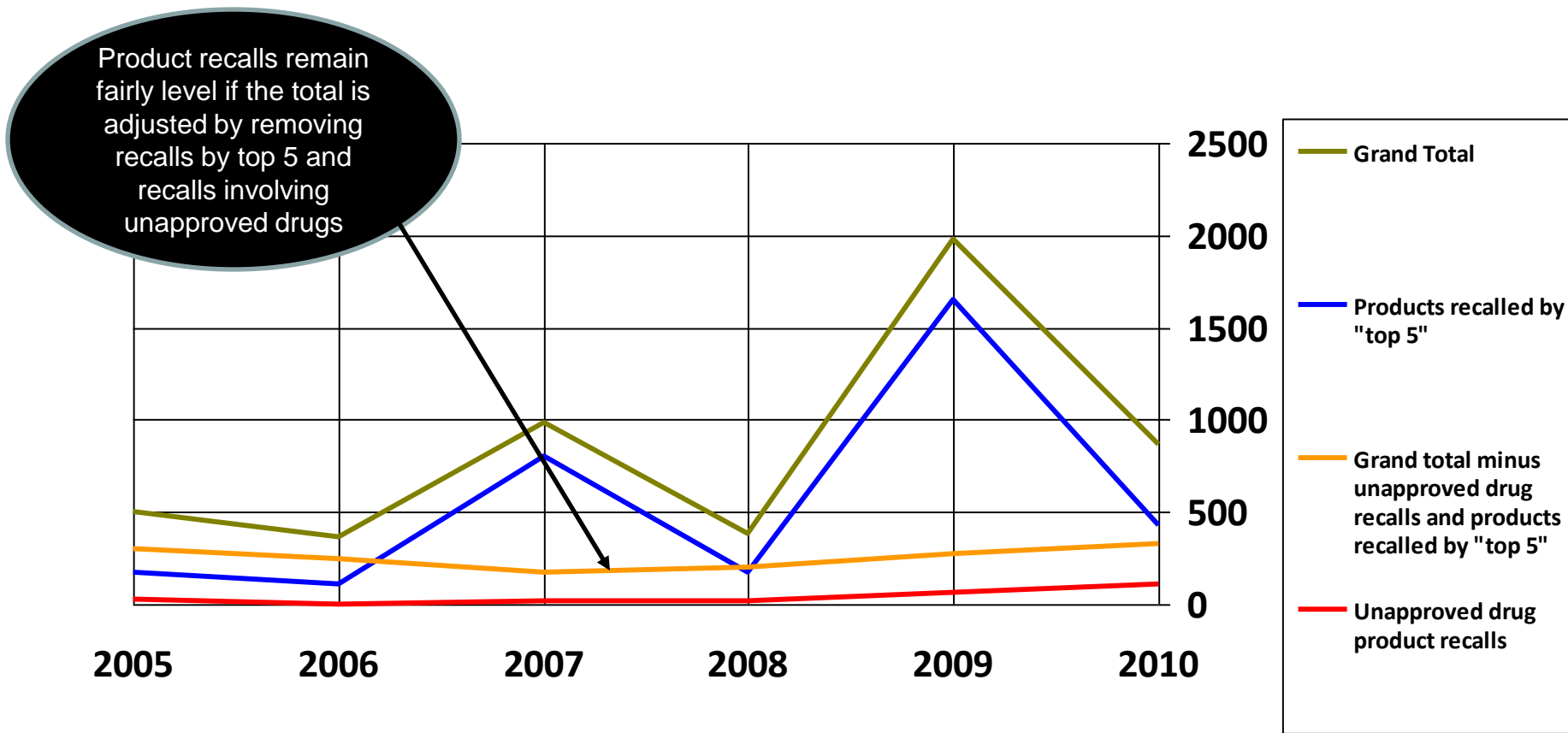


# Total Number of Products Recalled Comparison Rx, OTC, Unapproved Drugs FY 2008 – 2<sup>nd</sup> QTR 2011



\* End of 2nd QT 2011

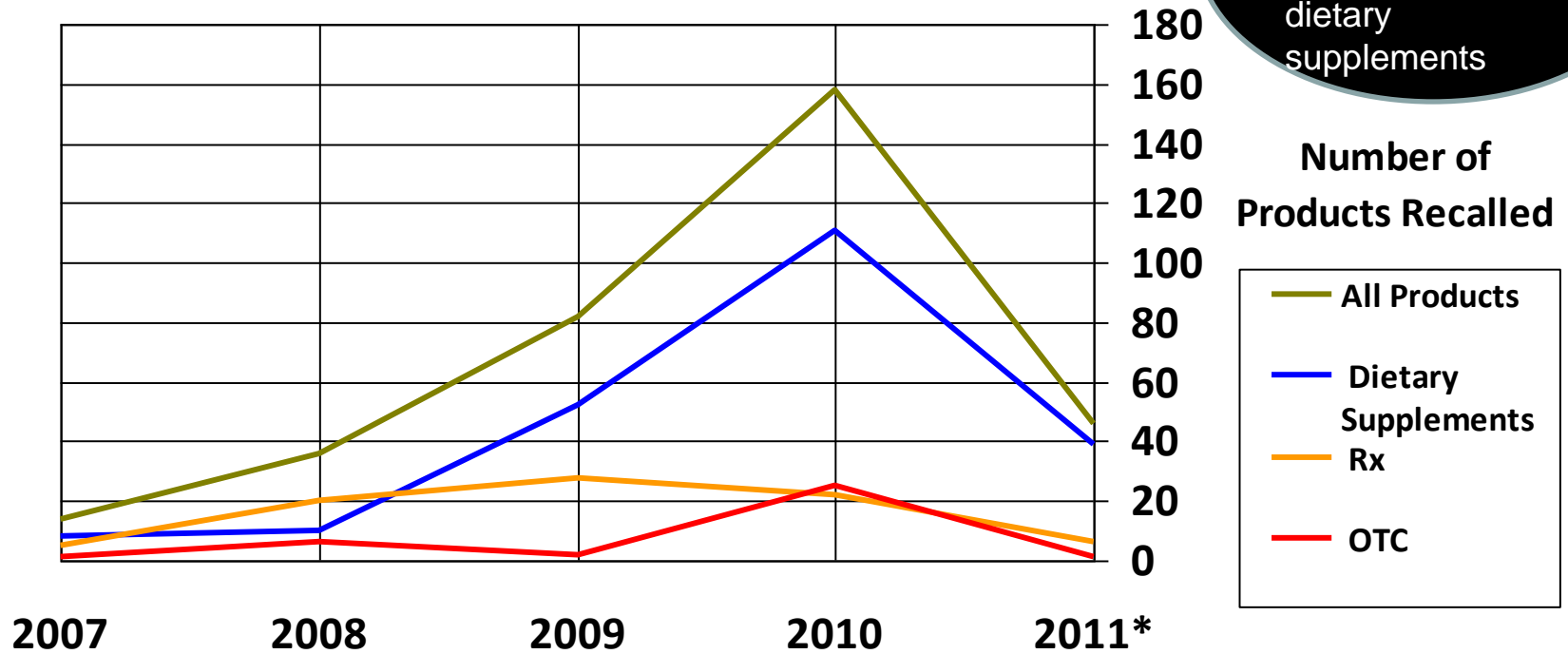
## Variation in Annual Product Recall Totals is Largely Influenced by Recalls of Unapproved Drugs and by Members of Annual Top Five FY 2005 - 2010





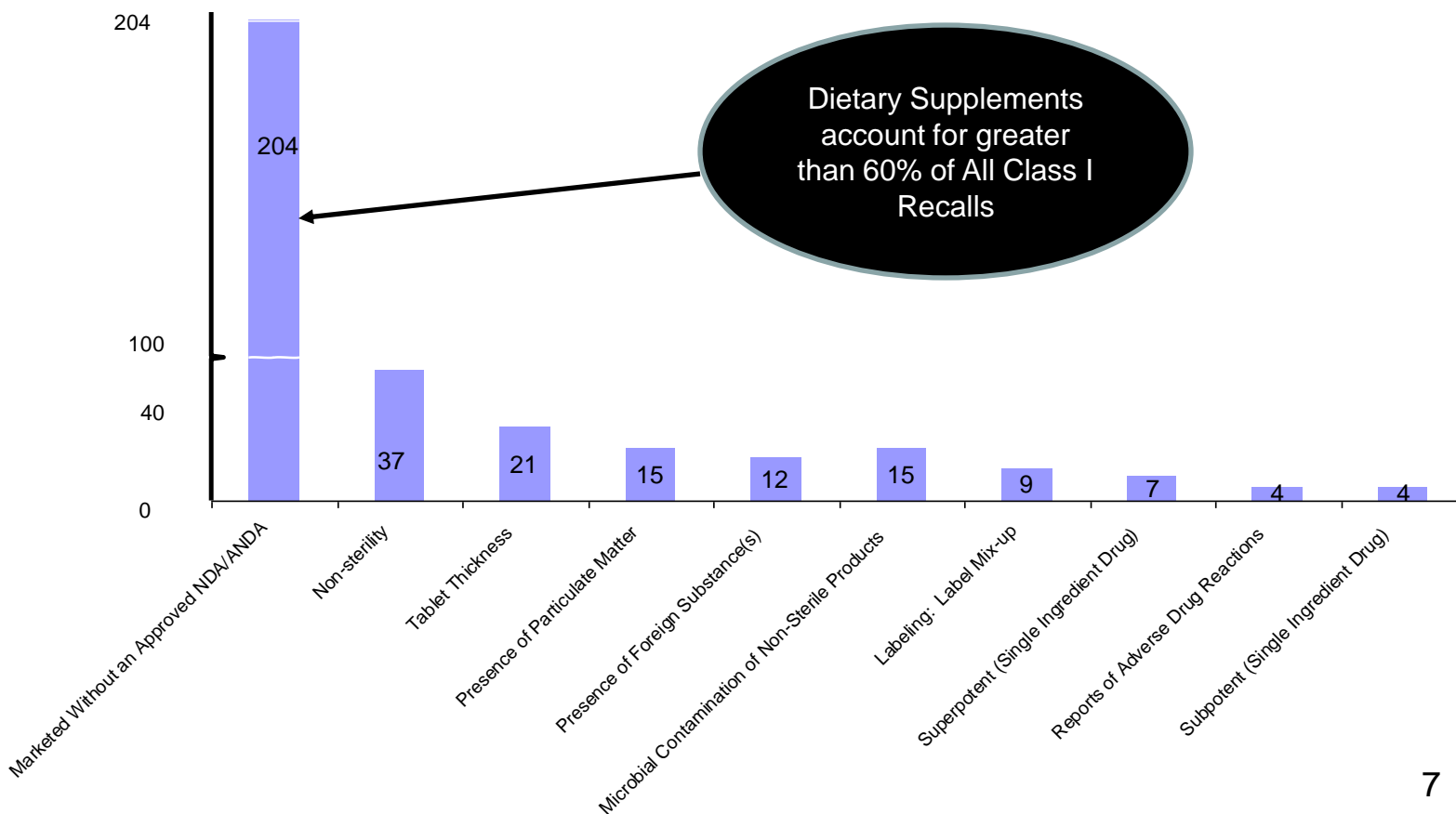
# Upward Trend in **Class I** Product Recalls Due to Dietary Supplements that Contain Undeclared API's FY 2007 to 2<sup>nd</sup> QTR 2011

Approximately 70% of Class I recalls during 2010 involved dietary supplements



6  
\* End of 2nd QT 2011

# Top 10 CDER Reasons for Class I Product Recalls FY 2005 Through 2010





## Top Reasons for Class I Product Recalls FY 2005 to 2010 Account for 88% of Class I Recalls

Marketed Without an Approved NDA/ANDA - approximately 61%  
(includes dietary supplements containing undeclared APIs)

Non-sterile or presence of objectionable organism (in non-sterile drug product) - approximately 8%

Tablet Thickness (NTI drug) – approximately 6%

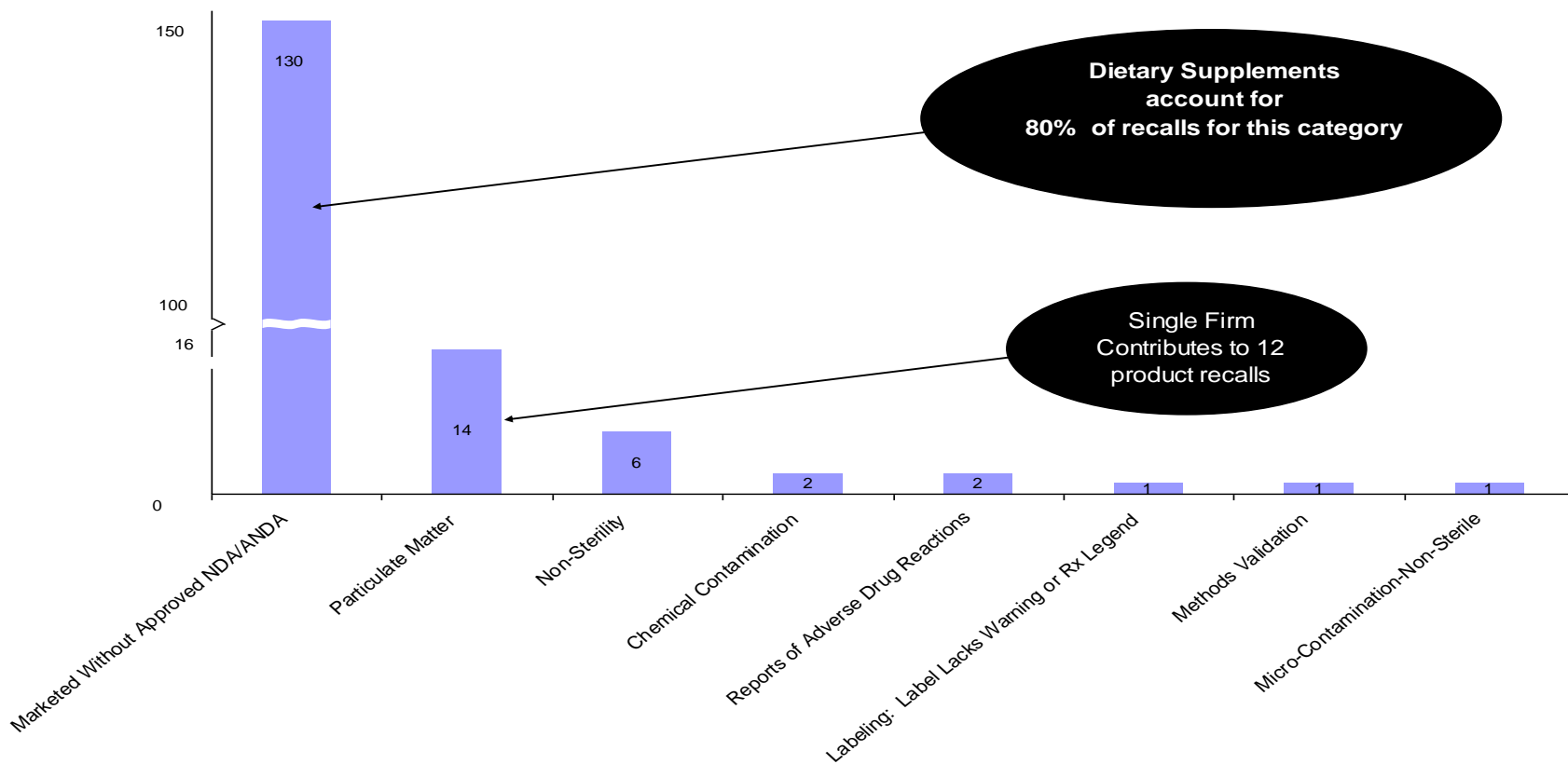
Presence of Particulate Matter- approximately 4%

Super- or Sub-potent (NTI drug) - approximately 3%

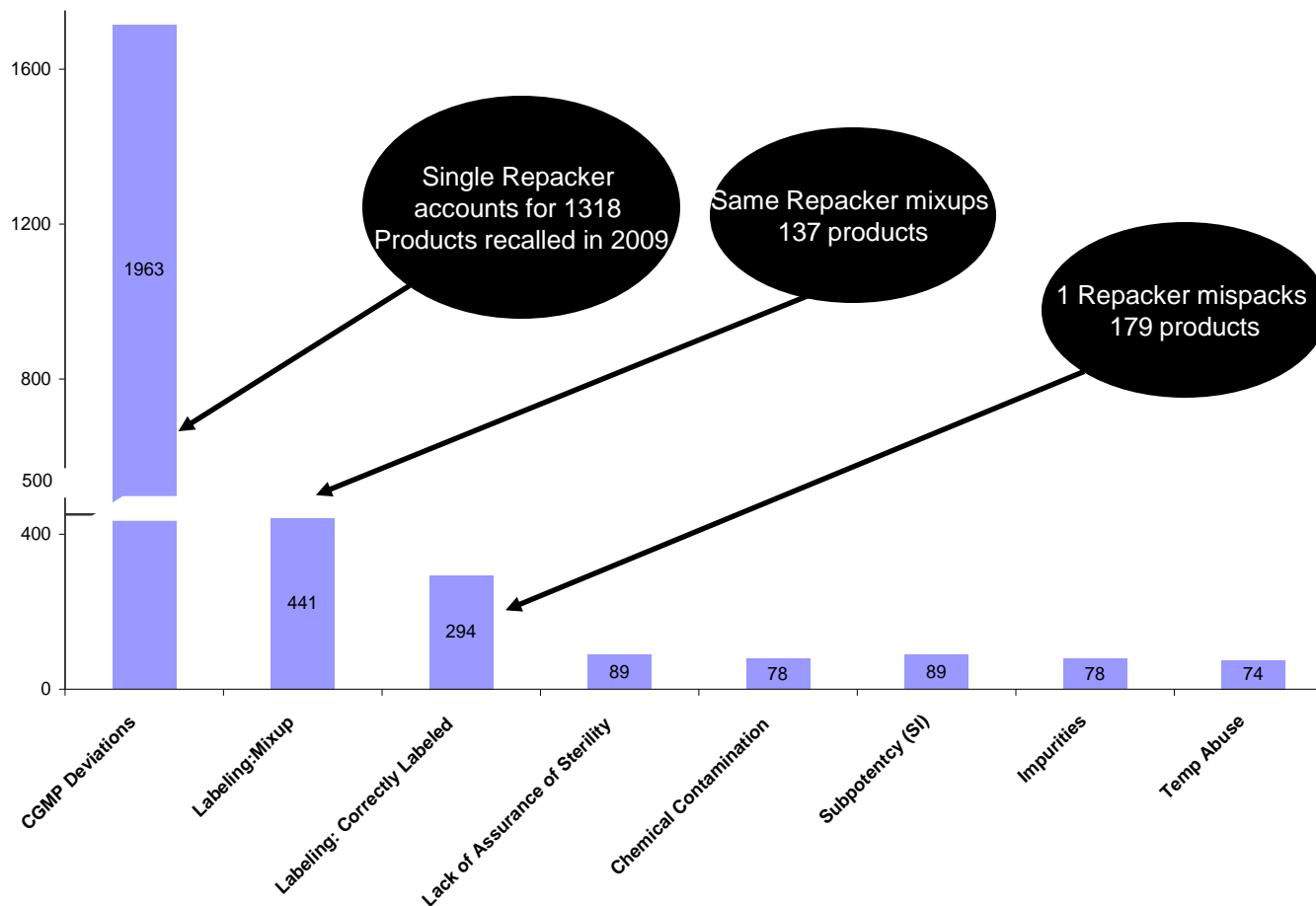
Contaminant Posing Serious Health Risk- approximately 3%

Labeling: Labeling Mix-up- approximately 3%

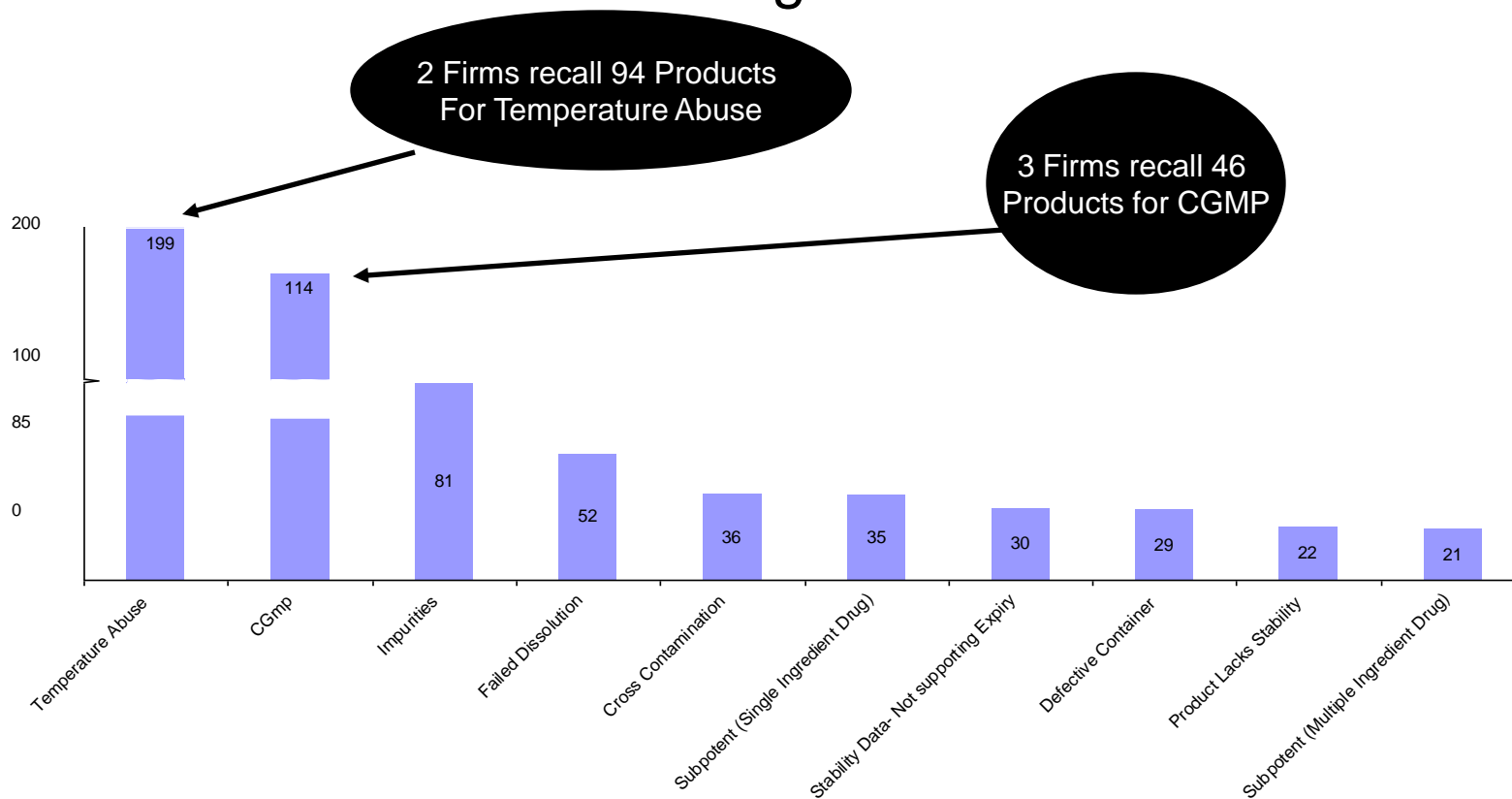
# Top 10 CDER Reasons for Class I Product Recalls FY 2010



# Top 10 CDER Reasons for Class II Product Recalls FY 2005 Through 2010

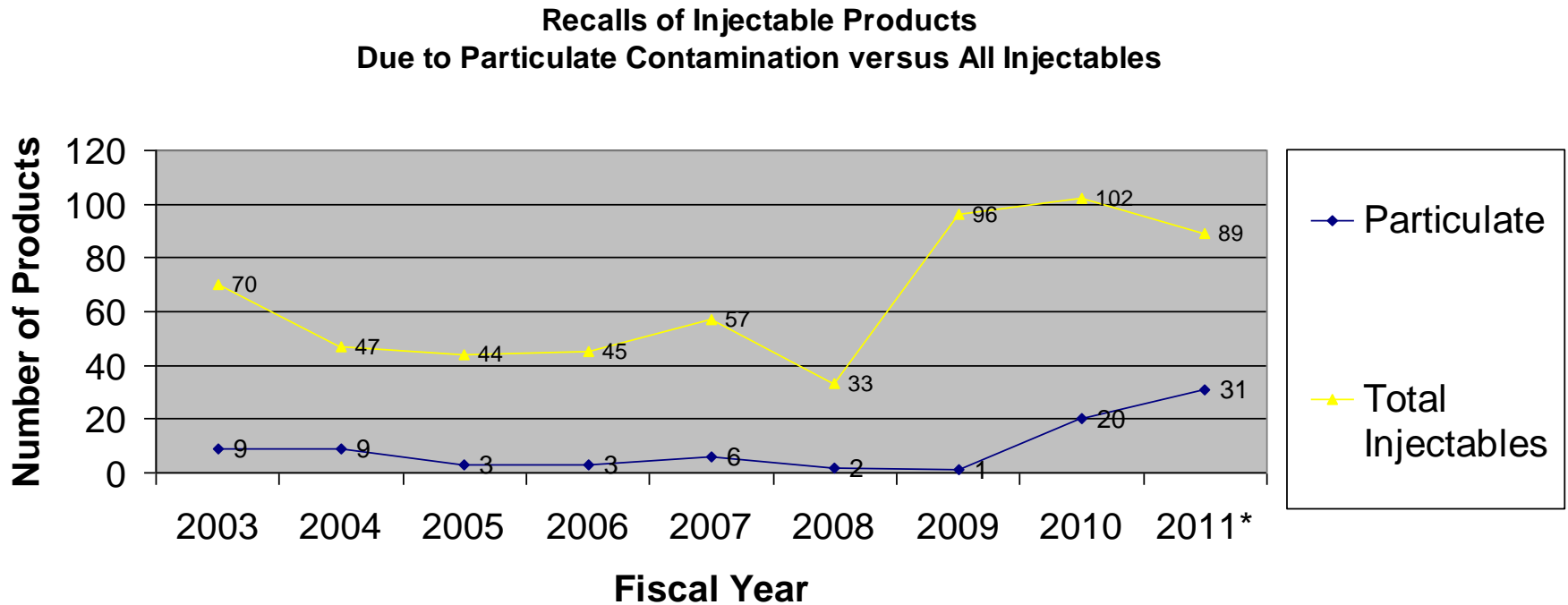


# Top CDER Reasons for Class III Product Recalls FY 2005 Through 2010





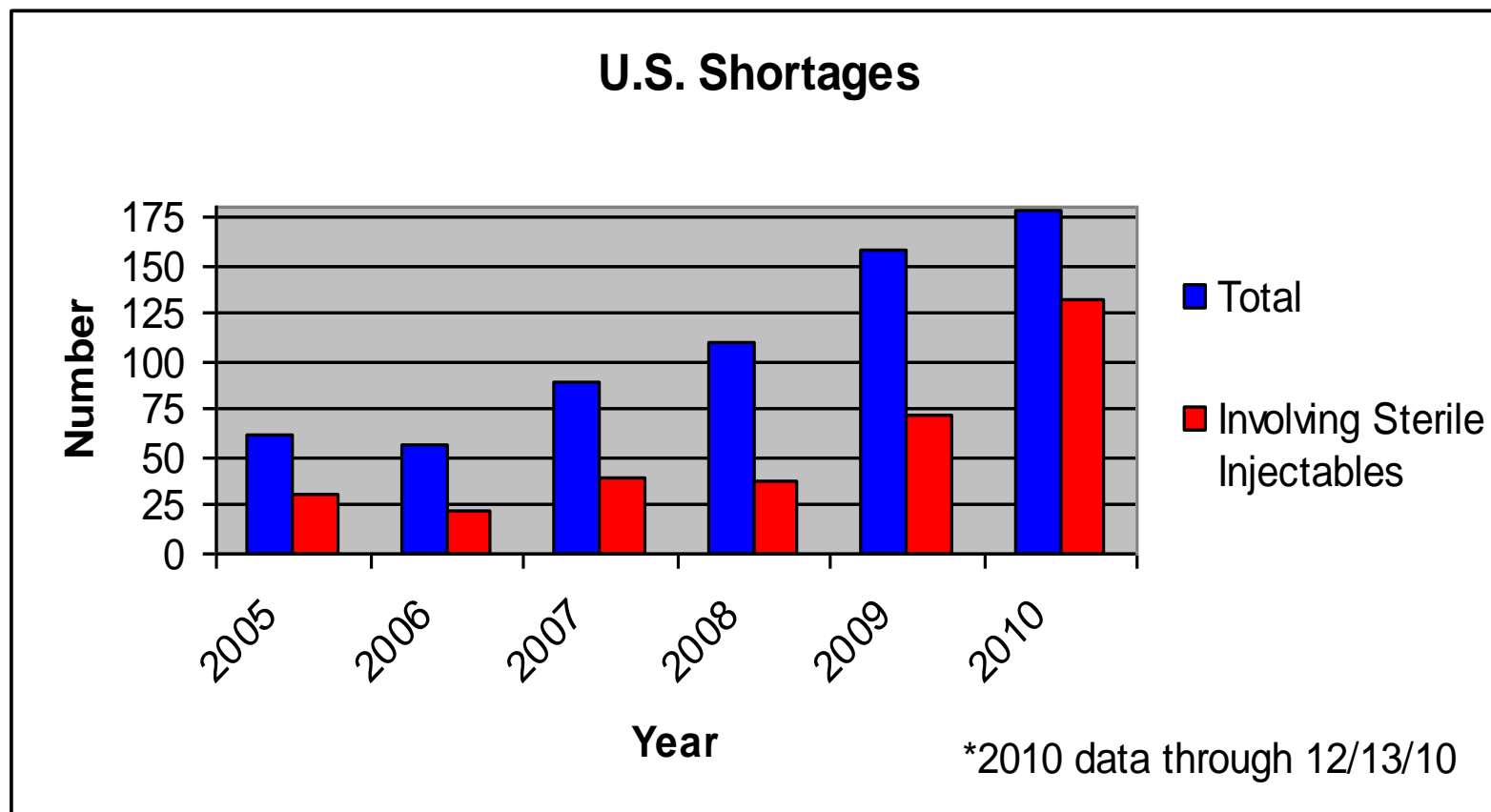
# Injectable Drug Product Recalls FY 2003 – 2011 Q2



12  
\* End of 2nd QTR 2011

# Shortage Trends – Past 6 years

CDER Drug Shortage Data Database



## Injectable Product Recall Summary

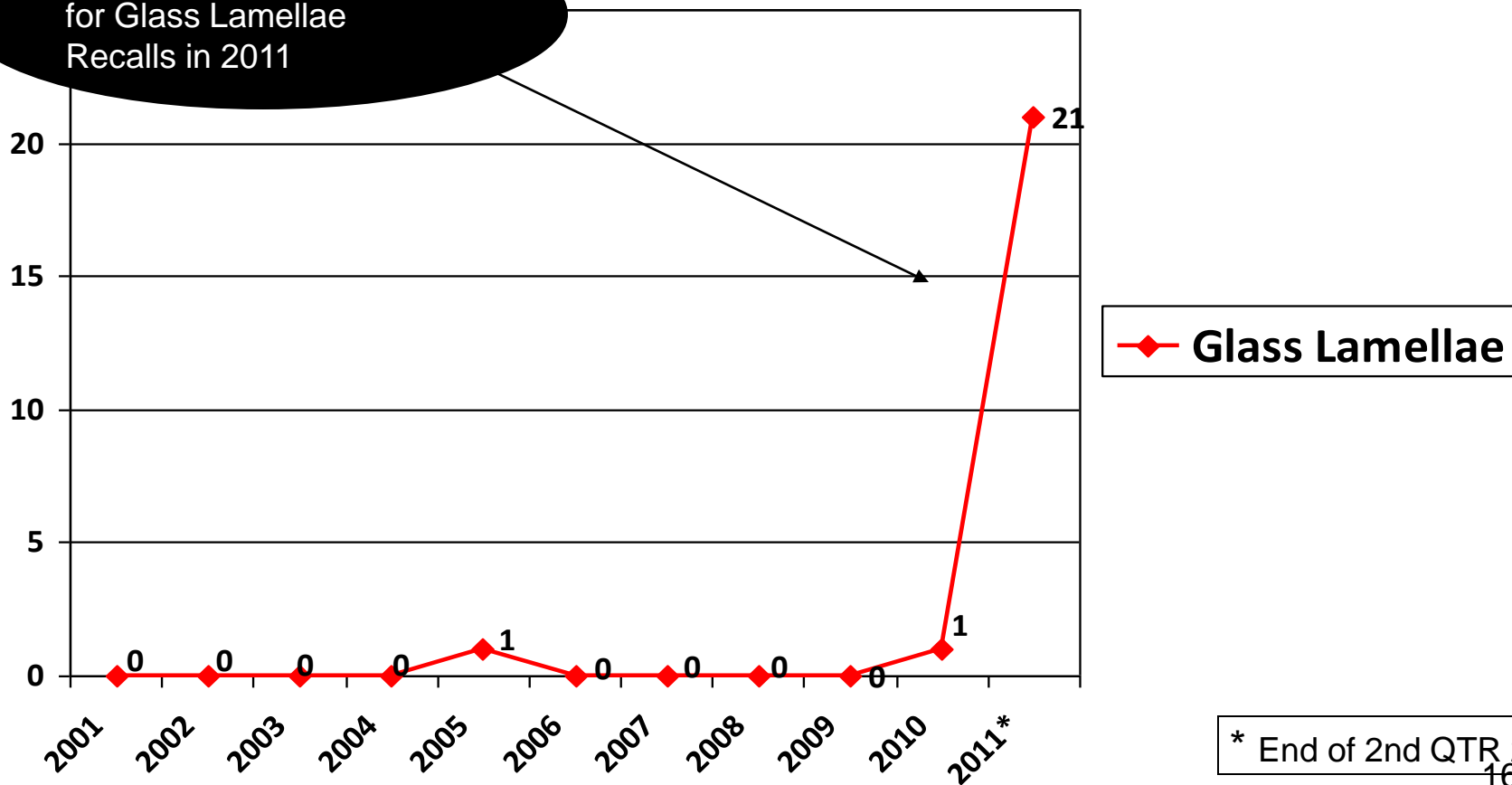
- Many Recent Recalls of Injectable Drugs Involve Particulates
  - Metal
    - Corrosion, abrasion
  - Glass
    - Glass delamination
  - Crystals of Drug Substance
  
- Particulates Can Form Due to Interactions Indicating Incompatibility of Drug with Immediate Surroundings
  - Equipment
  - Container Closure system

## Traceable Sources for Injectable Particulate Recalls FY 2003 – 2011 End 2<sup>nd</sup> QTR

- Majority of recalls due to particulates (52/84) involve incompatibility or instability
  - container closure interaction with product
    - 29 recalls
  - processing equipment interaction with product
    - 16 recalls
  - precipitation/crystallization
    - 7 recalls

# Glass Delamination Emerges as Source of Product Recalls in FY 2010-11

1 firm responsible 19 products for Glass Lamellae Recalls in 2011



\* End of 2nd QTR 2011

# The Glass Delamination Issue

- From what we know to be the root cause, the factors that contribute are prevalent. We only found 1 product recall (fluorouracil, 2005) prior to the recent surge however several FARs in the interim between 2005 and 2010 report glass lamellae. This leads us to believe:
  - The recent problem has probably been around much longer than 1 year (scattered Field Alert Reports in 2008)
  - The prevalence of glass lamellae is under reported
  - The recent surge might have something to do with changes in glass manufacturing processes
  - Vials from at least 3 suppliers have been associated with delamination and firm's need to consider better supplier controls
  - The delamination phenomena for the drug product recalled may not have been adequately studied during process development.

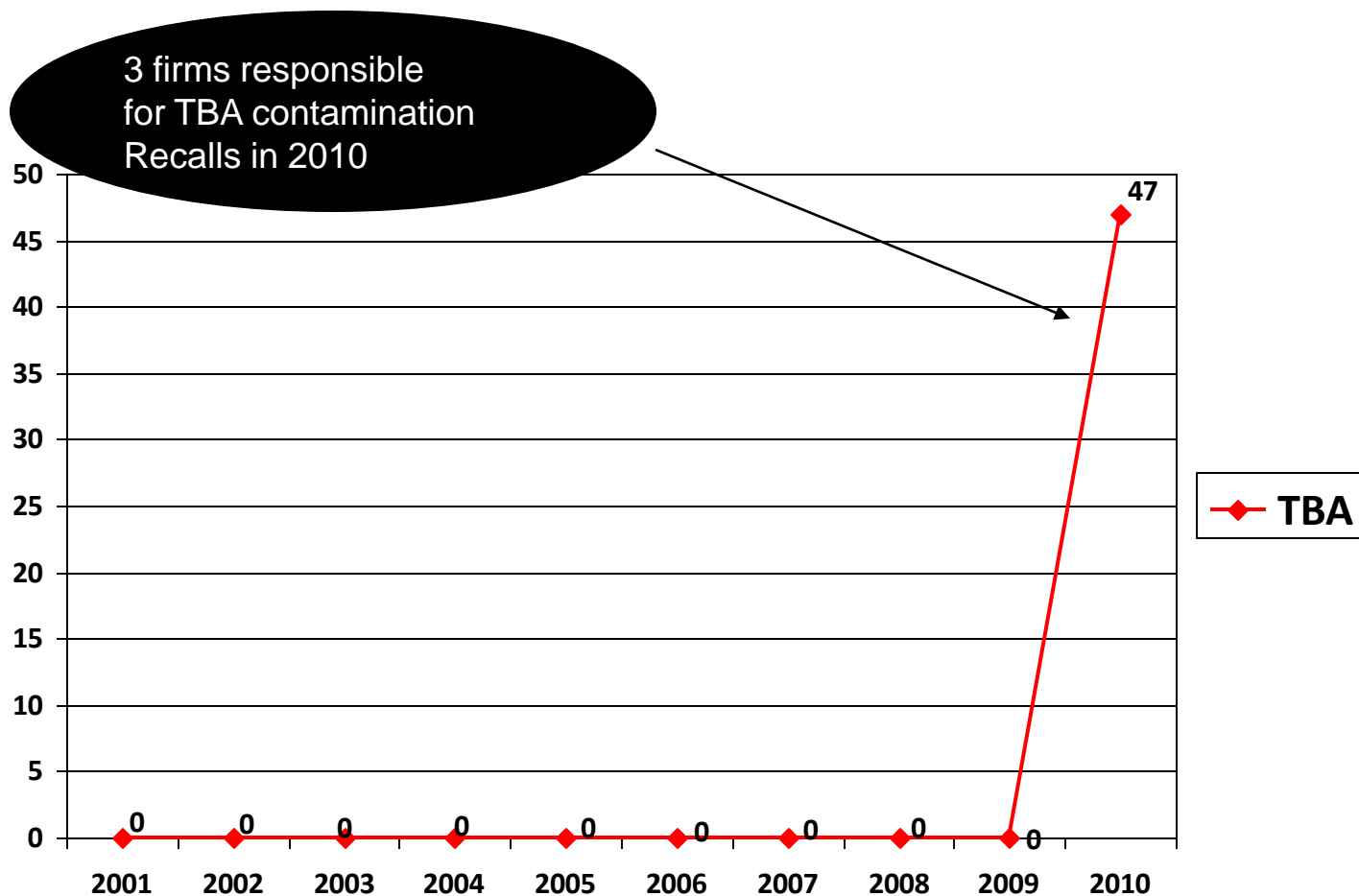
# Detection of Particulates in Injections Can Be Challenging

- Contribution from equipment, process, components, and packaging should never be considered acceptable
  - Standard of GMP
  - Standard of quality Visual inspection process is variable and unreliable
- Measurement methods do not characterize the types of particles present
  - Cannot readily detect anomalies through particle counting methods
- Formation of particles can be a slow process
  - Glass delamination manifested as glass lamellae

## Prevention and Detection Issues

- Better cleaning methods need to be developed to remove free particles
  - Equipment and containers/closures
- Better in-process controls and measurements need to be developed to detect anomalies and act in a timely manner
- Visual inspection processes need to be improved and standardized
- Inspection automation should be developed to overcome the limitations of visual inspection.

## 2,4,6-Tribromoanisole (TBA) Emerges As Source of Product Recalls in FY2010





# **What if you have a particulate recall?**

# Relevant Factors for Particulate Recall Classification

- Identification of particulates and their attributes
- What is the behavior of the particle once injected into the body
- Number and size of visible and sub-visible particulates
- What are the size of the particles? Is it the true particle size or is the size based on an aggregation of particles?
- Do the particles aggregate and/or disperse upon aggitation of container?
- Can an in-line filter be used to mitigate the risks of the particulates while not compromising the safety and efficacy of the drug?
- Ease of detectability
  - Is the product a solution, suspension, or lipid?
  - Is the product packaged in a clear or amber vial or container?

## Relevant Factors for Particulate Recall Classification (continued)

- How was the incident discovered?
- How many A/Es and customer complaints are there for the products that are the subject of the recalled lots?
- What's the route of administration (SubQ, IM, IV, intrathecal)?
- What is the frequency of use or administration?
- Patient population this product is administered to
- Is this issue only on this product or potentially in others (delamination, non-sterility) – containment is key?
- How was the scope determined to affect only the recalled lots?
- Does the firm expect a shortage with the removal of the product from the market (is the product sole source)?



Thank you