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# Best Practices in FDA 483 and Warning Letter Management and Recovery

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**This document is intended to facilitate an oral briefing. It is not intended for use as a stand-alone report.**

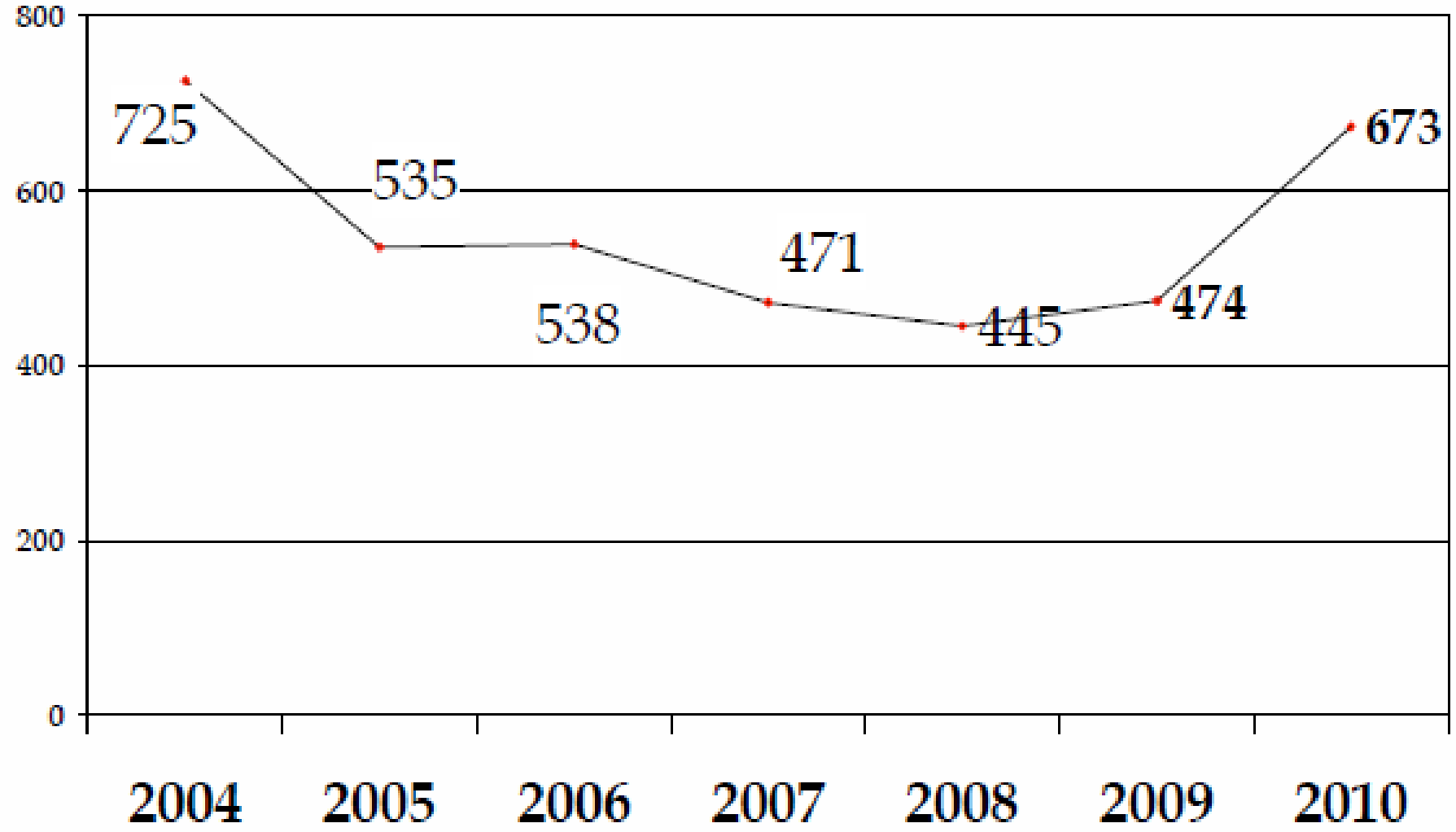
# Approach

- FDA Enforcement Initiative
- Recent Statistics of Warning Letters
- Commercial, Regulatory & Legal Impact of Warning Letters
- Recovery
- "Tips"/Mistakes in Responding to FDA 483 & Warning Letters
- FDA Close Out Letters

# Six Steps to Strengthen Enforcement at FDA – Dr. Hamburg (FDLI: August 6, 2009)

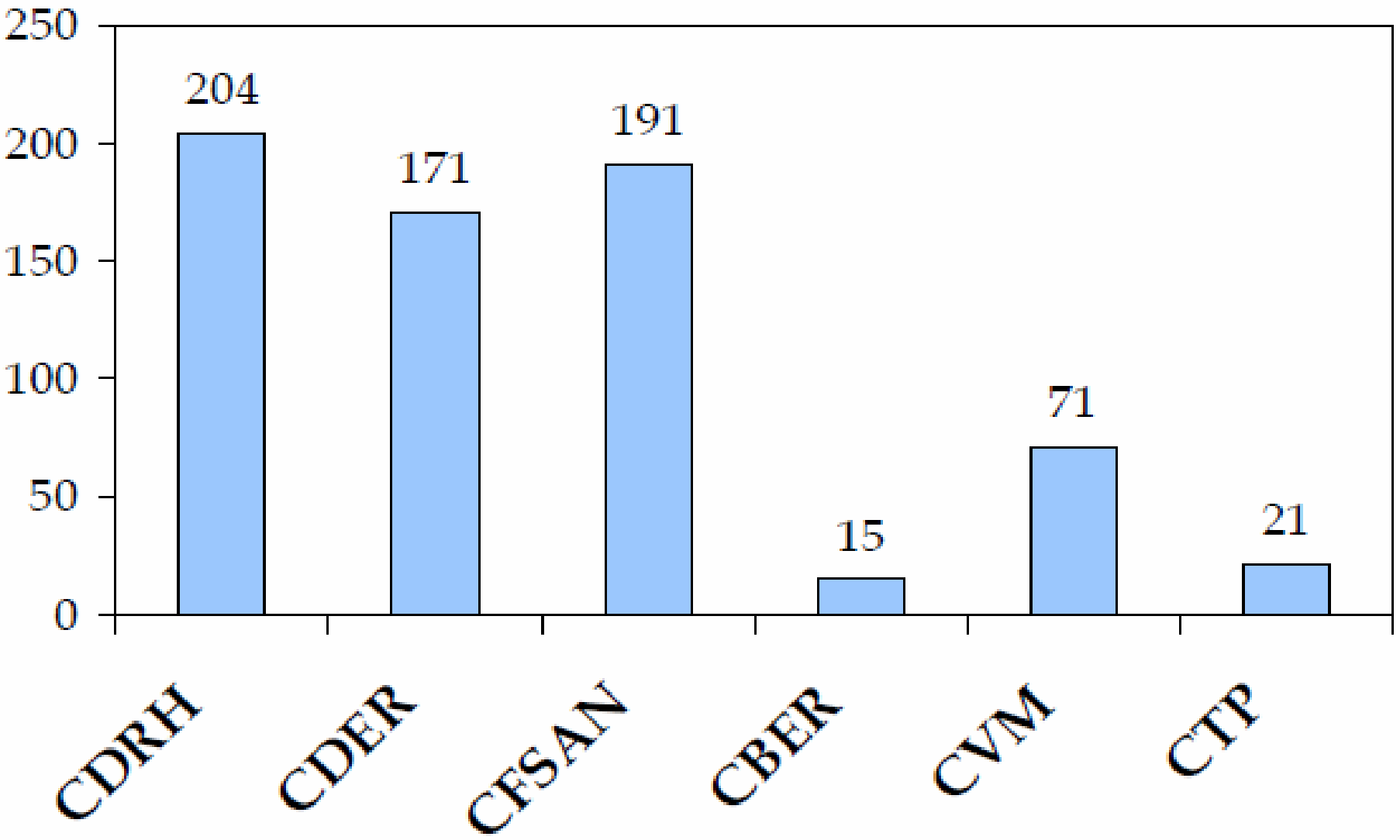
1) Post inspection deadlines
   - Generally no more than 15 working days
2) Reasonable steps to speed the issuance of Warning Letters
   - More streamlined process
3) Work more closely with regulatory partners
4) Prioritize enforcement follow-up
   - After a Warning Letter or major product recall
5) Act swiftly and aggressively to protect public health
   - No longer multiple Warning Letters
   - Immediate action even before we issue a Warning Letter
6) Develop a formal Warning Letter "close out process"
   - Close out letter sent and posted on the web

# FY 2004 – 2010: FDA Warning Letters




Source: FDA Enforcement Statistics Summary FY 2010

# FY 2010: Warning Letters by FDA Center



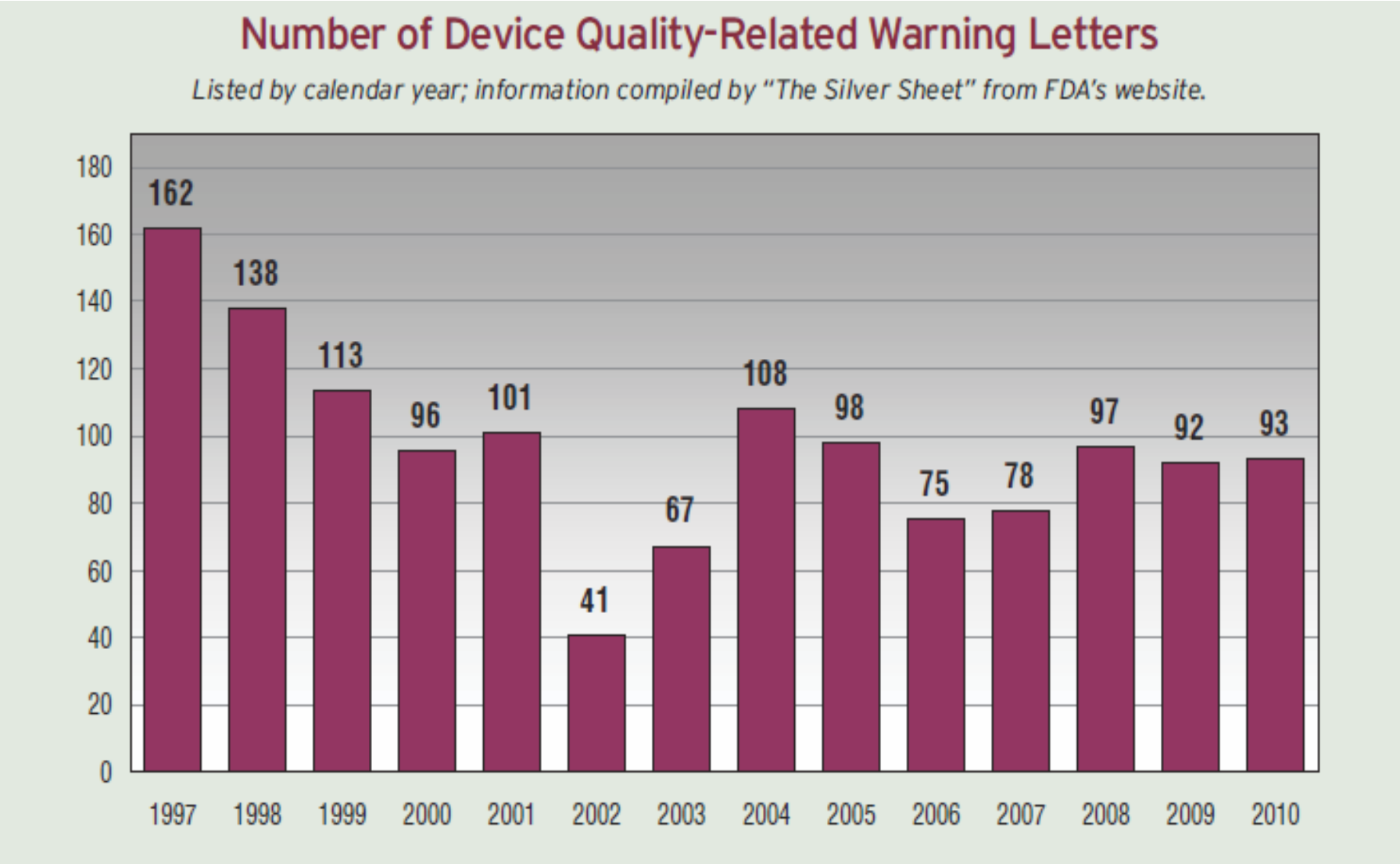

Source: FDA Enforcement Statistics Summary FY 2010

# 2010 Warning Letters

- From January 2010 to December 2010, FDA issued 89 Warning Letters to medical device firms for QS/GMP deficiencies

| QS subsystem | # WLs w/ cite | % |
|---|---|---|
| CAPA | 81 | 91 |
| P&PC | 69 | 78 |
| MGMT | 43 | 48 |
| DESIGN | 49 | 55 |
| DOC | 33 | 37 |

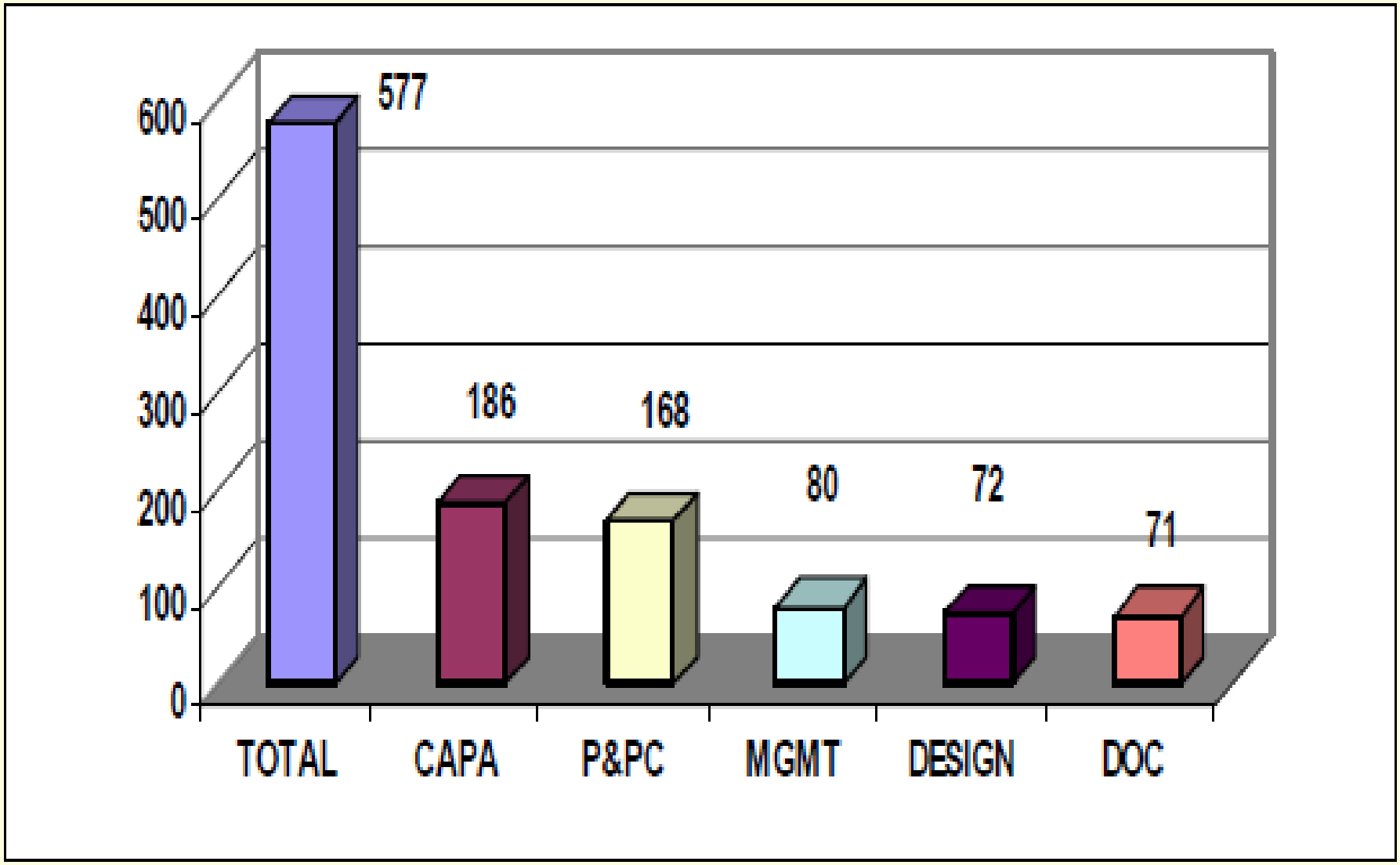
# Number of Device Quality-Related Warning Letters



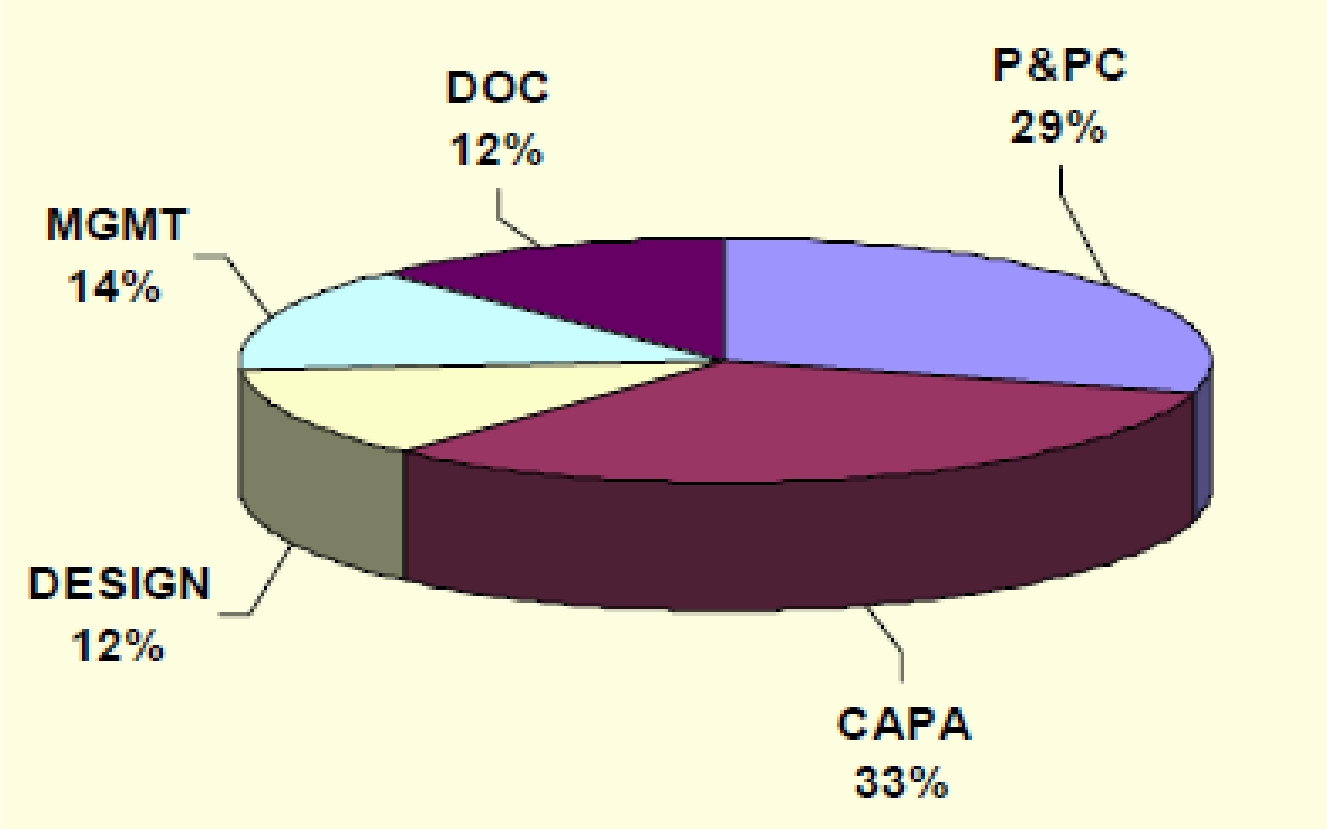
# 2010: Warning Letter Citations by Quality System Subsystem

| | | |
|---|---|---|
| CAPA | = | 186 |
| P&PC | = | 168 |
| MGMT | = | 80 |
| DESIGN | = | 72 |
| DOC | = | 71 |
| **Total** | **=** | **577** |

# 2010: Warning Letter Citations by Quality System Subsystem



# 2010: Warning Letter Citations by Quality System Subsystem



# 2010: Quality System Citations by Subsystem

| P&PC | | CAPA | MGMT | DES | DOC |
|---|---|---|---|---|---|
| 820.50 | 820.120 | 820.90 | 820.5 | 820.30 | 820.40 |
| 820.60 | 820.130 | 820.100 | 820.20 | | 820.180 |
| 820.70 | 820.140 | 820.198 | 820.22 | | 820.181 |
| 820.72 | 820.150 | | 820.25 | | 820.184 |
| 820.75 | 820.160 | | | | 820.186 |
| 820.80 | 820.170 | | | | |
| 820.86 | 820.200 | | | | |
| | 820.250 | | | | |

# FY 2011 – Current: Medical Device Warning Letters

| | |
|---|---|
| Medical Device Warning Letters | 163 |
| GMP/QSR Warning Letters | 109 |
| Medical Device Close Out Letters | 2 |

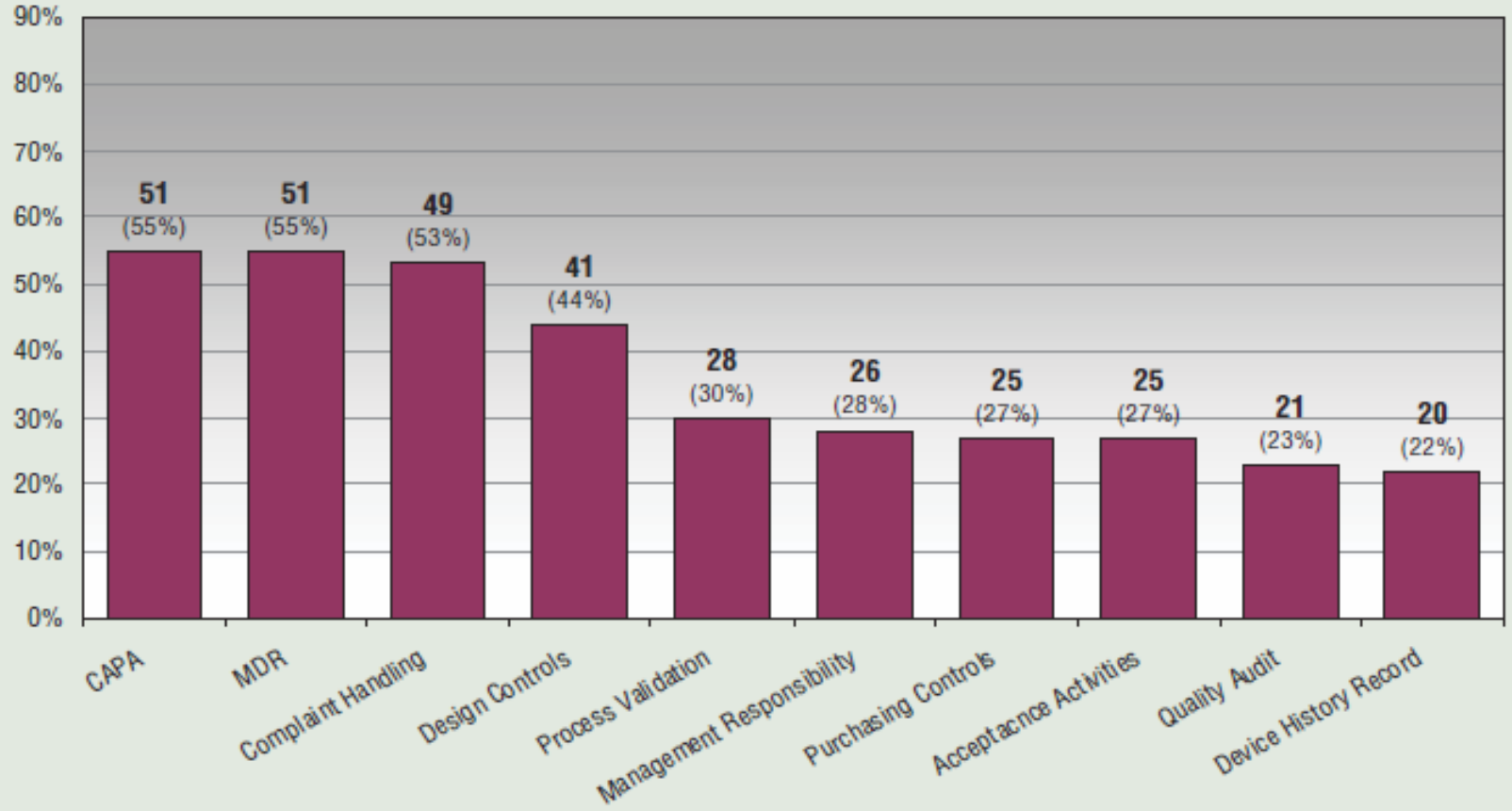
# FY 2011 – Current: Top Warning Letter Citations

| Citation | Warning Letters | Percentage of QSR/GMP Warning Letters |
|---|---|---|
| CAPA | 64 | 59% |
| Design Controls | 56 | 51% |
| Production and Process Controls | 35 | 32% |
| Management Responsibility | 27 | 25% |

# Top Warning Letter Citations in 2010

## Top 10 Warning Letter Citations In 2010

*Graph shows the numbers and percentages of warning letters that included citations in the listed area. Information compiled by "The Silver Sheet" from 93 quality-related warning letters posted on FDA's website during calendar year 2010.*

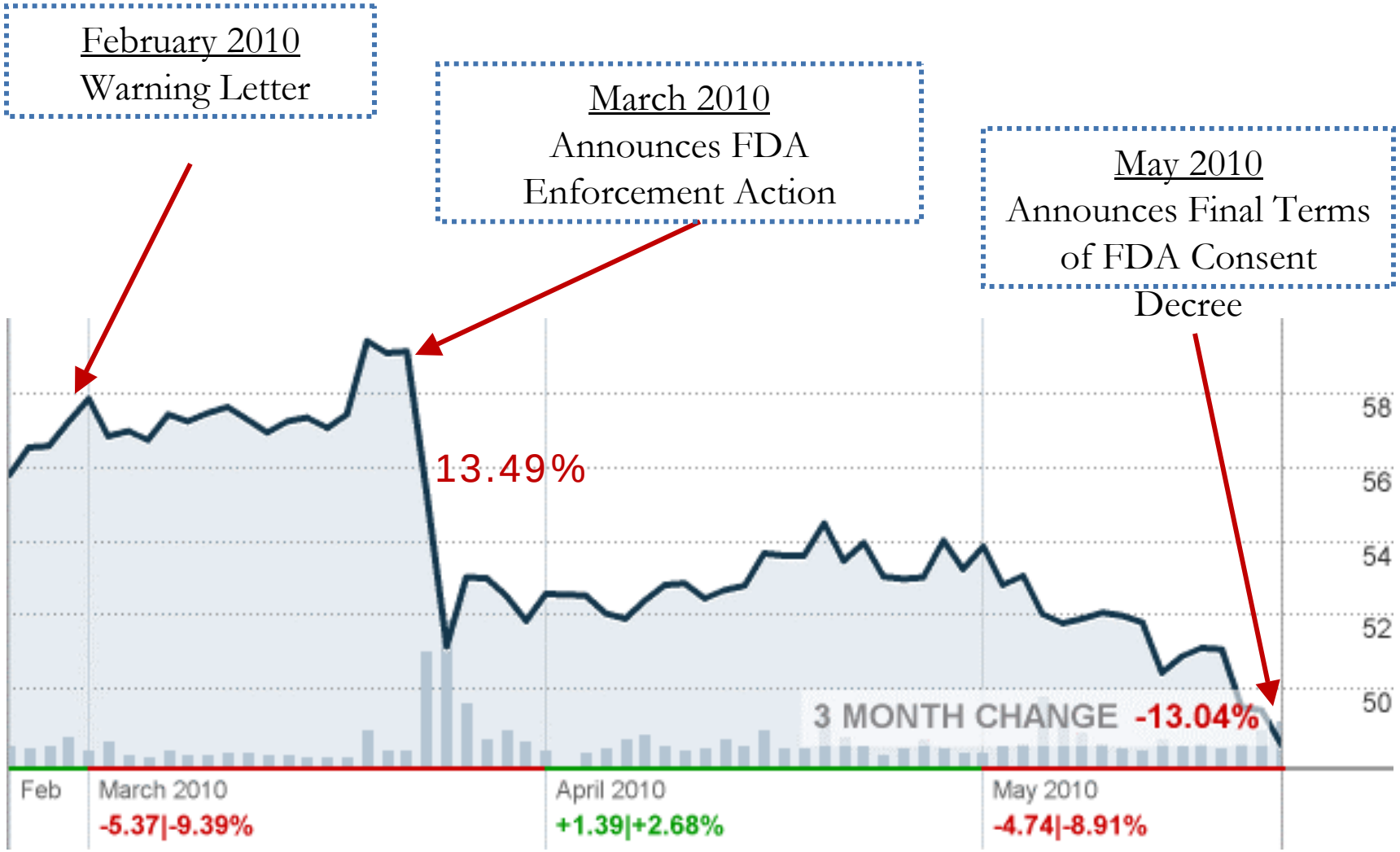


# Impact of Warning Letters and Enforcement Actions

# Multidimensional Impact of Compliance Actions

| | | |
|---|---|---|
| I. | **Immediate Impact** | • Press Releases<br>• Played up by competition<br>• BOD Involvement<br>• Financial Stock Impact |
| II. | **Product Liability and Potential Securities Issues** | • Patients and the legal systems are quick to embrace compliance actions as a basis/support for claims<br>• May extend for years |
| III. | **FDA** | • May impact product approval<br>• Raise scrutiny of company<br>• Increase Pressure to Recall |

# A Case Study 2010



# Recovery: Regaining Credibility

- Company Press Releases
- BOD Involvement
- Comprehensive Response to FDA
- Meetings with FDA and CDRH
- FDA Close Out Process

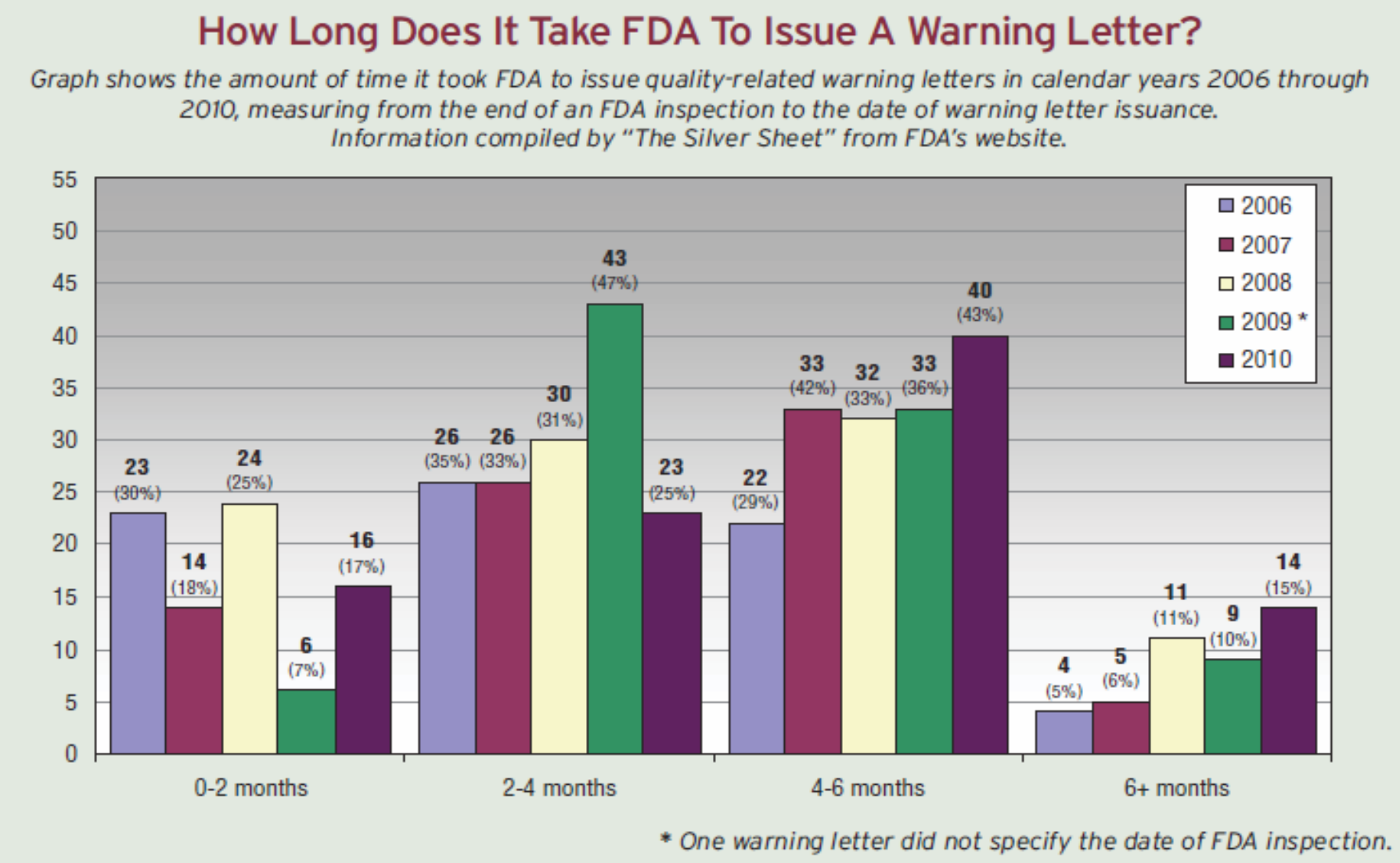
# 10 Common Mistakes/"Tips" for Responding to the Warning Letter

- Know your Audience
- The Response is your First Impression
- Understanding the Observation/Violation
- Establish a Comprehensive Corrective Action Plan
  - Following Through on CAP
- Address the Specific Observation
- Identify Root Cause Solutions (Systems)
- Consider Retrospective Review
- Establish Reasonable and Practical Time Frames
- Attach Objective Evidence of Accomplishments
- Review Internal Audit Program

# Additional "Tips" for Responding to the Warning Letter

- Do Not admit to deviations
- Address items that are discussed but do not appear on FDA 483?
- Third Party Review
- Keep FDA apprised of your progress (30-60 days)
- Send the response within 15 business days

# How Long Does it Take FDA to Issue a Warning Letter?



# FDA Close-out Process

- " if the FDA can determine, usually based on re-inspection, that a firm has fully corrected the violations raised in a warning letter, we will provide to the firm a "close-out" letter indicating that the issues in the warning letter have been successfully addressed."
- These letters would be posted on the web
- Applies to Warning Letters issued after September 1, 2009

# FY 2010: Medical Device Warning Letters

| | |
|---|---|
| Medical Device Warning Letters | 171 |
| GMP/QSR Warning Letters | 93 |
| Medical Device Close Out Letters | 6 |

# FY 2011 – Current: Medical Device Warning Letters

| | |
|---|---|
| Medical Device Warning Letters | 160 |
| GMP/QSR Warning Letters | 108 |
| Medical Device Close Out Letters | 10 |

# Thank You!

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