
# The Role of Standards at CDRH

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# Center for Drug Evaluation and Research

**The two E's**

- **Efficacy**
- **Exclusivity**

**Safety**

- **Pharmacological –Expected, well accepted "Cost of Business";all drugs have side effects**
- **Idiosyncratic- Stronger Public Reactions; Sometimes → Drug Withdrawal**

# Center for Biologics Evaluation and Research

Biotech

- Much like Drugs
- More Novelty
- Only Exclusivity from Orphan Drugs
- Large Molecules – no generics

**Blood, Tissues, Vaccines, Xeno**

- **Legal definitions date from WW II**
- **Fear of Infectious Diseases**
  - **HIV**
  - **Hepatitis**
  - **TSE**
- **Public perception of risk**

# Center for Devices and Radiologic Health

Shaped by Diversity of Risk

Most Detailed Laws

Youngest “Grandfathers”

(some at birth)

Radiologic Health Program Consumed by Device Program

# Origins of the Centers' Culture

Unsafe Manufacturing – Adulteration

- Horse Jim
- Morphine Cough Syrup
- Ethylene Glycol
- Heart Valves

"False and Misleading"

Fraud

# Origins of the Centers' Culture

Unethical Research

- Tuskegee
- Willowbrook
- Long Island Jewish Hospital

Research Fraud

- IBT (animal)
- Clinical Fraud

# **The Goods** (Regulations and Guidance)

The Problems:

Manufacturing Fraud

Laboratory Fraud

Clinical Research Abuse

Poor Tissue Screening

Poor Regulatory Practice

Part of the Solution:

- Good Manufacturing Practice
- Good Laboratory Practice
- Good Clinical Practice
- Good Tissue Practice
- Good Review Practice
- Good Guidance Practice

# Origins of the Centers' Culture: Performance Anxiety

"Drug Lag"

Backlogs

- Drugs
- Generic Drugs
- Device 510(k)'s
- Blood Devices

Reinventing Government (NPR)

PDUFA

Re-engineering

# Origins of the Centers' Culture: Evidence Standards

Safe Pure and Potent (1904)

Unadulterated, Not Misbranded (1906)

Safe (1932)

Safe and Effective (1962)

- Adequate and well controlled trials

Well Controlled Investigations … and other valid scientific evidence … sufficient to determine effectiveness (1976)

# Origins of the Centers' Culture:
# Diverging Evidence Standards

Food Supplements

Devices (Class I,II,III)

Generic Drugs

Drugs and well characterized biologics

Pediatric Indications

Humanitarian Device Exemptions

Monograph Products

- OTC
- Blood Products

# Forces Shaping Pharmaceutical Medicine

2000

- New Discovery Research and Technology
- Demand for New Medicines and Faster Access
- Mergers, Reorganizations, Process Changes
- Global Market: International Harmonization and Global Competition
- Changing Health Care Environment
- New Laws

# Changes

## Technology

- Process
  - Computers
  - E-Mail
  - Teleconferencing
  - Internet
- Product Development
  - High through-put screening
  - “Rational Drug Design”
  - Bioengineering
  - Miniaturization

# Regulatory Changes

Process

- Early Access to Investigational Products
- Industry – FDA interactions
  - Modular PMA (NDA / BLA)
  - Early Meetings / Agreements
  - Least Burdensome Regulatory Path
- Special Populations
- Regulatory Changes
  - Guidance (transparency)
  - International Harmonization
  - New Laws to Implement

# Regulatory Overview

## Regulatory Hierarchy

- Statute
  - FD&C / FDAMA (1904;1936;1962;1997)
  - PHS Act (1902;1944)
- Regulations
  - Enforceable implementation of Statute
- Guidance
  - Best Advice
  - Non-enforceable when not regulation based

# Legal Authorities

Drugs

- Approved under FD&C Act
  - Mechanisms: NDA, aNDA
  - Regulations: 21 CFR 200's

Biologics

- Licensed under PHS Act
  - Mechanisms: ELA, PLA, BLA
  - Regulations: 21 CFR 600's

Devices

- Approved or Cleared under Device Acts
  - Mechanism :510(k), PMA, a501(k), s510(k)
  - Regulations: 21 CFR 800's

# Laws Enforced by FDA

http://www.fda.gov/opacom/laws/lawtoc.htm

- Food Drug and Cosmetic Act
- Public Health Services Act
  - National Vaccine Program
- Federal Advisory Committee Act
- Administrative Procedures Act
- Orphan Drugs
- Trademark Act
- Federal Trade Commission Act
- Controlled Substances Act
- … and others

# FDA Modernization Act of 1997
## *(FDAMA)*

- Signed into law November 21, 1997
- Amends the Food, Drug & Cosmetic Act
- Amends the Public Health Service Act
- Renews the Prescription Drug User Fee Program with amendments (PDUFA 2)
- Effective 90 days after enactment unless otherwise specified

# Themes of FDA Modernization Act

- Interactive process for product review
- Decisive action
- Patient access
- Codifies reengineering
- Agency discretion, not mandatory requirements
- FDA review accountability/timeliness

# FDAMA Accomplishments

- Completed
  - 24 guidance documents and
  - 6 final rules
- Recognized
  - > 500 consensus standards
- Exempted
  - more than 60 Class II devices
- Approved
  - 13 third parties for 510(k) reviews
- Designated
  - > 150 device types for 3rd party review

# FDAMA Accomplishments

- Piloted
  - Sentinel postmarket reporting
- Instituted
  - interactive “determination” and “agreement” meetings with sponsors
- Rescinded
  - 55 tracking orders
- Chartering
  - advisory panel for scientific disputes
- Expanded
  - stakeholder participation through open meetings nationwide

# Regulations Published in ’99/00

113 regulations and notices published in ‘99/00 so far:

- 18 final rules
- 6 Direct to Final Rules
- 17 Proposed Rules
- 69 Notices
- 3 Advanced Notices of Public Rule Making

# Reengineering

## Examples of Reengineered Process

- New 510(k) paradigm
- Regulations development
- Recalls
- GMP inspections
- Products development protocol (PDP)
- Modular PMA review
- Standards
- QSIT

# Standards

## Strategy

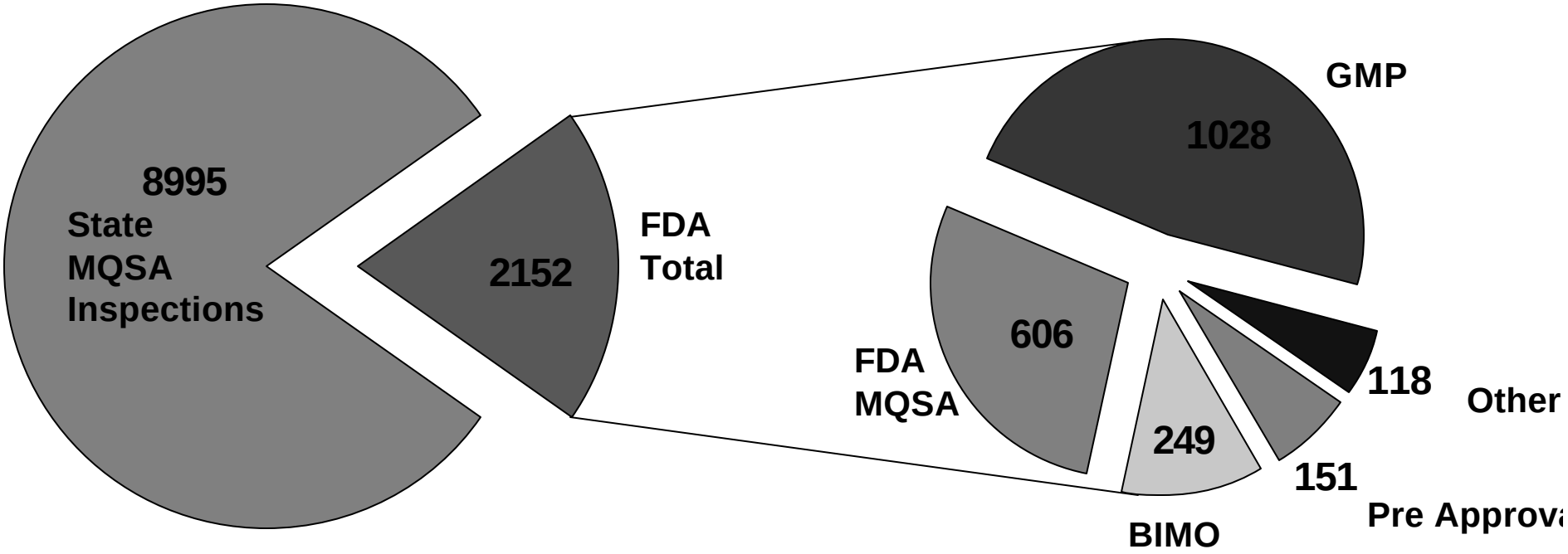
Simplify and streamline the regulatory application process by asserting conformance to standards

## Conformance

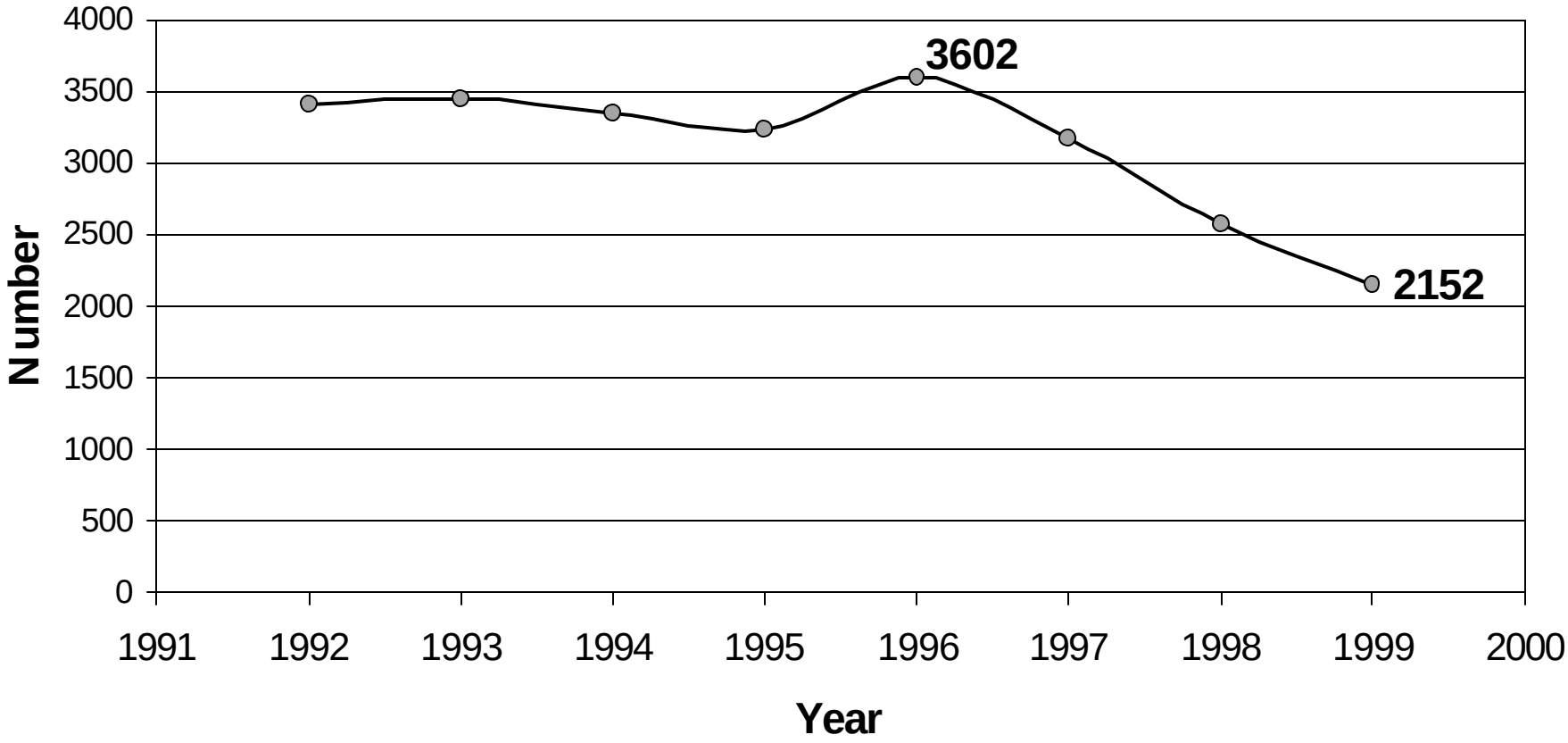
Who assesses ?

- FDA field inspections
- State inspectors (MQSA, CLIA)
- 3rd Parties ?
- MRA ?

# 1999 Device Inspections

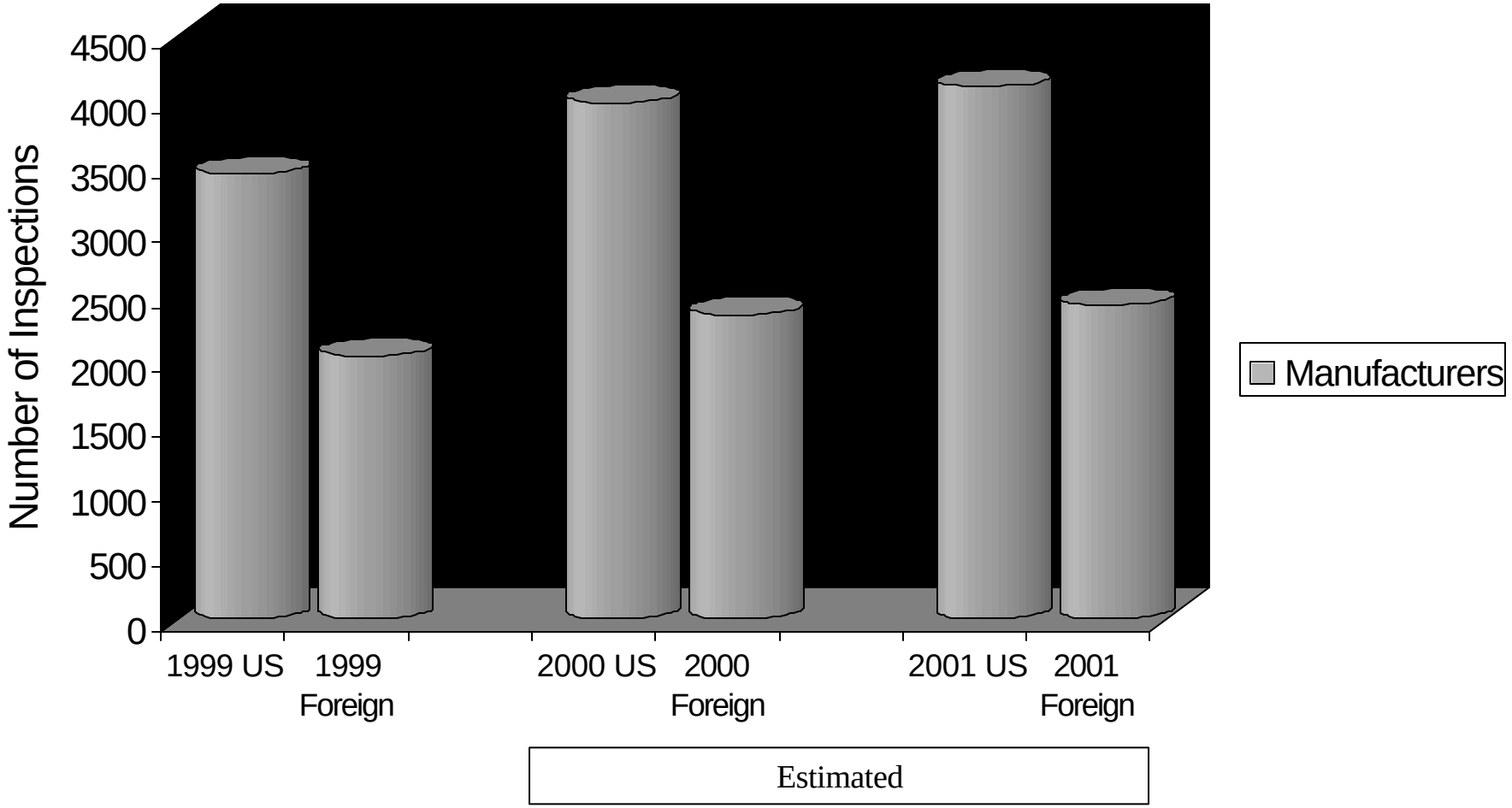


# CDRH Establishment Inspections



# Device Inspections: US and Foreign

## Class II and III with relabelers



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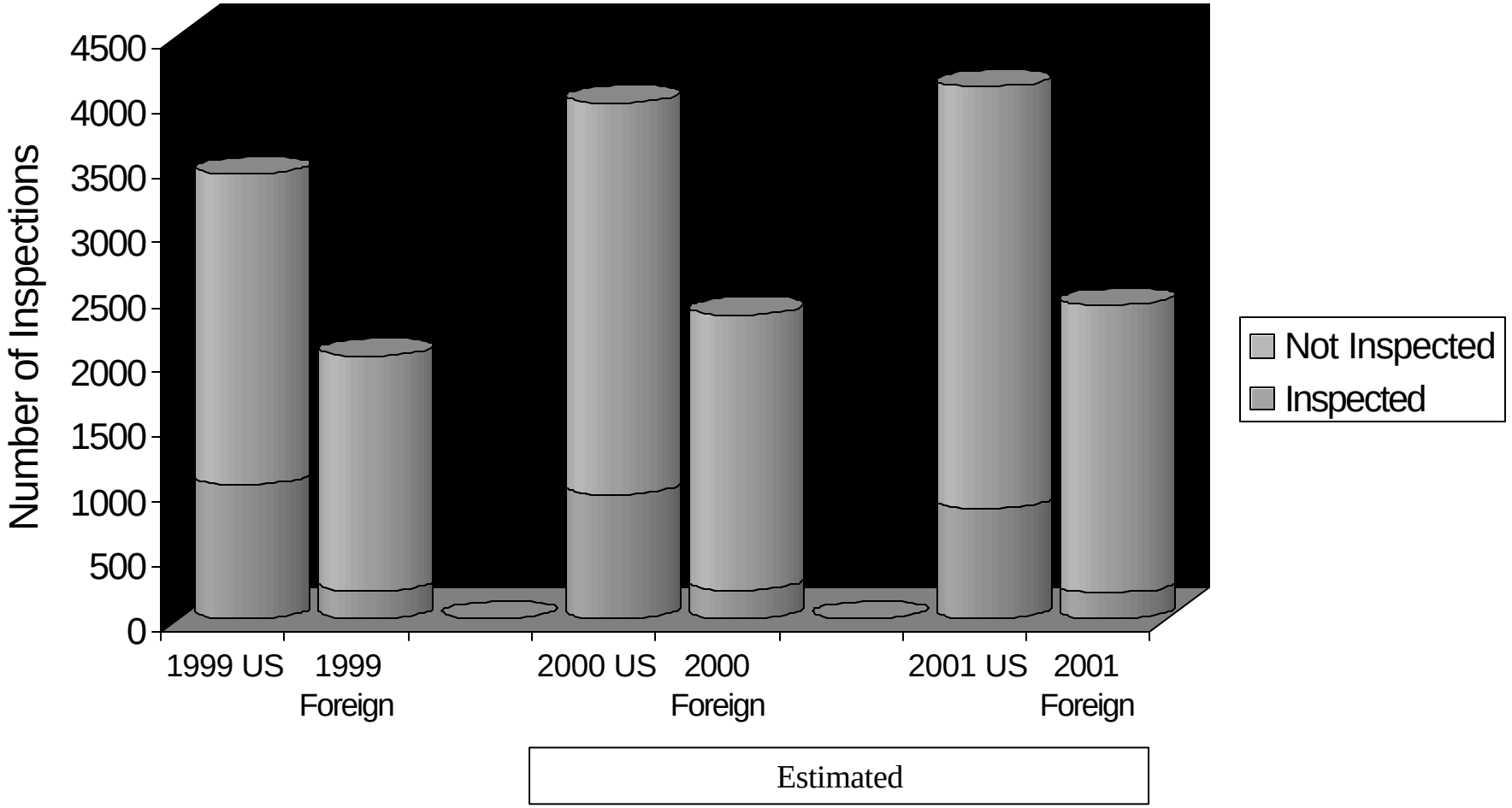

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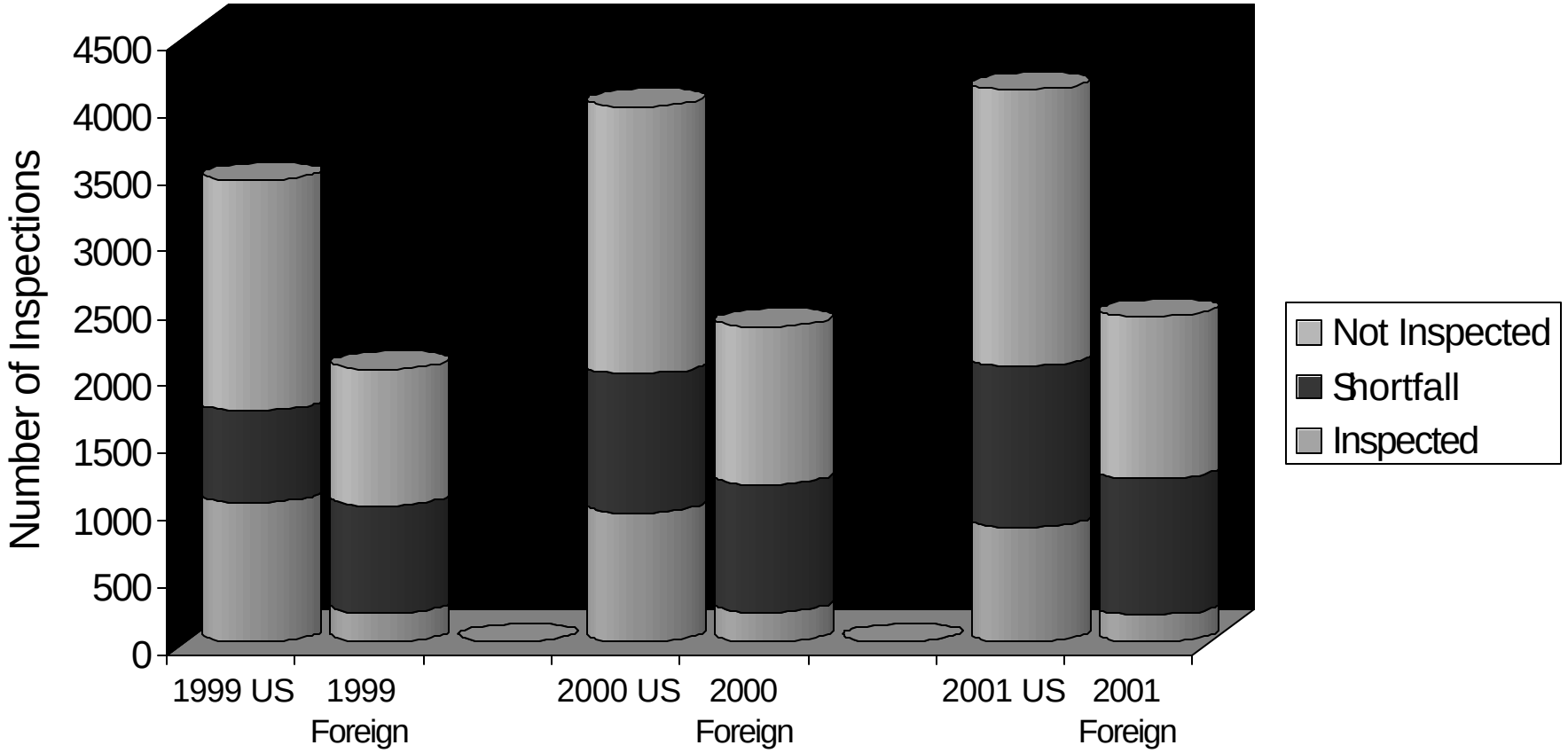

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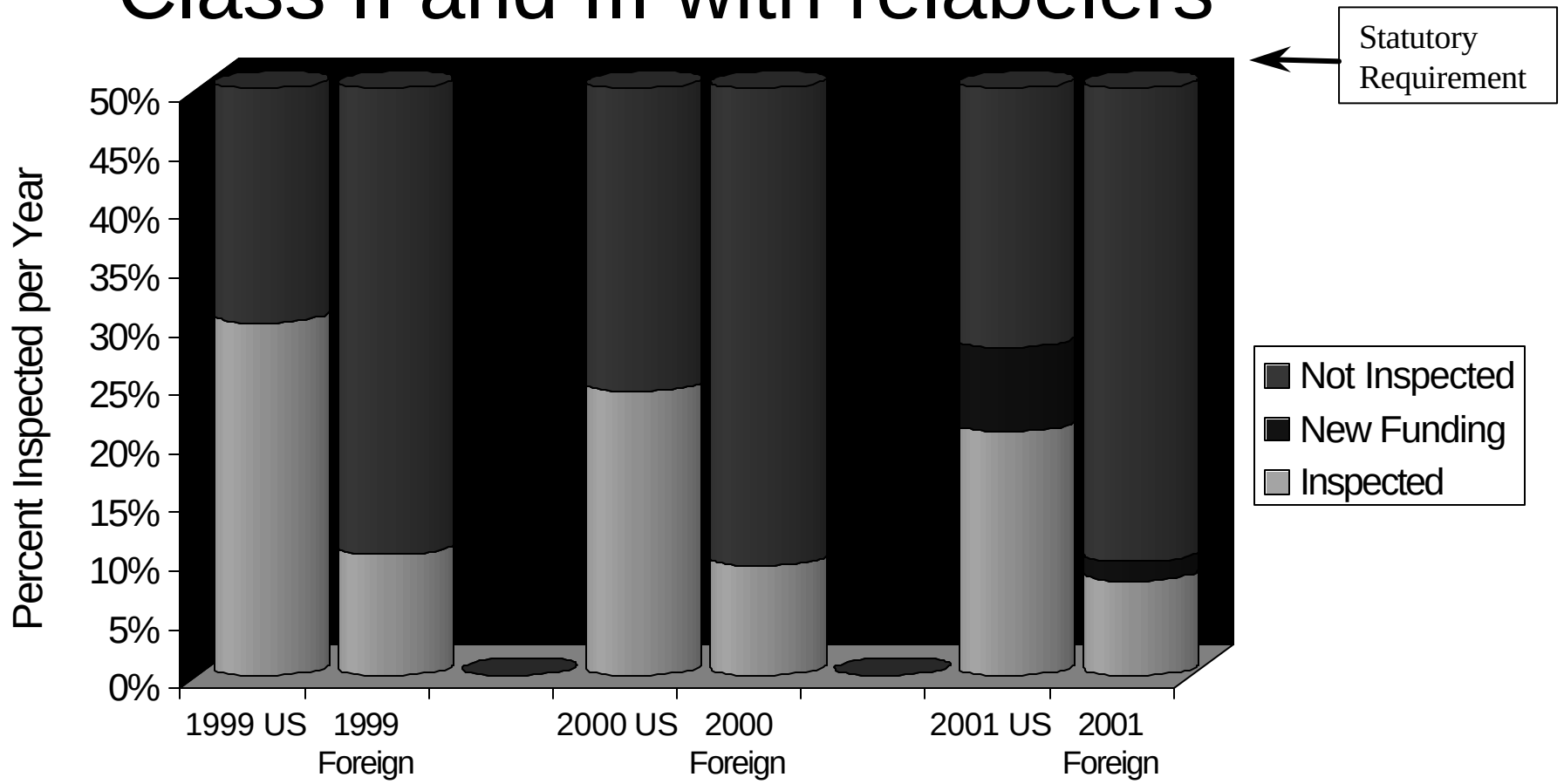


# Inspections: How to get more from decreasing $$$?

Changes are allowing Field to make best use of its time and resources in device inspections:

- "Grassroots" changes
- Reengineering changes
  - QSIT : Quality System Inspection Technique
  - HAACP: Hazard Analysis and Critical Control Points
- Conformance to Standards ?

# Inspections: "Grassroots" Changes

- Pre-announced inspections
- Annotation of 483's
  - Company corrections
- Post-inspection letters to all
  *vs.* only Warning Letters
- Warning Letters
  - 15 days to respond to 483's
  - Untitled letter if response satisfactory

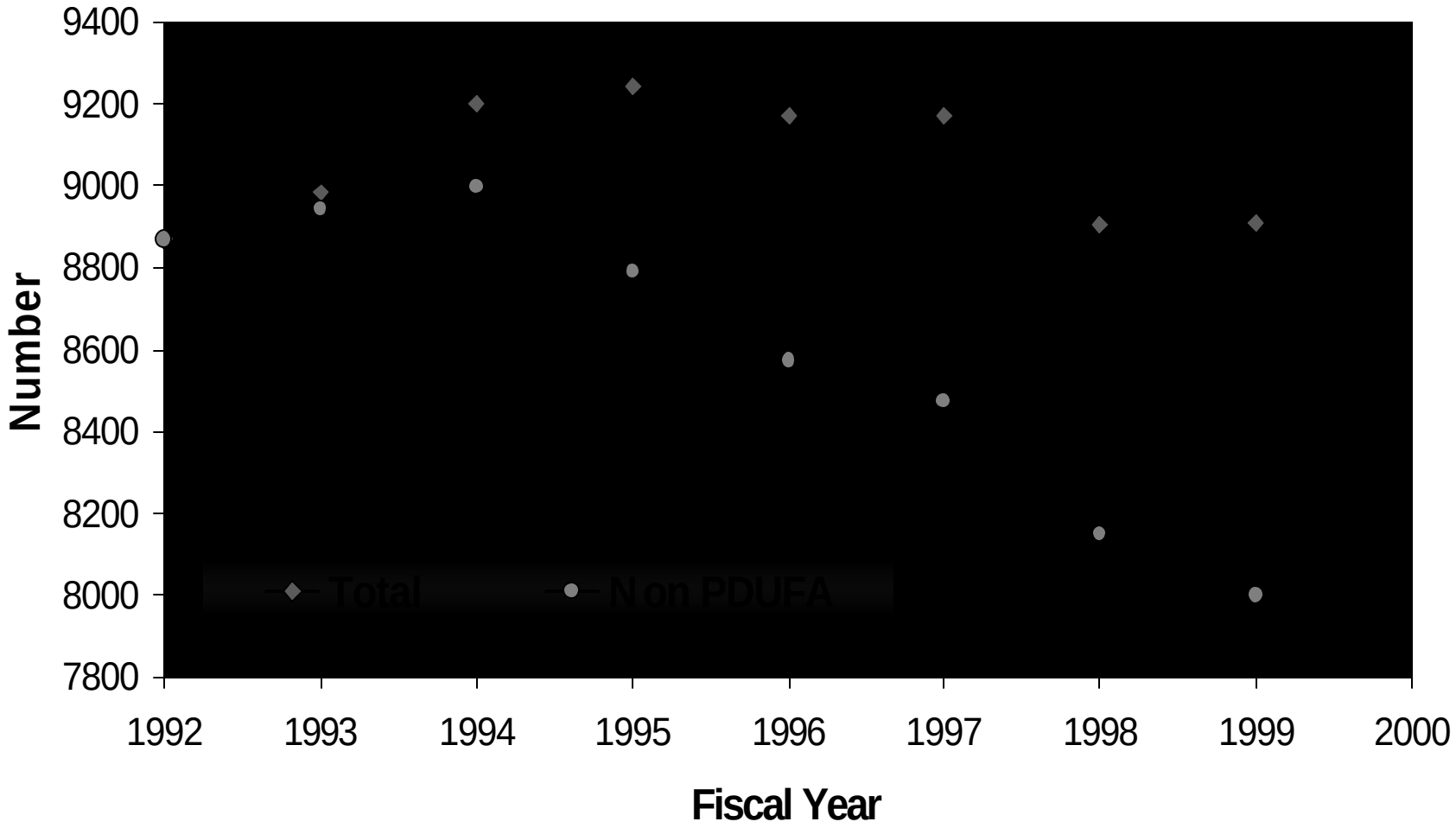
# QSIT:
## Quality System Inspection Technique

- Paradigm shift: looking at systems rather than at product problems
- Inspection focuses on four subsystems
  - Management controls
  - Design controls
  - Corrective and preventive action (CAPA)
  - Production and process controls

# HACCP:
## Hazard Analysis & Critical Control Points

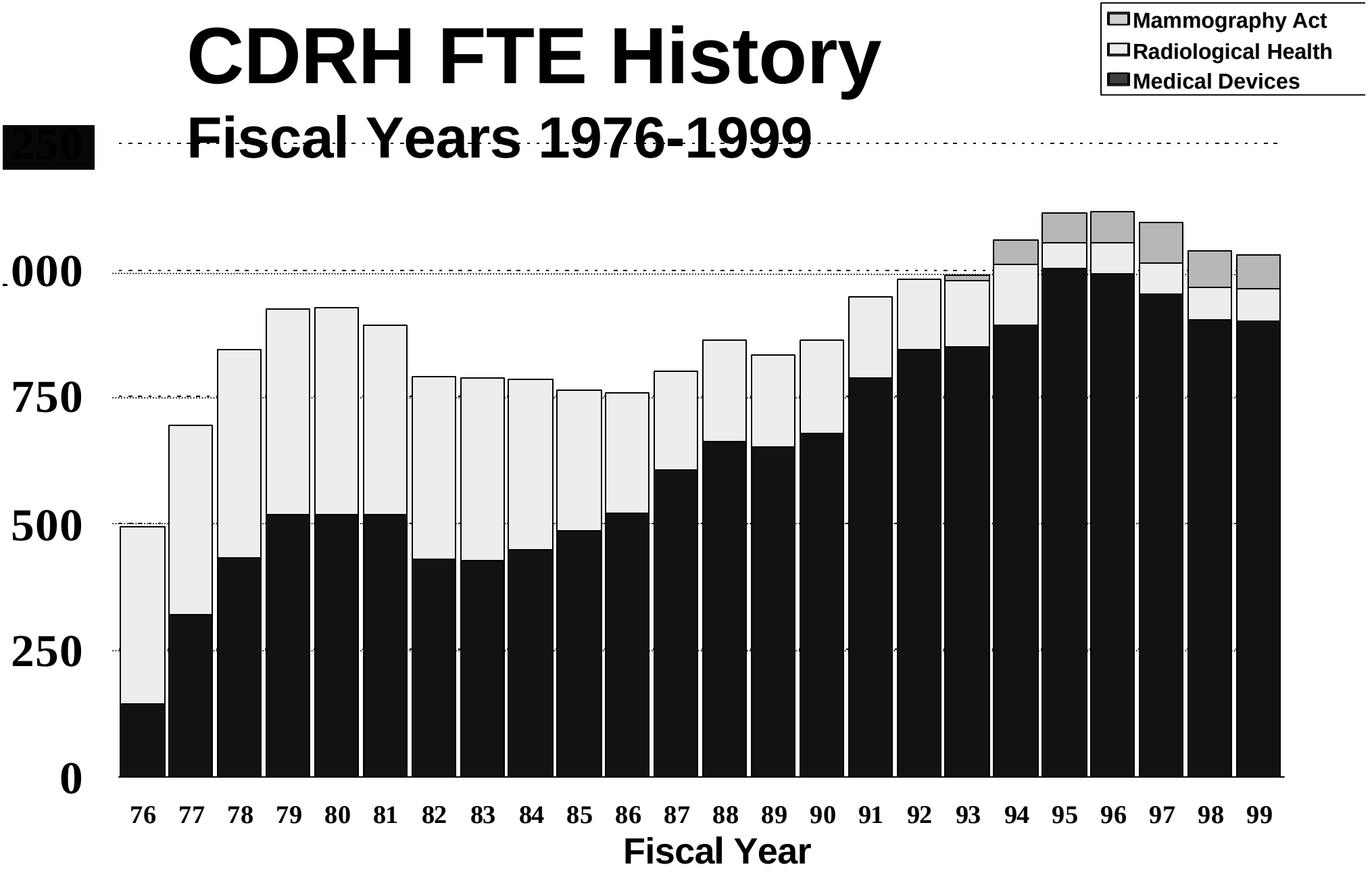
- Goal: to prevent production problems
- Inspectional approach: mfrs. determine their critical control points, control them
- Investigators and auditors focus on critical control points

# Total FDA Work Force and the Prescription Drug User Fee Act (PDUFA)

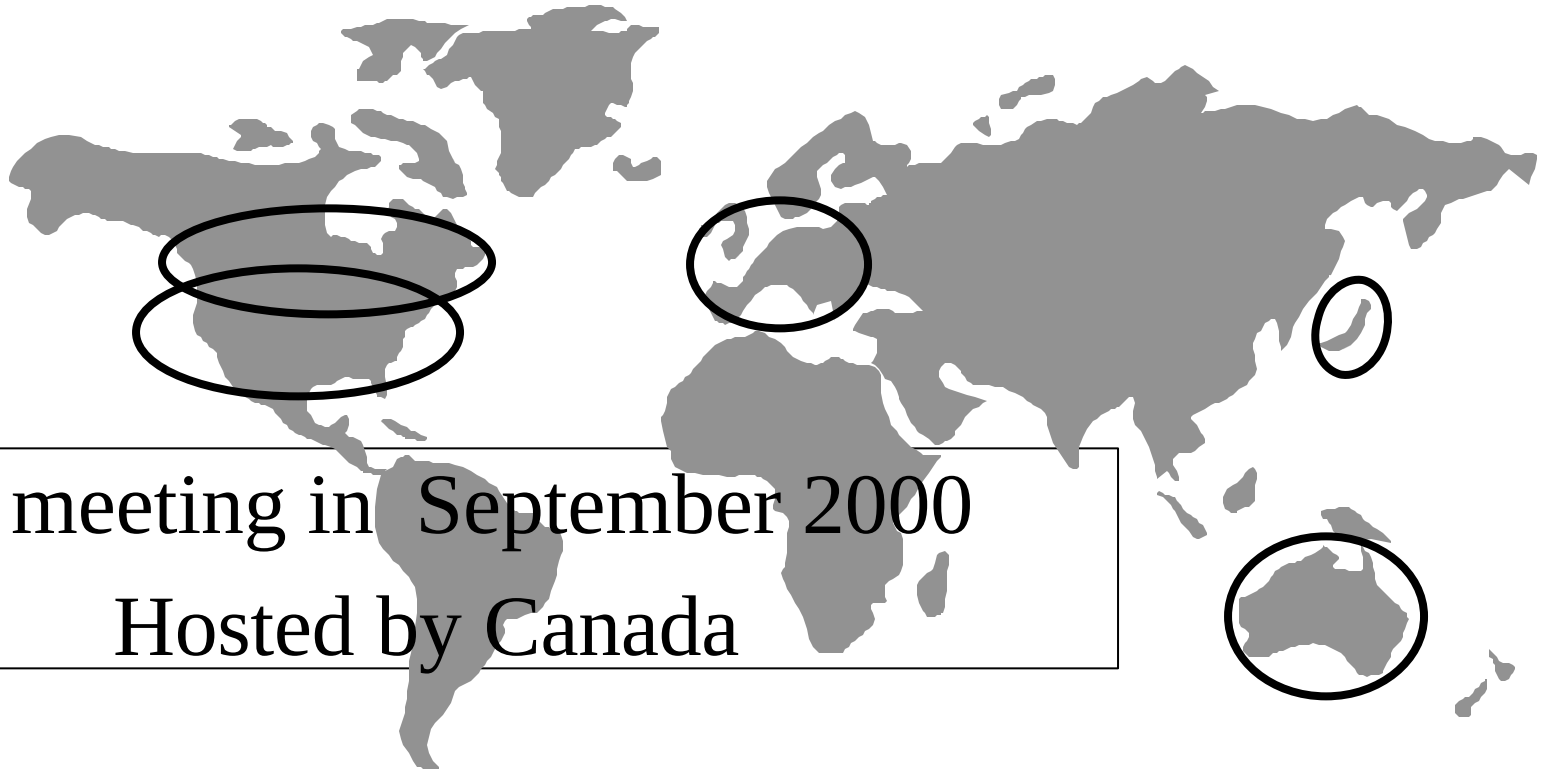


# CDRH FTE History

## Fiscal Years 1976-1999



# Global Harmonization



8th meeting in September 2000

Hosted by Canada

Http://www.ghtf.org/default.htm

# Global Harmonization

Four study groups:

- Regulatory Requirements / Premarket Review
- Device Vigilance / Post-Market Surveillance
- Quality System Requirements and Guidance
- Auditing

# Hot Topics and Standards

- Reuse of Single Use Devices
  - Problem: Thousands of health care facilities engaged
  - Standards in lieu of applications for low risk reuse ?
- Genetic Tests
  - Problem: 700 “home brew” genetic tests in commerce
  - Standards for consent, counseling, test procedures ?
- Tissue Based Products
  - Problem: Broad spectrum of products and practices often produced by individual surgeons
  - Good Tissue Practices – Standards to prevent infectious disease transmission

# Device Regulatory Well Laid Plans

- 510(k)'s will fade away
- PDP's will be widely used
- 3rd party review will be widely used
- Standards will be embraced in the 510(k) process

# CDRH: The Future

The question isn’t whether we will have standards …

The question is how useful can we make standards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