Materials System

- Written procedures, adherence verification
- Quarantine provisions
- Sampling, testing or examination, re-testing, re-exam
- Identification and acceptance / rejection

Materials System

- Storage controls – including validation of handling
- Finished product distribution, return, salvage - including lot documentation -

Facilities & Equipment System

Facilities

- Layout / design, engineering
  - Separation of operations
  - Air handling
  - Lighting water / sewage
  - Cleaning / sanitation, maintenance, pest control
- Renovation, revitalization
- Non-process utilities (waters, gases, HVAC)

Packaging & Labeling System

- Pre-operational preparations
  - Label characteristics (cut, size, color, TEP)
  - Label storage, proofing
  - Identification of equipment, line separation
- Pack / label – Definition –
  - Pack /label record
  - Label specimen

Packaging & Labeling System

- Pack / label Operations control
  - Validation
  - Label issue, exam, reconciliation, destruction (w/lot numbers)
  - Expiration dating (print control)
  - Examination of finished product
- Line clearance, inspection, documentation

Laboratory Controls System

- Staffing & Equipment
  - Adequate numbers of staff
  - Calibration program
  - System suitability
- Specs., standards, sampling plans, change control
- Methods, reference standards, change control, OOS SOP

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Overview of the Pre-Approval Inspection (PAI) Process

Alicia M. Mozzachio, Consumer Safety Officer
International Compliance Team (ICT)
Division of Manufacturing & Product Quality
Office of Compliance
Center for Drug Evaluation & Research (CDER)

1

Agenda

- Overview of the Pre-Approval Inspection (PAI) Program
- Roles of reviewers, field offices and CDER's Office of Compliance
- Past, Present and Future PAI Inspection Strategies

2

PAI Program Overview

- The Food, Drug and Cosmetic (FD&C) Act provides that FDA may approve a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) only if the method used in, and the facilities and controls used for, the manufacture, processing, packaging, and testing of the drug are found adequate to ensure and preserve it's identity, strength, quality and purity.

3

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Objectives of Pre-Approval Inspection Program

- Assure applications are not approved if the applicant has not demonstrated ability to operate with integrity and in compliance with current GMPs
- Assure adherence to application commitments (facilities, equipment and controls)
- Assure the authenticity and accuracy of data submitted in applications

4

CDER Reviewer's Role

- Reviews data submitted in application
- Assists in establishing specifications for manufacture and control based on submitted data

5

District's Role

- Conducts inspections of manufacturing sites referenced in applications to
  - Assure CGMP compliance
  - Verify authenticity/accuracy of data in applications
  - Report other data which may impact approval of applications

6

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Office of Compliance's Role

- Serves as liaison between field offices and review offices
  - Receives and processes inspection requests
  - Monitors status of inspections
  - Reviews reports/recommendations
  - Forwards final recommendations to review offices

7

New and Generic Drug Manufacturing Team HFD-323

- Serves as liaison between CDER review divisions and ORA field offices
- Conducts CGMP evaluations of domestic establishments listed in applications
- Issues assignments and monitors inspections
- Monitors PDUFA timeframes and generic goal dates

8

International Compliance Team HFD-325

- Serves as compliance branch for overseas inspections of human drug product and API manufacturers
- Reviews inspection reports and conducts CGMP evaluations of foreign establishments listed in applications
- Initiates regulatory actions in the foreign arena
- Assists in developing cooperation agreements with foreign governments

9

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Pre-Approval Inspection Strategies

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Pre-Approval Inspection Strategy- Past

- Were assigned in every instance for:
  - Narrow therapeutic drugs
  - New chemical entities
  - Generic version of top 200 drugs
  - CGMP status is greater than 2 years
  - First application for applicant holder
  - First generic version
  - HQ review finds discrepancies that warrant inspection

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Pre-Approval Inspection Strategy - Present

- PAI program changes effective September 2003
  - Eliminated mandatory inspection categories for
    - Generic versions of the top 200 prescription drugs
    - Narrow therapeutic drugs

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Oct 1, 2007 - Visit by Dr. Hiyama, Chief, Division of Drugs, Japan

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Pre-Approval Inspection Strategy - Present

- PAI program changes (continued)
  - Divides inspection requests into 2 categories:
    - "Regularly Prompt a Request from CDER"
    - "Potential Inspection Categories for District Decision"

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Pre-Approval Inspection Strategy - Present

- Regularly Prompt a Request from CDER:
  - New molecular entities (includes drug product/API)
  - Priority NDAs
  - First application filed by an applicant
  - For cause inspection

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Pre-Approval Inspection Strategy - Present

- Regularly Prompt a Request from CDER:
  - For original applications, if current CGMP status is unacceptable or greater than 2 years
  - Certain pre-approval supplements (site change or major construction) if CGMP status is unacceptable
  - Treatment Investigational New Drugs (INDs)
  - Clinical supplies manufacturer if warranted to protect patients or public health

15

Oct 1, 2007 - Visit by Dr. Hiyama, Chief, Division of Drugs, Japan

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Pre-Approval Inspection Strategy - Present

- Potential Inspection Categories for District Decision
  - Other standard NDAs and supplements beyond those assigned by CDER
  - Inspectional audits above and beyond those which are specifically assigned by headquarters

16

Pre-Approval Inspection Strategy - Present

- Reasons for changes:
  - Provide FDA field offices with greater flexibility in determining if a PAI is necessary, based on most current knowledge and CGMP status of an establishment
  - Encourage more field involvement with selection of firms and applications for inspection
  - Leverage our inspectional resources, where practical, for post approval and/or CGMP coverage

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Pre-Approval Inspection Strategy - Present

- Decrease of PAI's allows resources to be used for
  - Systematic CGMP inspections
  - Examination of post approval experiences (change control, filed supplements etc) as well as other district priorities

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Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections

Pre-Approval Inspection Strategy - Future

- Reflect recommendations of Agency's CGMPs for the 21st Century Initiative
- Enhance communications between CDER review divisions, CDER Office of Compliance, and ORA District Offices on application specific issues
- Address the roles of the Pharmaceutical Inspectorate and center specialists on inspections
- Incorporating risk-based concepts in inspections and sample collections

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Pre-Approval Inspection Strategy - Future

- Other changes under consideration:
  - Customize scope and depth of pre-approval inspection based on the specific circumstances or reasons for PAI
  - Clarify roles and responsibilities of CDER and ORA in the drug approval process

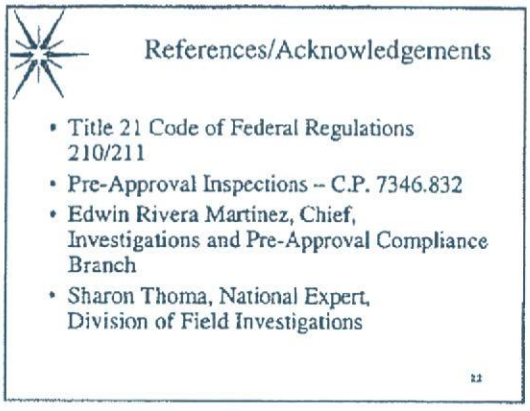
20

Summary

- PAI program has evolved to meet 21st century needs
- Latest revisions should help reduce the number of pre-approval inspections
- Additional changes planned to incorporate more risk-based approaches to the assignment and conduct of pre-approval inspections

21

Alicia Mozzachio, Consumer Safety Officer - Preapproval Inspections



CDER's Risk-Based Site Selection Model for cGMP Inspections

2007 PDA/FDA JOINT REGULATORY CONFERENCE

September 25, 2007

Sawyie Brenda Wang, IE
Team Leader, DCRMS
Office of Compliance
Center for Drug Evaluation and Research

Risk-Based Site Selection Model History

- The Risk-Based Model Working Group Formed in 2003.
- Implemented a nationally consistent approach to surveillance evaluation of factory operations by inspection for FY2005.
- Continue to Refine the Models for FY2006 and FY2007.

Tiers

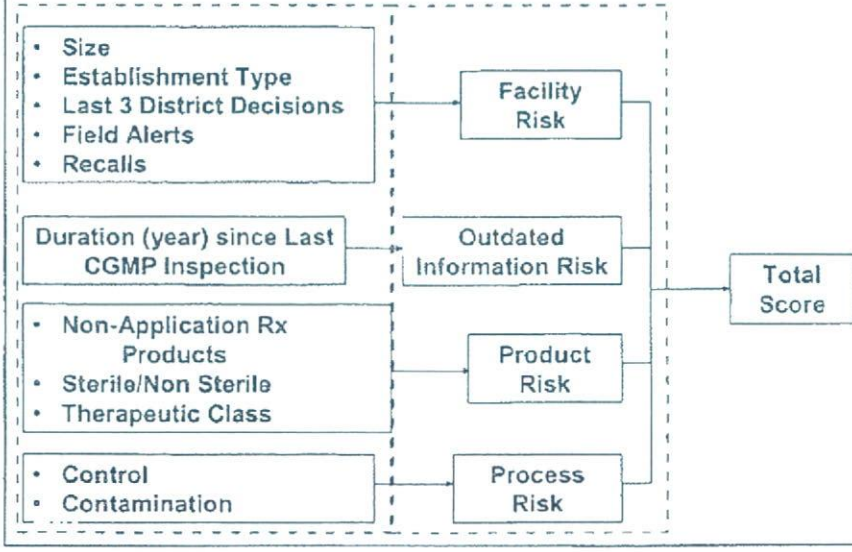
Tier 1

- Specific sites in this category vary each year
- 100% of sites are inspected

Others

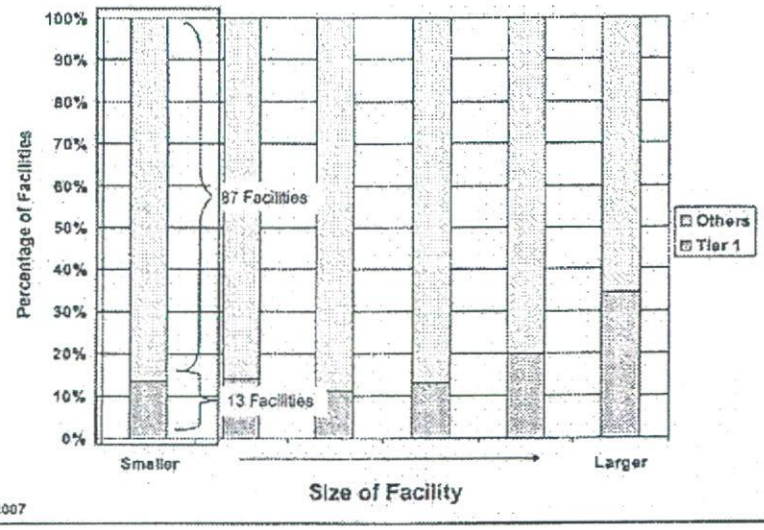
- All Drug sites not in Tier 1
- About 25% of sites are Inspected
- Selection at each field office discretion

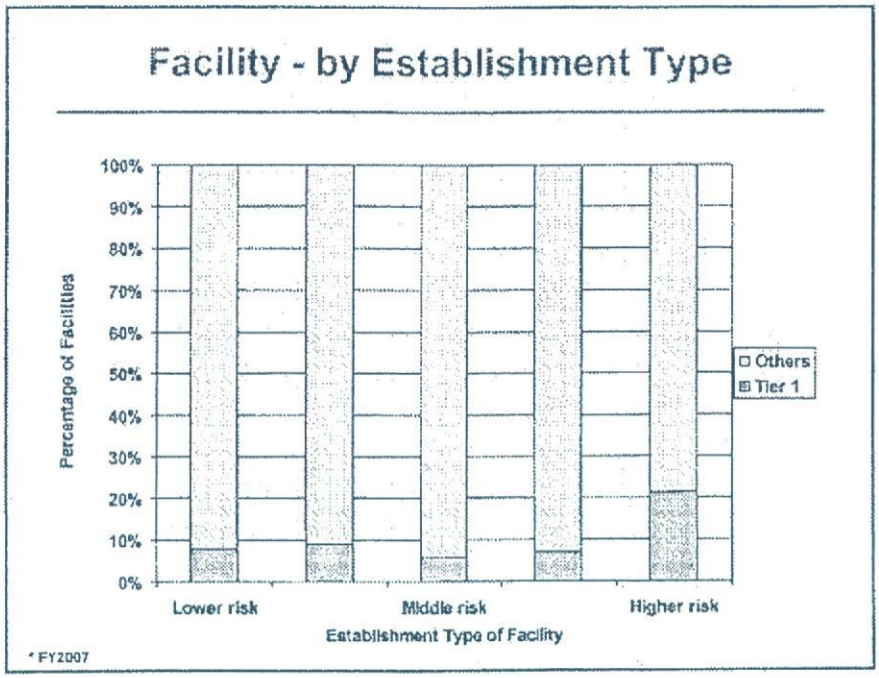
FY06 Risk-Based Site Selection Model Factors and Components

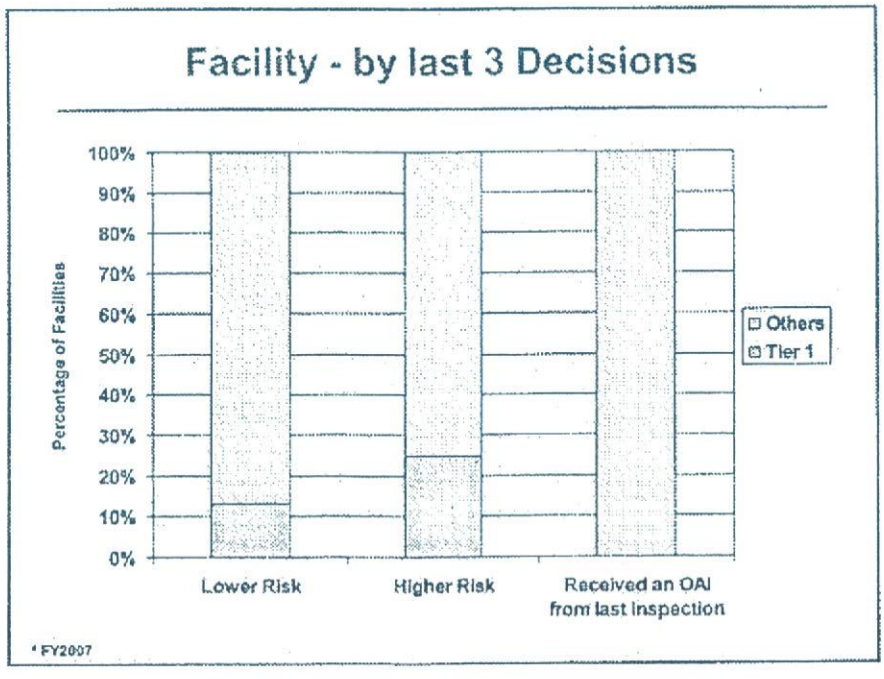


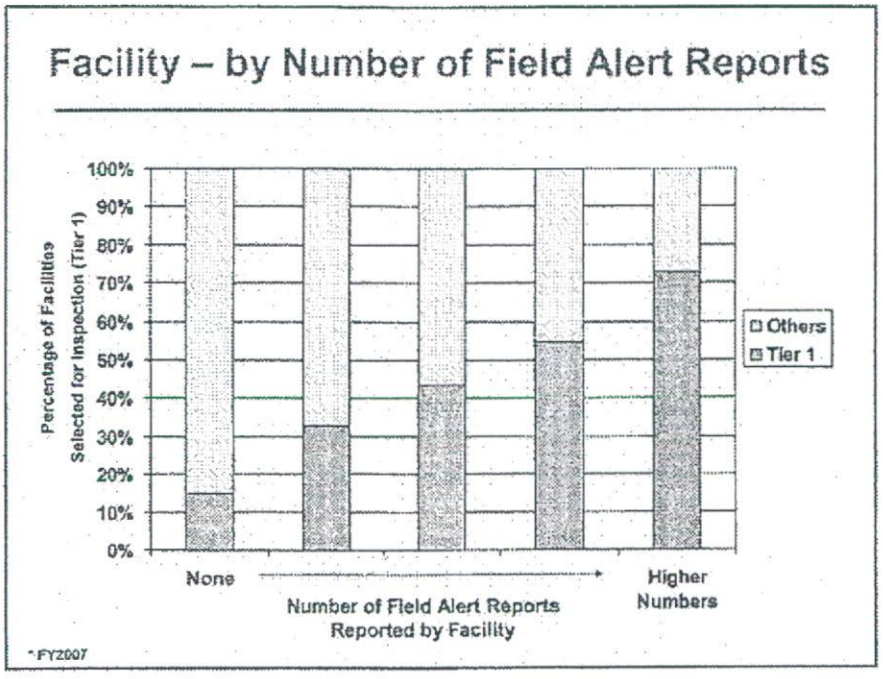
FY 2007 Sites Distribution

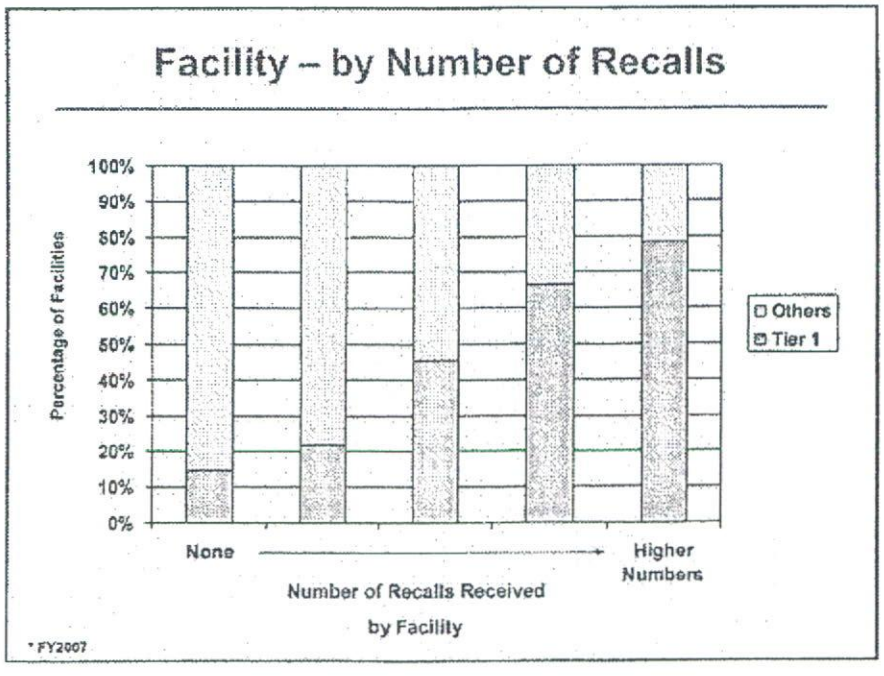
Facility - by Size

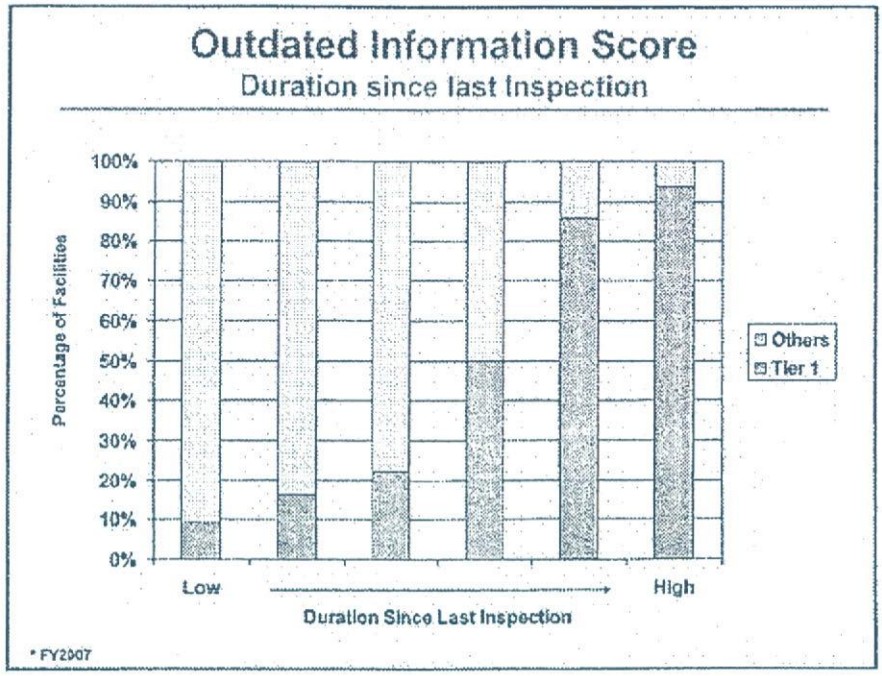


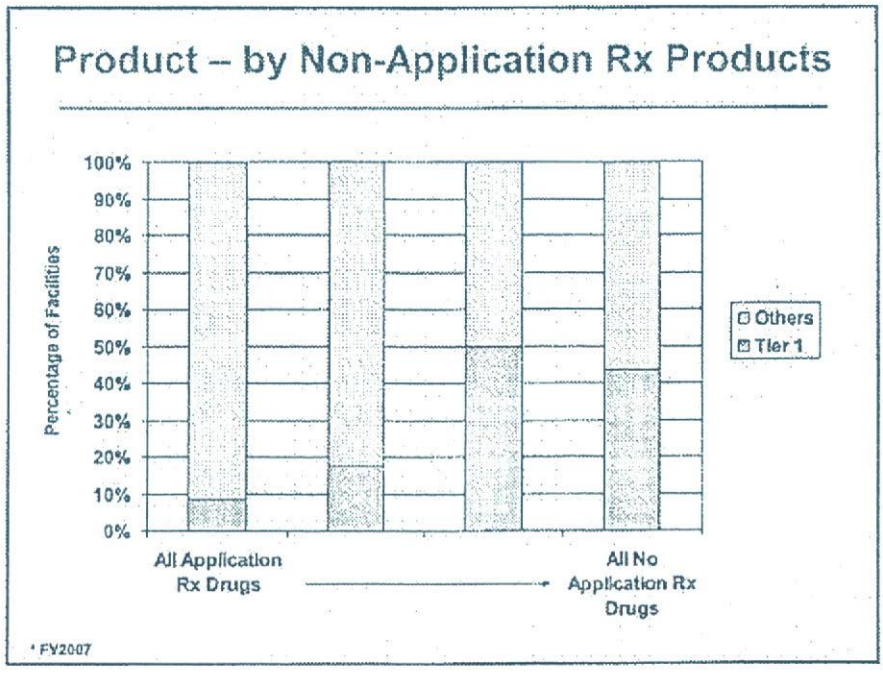

Facility - by Establishment Type
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
Lower risk
Middle risk
Higher risk
Establishment Type of Facility
* FY2007

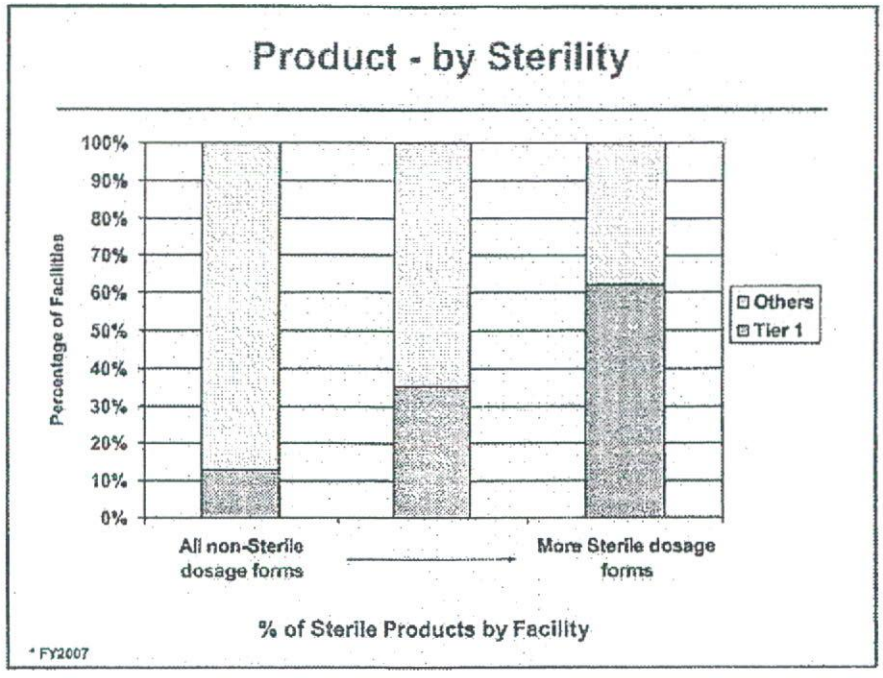

Facility - by last 3 Decisions
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
Lower Risk
Higher Risk
Received an OAI from last Inspection
* FY2007

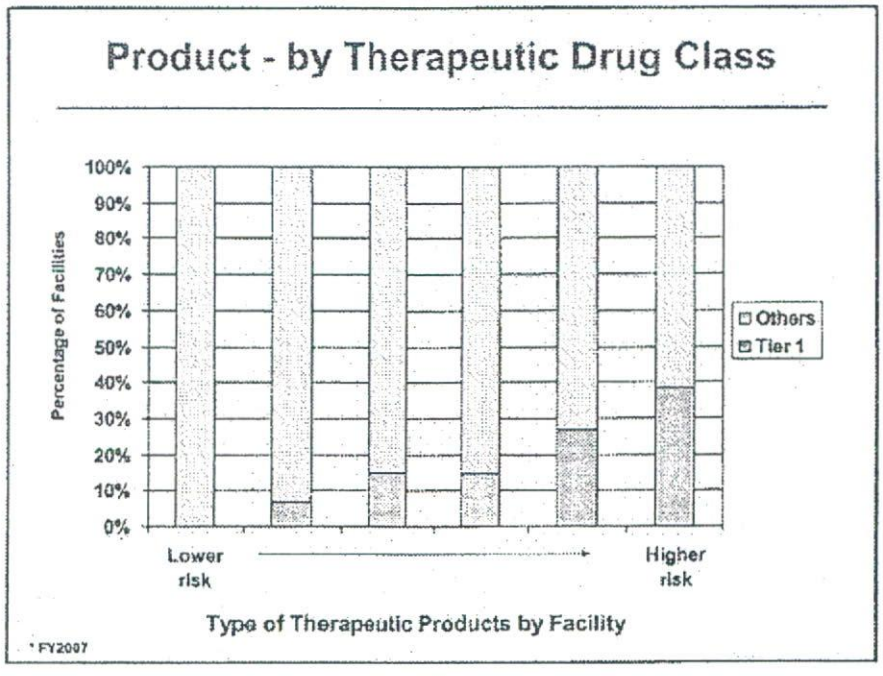

Facility – by Number of Field Alert Reports
Percentage of Facilities Selected for Inspection (Tier 1)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Others
Tier 1
None
Higher Numbers
Number of Field Alert Reports Reported by Facility
* FY2007

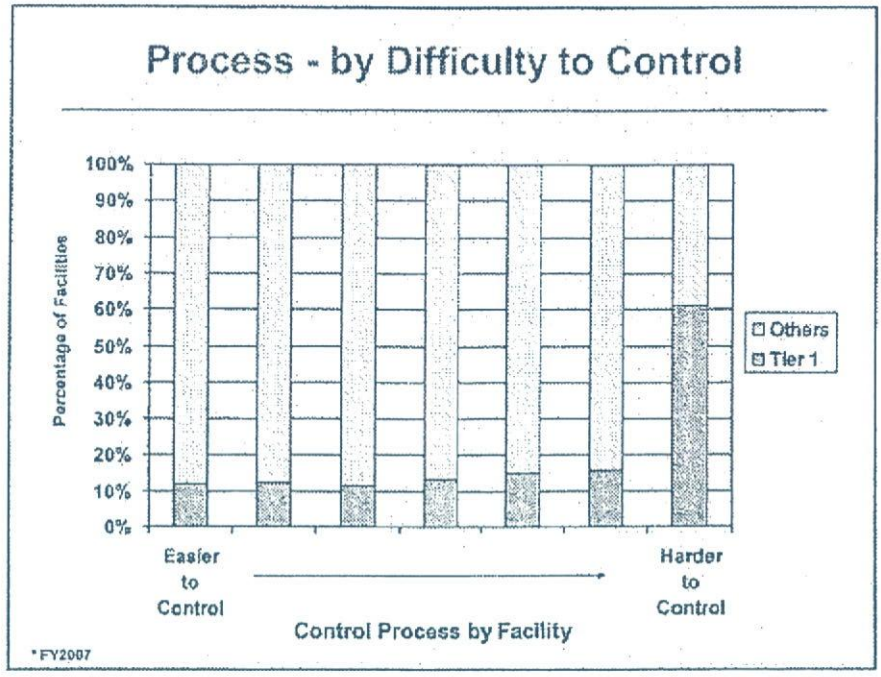

Facility – by Number of Recalls
Percentage of Facilities
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Others
Tier 1
None
Higher Numbers
Number of Recalls Received by Facility
* FY2007

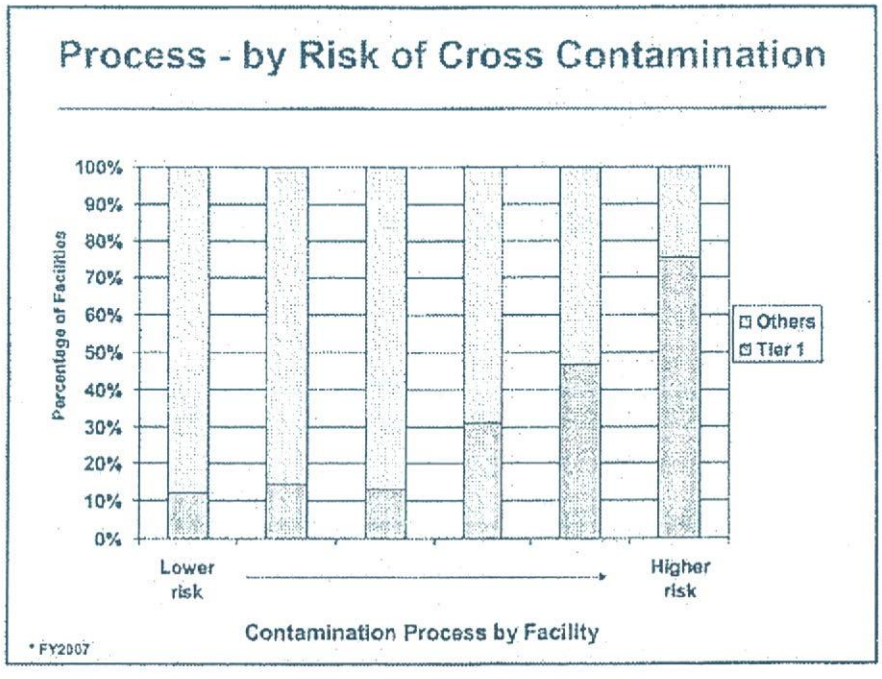

Outdated Information Score
Duration since last Inspection
Percentage of Facilities
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Low
High
Duration Since Last Inspection
Others
Tier 1
* FY2007

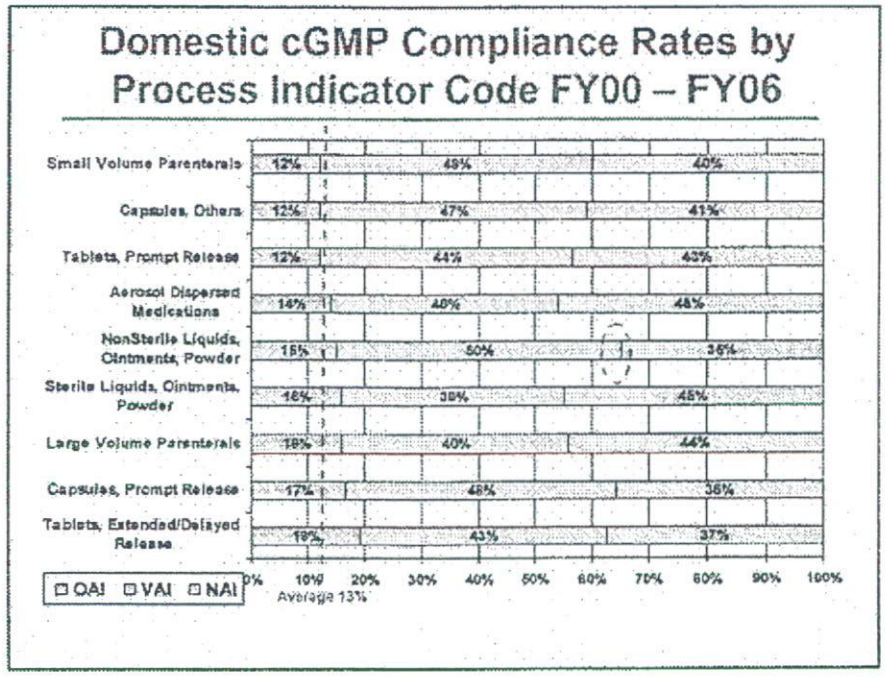

Product – by Non-Application Rx Products
Percentage of Facilities
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
All Application Rx Drugs
All No Application Rx Drugs
Others
Tier 1
* FY2007

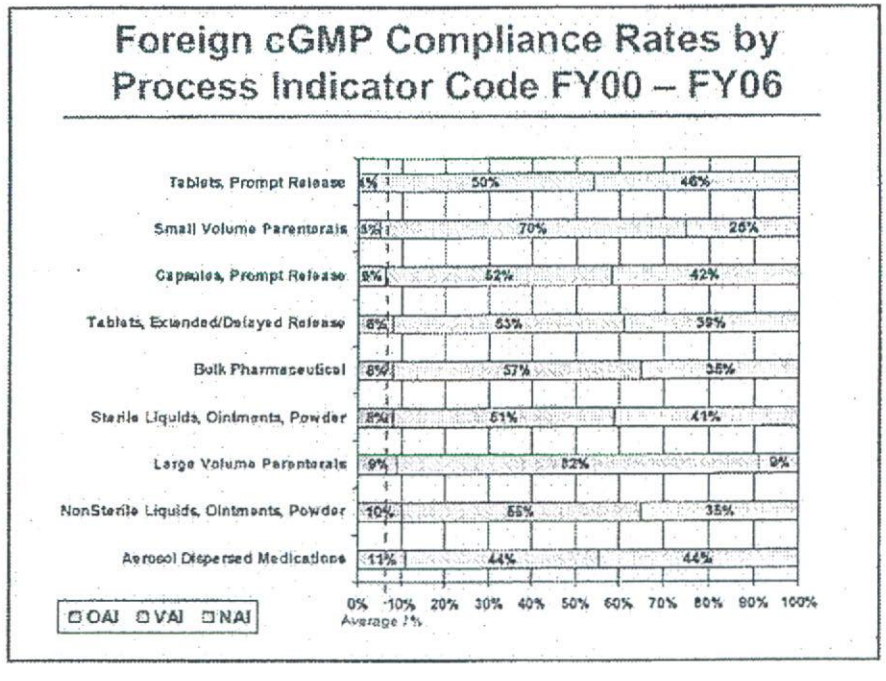

Product - by Sterility
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
All non-Sterile dosage forms
More Sterile dosage forms
% of Sterile Products by Facility
* FY2007

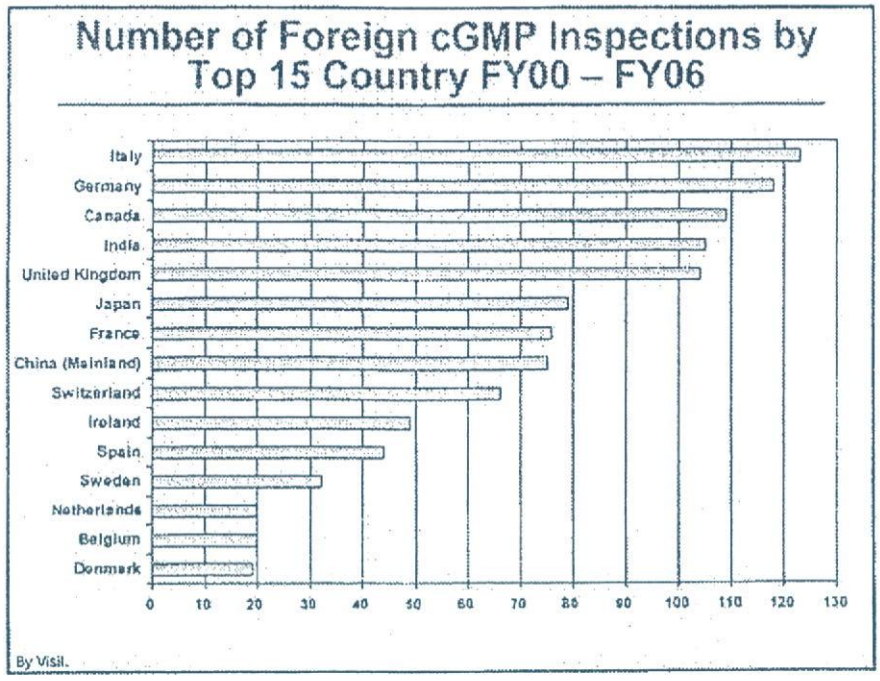

Product - by Therapeutic Drug Class
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
Lower risk
Higher risk
Type of Therapeutic Products by Facility
* FY2007

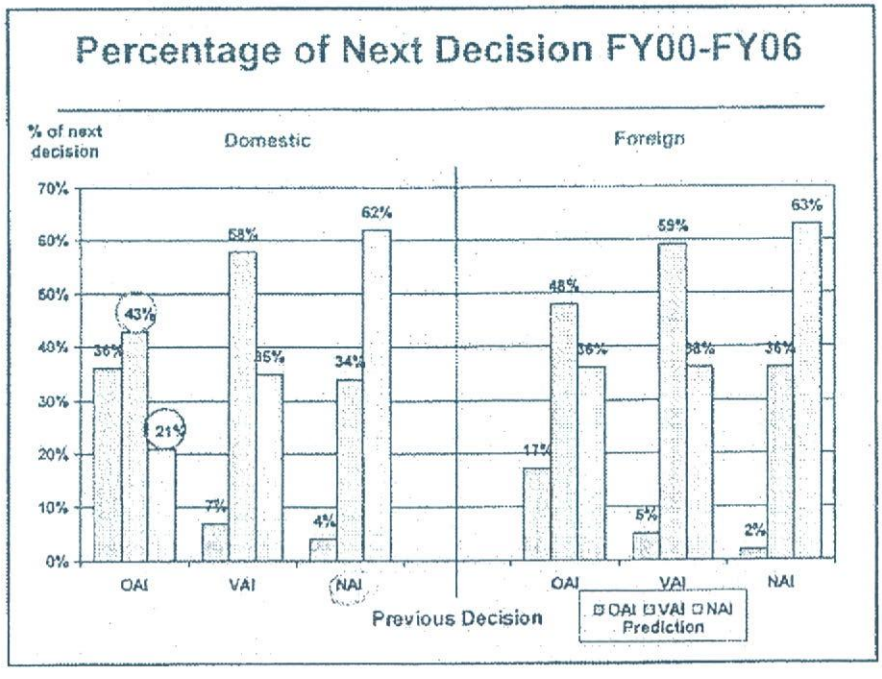

Process - by Difficulty to Control
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
Easier to Control
Harder to Control
Control Process by Facility
*FY2007


Process - by Risk of Cross Contamination
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of Facilities
Others
Tier 1
Lower risk
Higher risk
Contamination Process by Facility
*FY2007


Domestic cGMP Compliance Rates by Process Indicator Code FY00 – FY06
Small Volume Parenterals
12%
48%
40%
Capsules, Others
12%
47%
41%
Tablets, Prompt Release
12%
44%
43%
Aerosol Dispersed Medications
14%
40%
46%
NonSterile Liquids, Ointments, Powder
15%
50%
35%
Sterile Liquids, Ointments, Powder
16%
39%
45%
Large Volume Parenterals
16%
40%
44%
Capsules, Prompt Release
17%
46%
36%
Tablets, Extended/Delayed Release
19%
43%
37%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Average 13%
OAI
VAI
NAI


Foreign cGMP Compliance Rates by Process Indicator Code FY00 – FY06
Tablets, Prompt Release
4%
50%
46%
Small Volume Parenterals
5%
70%
25%
Capsules, Prompt Release
8%
52%
42%
Tablets, Extended/Delayed Release
8%
53%
39%
Bulk Pharmaceutical
8%
57%
35%
Sterile Liquids, Ointments, Powder
8%
51%
41%
Large Volume Parenterals
9%
82%
9%
NonSterile Liquids, Ointments, Powder
10%
55%
35%
Aerosol Dispersed Medications
11%
44%
44%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Average 7%
OAI
VAI
NAI


Number of Foreign cGMP Inspections by Top 15 Country FY00 – FY06
Italy
Germany
Canada
India
United Kingdom
Japan
France
China (Mainland)
Switzerland
Ireland
Spain
Sweden
Netherlands
Belgium
Denmark
0
10
20
30
40
50
60
70
80
90
100
110
120
130
By Visil.


Percentage of Next Decision FY00-FY06
% of next decision
Domestic
Foreign
70%
60%
50%
40%
30%
20%
10%
0%
36%
43%
21%
7%
58%
35%
4%
34%
62%
17%
48%
36%
5%
59%
36%
2%
36%
63%
OAI
VAI
NAI
OAI
VAI
NAI
Previous Decision
OAI VAI NAI
Prediction