Pre-Conference Training
Rama Gardens Conf. Center, Bangkok, 23 Nov. 2008

Managing an IRB for GCP Inspection / Audit

GCP Related Issues for IRB Management

or

"Areas for Improvement"

[GCP Findings from Audits and Inspections]

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Agenda

- Global IRB Findings (from Roche GCP Audits)
- CDER Inspections of IRBs in the US
- FDA Inspections in Asia Pacific - Roche Experience
- Criteria for FDA Acceptance of Foreign Non-IND Data

Global IRB Findings (1)

- **Documents reviewed and / or approved not identified (by version / date etc.) [ICH GCP 3.1.2 and 8.2.7]**
  - So what was actually reviewed and approved ? Especially important for the ICF !

- **Not all "written information" given to patients reviewed and approved [3.1.2 and 4.4.1]**
  - So were the patients unduly influenced ?

- **Payments / compensation to patients not reviewed and approved [3.1.2, 3.1.8 and 3.1.9]**
  - Problems of coercion or undue influence ? – as above

Global IRB Findings (2)

- **Qualification of PI inclusive CV not reviewed [3.1.2, 3.1.3 and 4.1.1]**
  - How do we (surveyors / auditors / inspectors) know that the IRB knows this *investigator* ?

- **Submittance of e.g. Annual Reports not enforced – PI not reminded when "forgetting" to submit reports and / or no "penalty" [3.1.4 and 4.10.1]**
  - Can the IRB perform an adequate "continuous review" ?

Global IRB Findings (3)

- **Inadequate composition [3.2.1]**
  - Missing the non-scientific and / or independent member
- **Or if part of IRB: not always present at meetings**
  - Has the review been mainly scientific ?
- **“Meetings” by email – not always Face to Face [3.2.3]**
  - Has there been a possibility of free / unbiased discussions and deliberations ?

Global IRB Findings (4)

- **Expedited review of approval procedure not specified [3.3.5]**
  - How do we know who made a decision ?
- **Not timely in notifying decisions re. protocol amendment to the investigator [3.3.9]**
  - Thus delaying implementation of any changes or updates of which had had the approval of the IRB
- **Requirements & timelines for submitting ADRs / SAEs / SUSARs not specified [3.3.8 and 4.11.1]**
  - How will the PI know *what* to submit *when* ?

Global IRB Findings (5)

- **Membership list does not always specify the period of the function [3.4]**
  - How do we know that it is current ?
- **No written procedures! [3.2.2 and 3.3]**

- **Observations that we can not put down as “findings” (no evidence or regulations)**
  - “Rubber stamping” – no questions / comments at all
  - No follow-up or repercussion if late or no submissions of annual report, local SAEs etc

CDER Inspections of IRBs in the US

Classifications and Deficiencies for FY 2002-04 (and updates from 2006)

Personal communication for Dr. Johansen from

Good Clinical Practice Program

Office of Science and Health Coordination

Office of the Commissioner

U.S. Food and Drug Administration

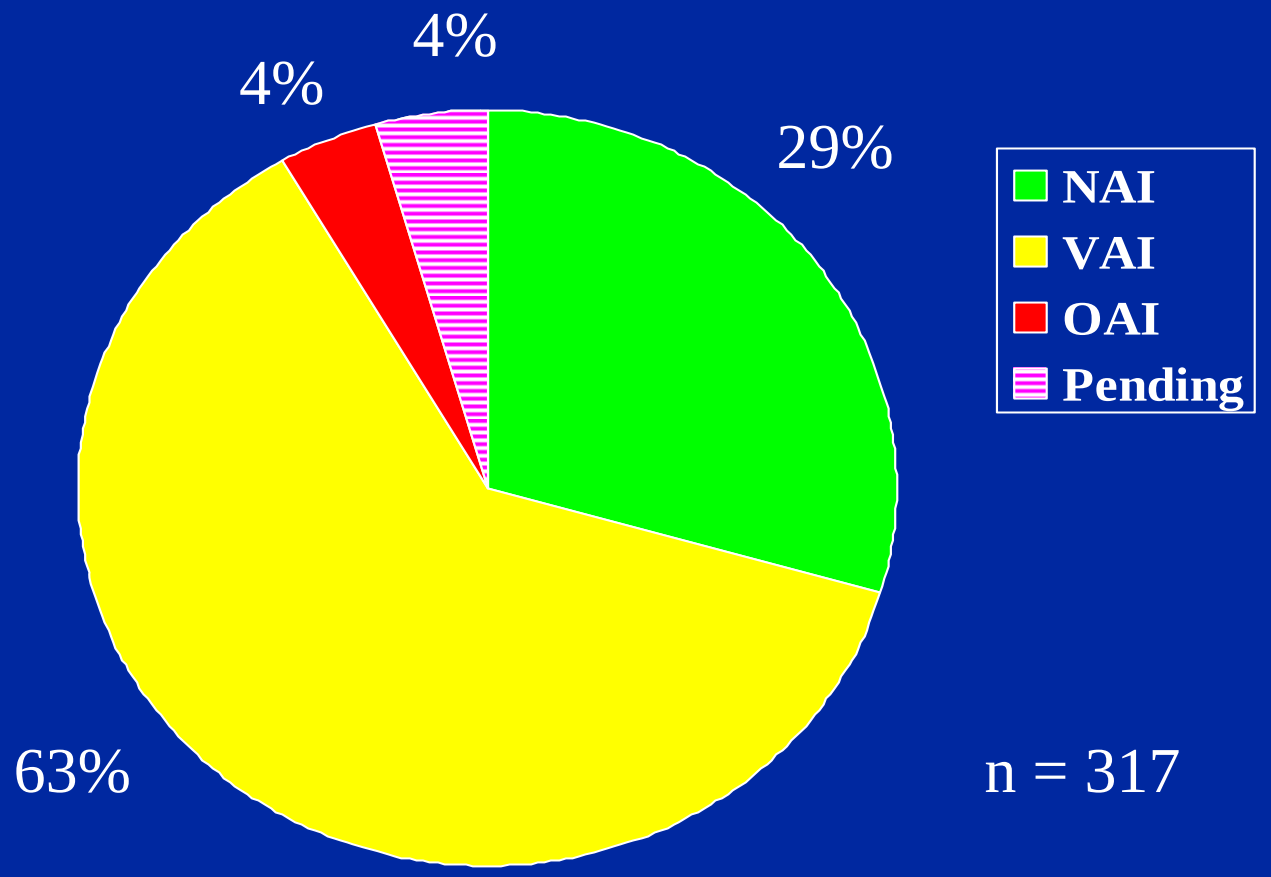
FDA Recognizes the Importance of IRB Inspections to Implementing GCP

- FDA has inspected U.S. IRB's since 1980
- FDA performs 250-300 IRB inspections per year from an inventory of approximately 1600
- 4-5% of inspections result in official action (OAI)
  - Required action is most typically a notification to FDA (15 days) of steps to come into compliance
  - In 3 cases (FY 99): Sanctions imposed

Definitions of FDA Inspection Classifications

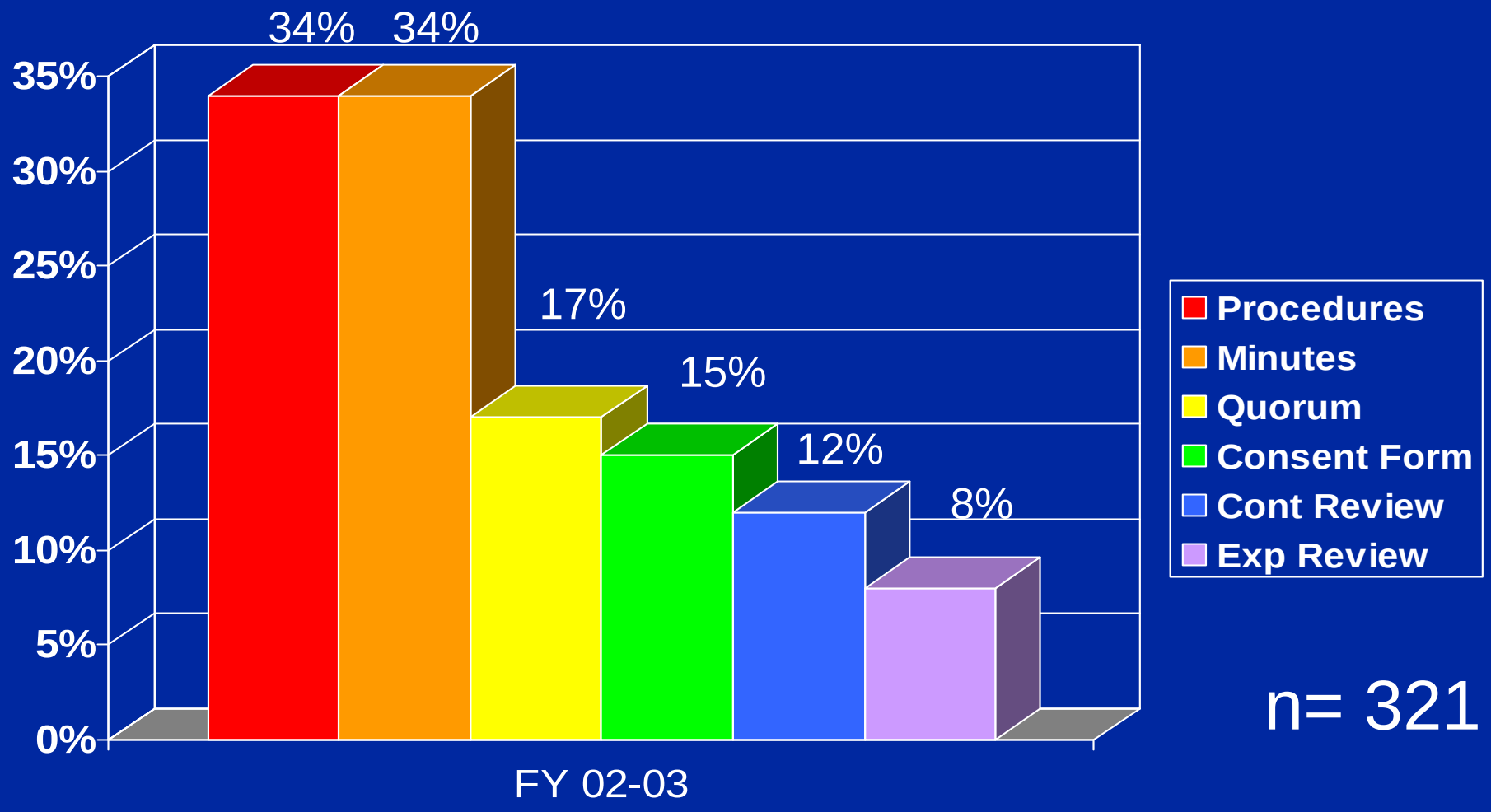
NAI	**N**o **A**ction **I**ndicated (no significant findings)
VAI	**V**oluntary **A**ction **I**ndicated (significant findings)
OAI	**O**fficial **A**ction **I**ndicated (major / serious findings)

IRB Classifications
All Centers - FY'03



IRB Deficiency Categories

FDA Inspections - CDER, FY 02-03



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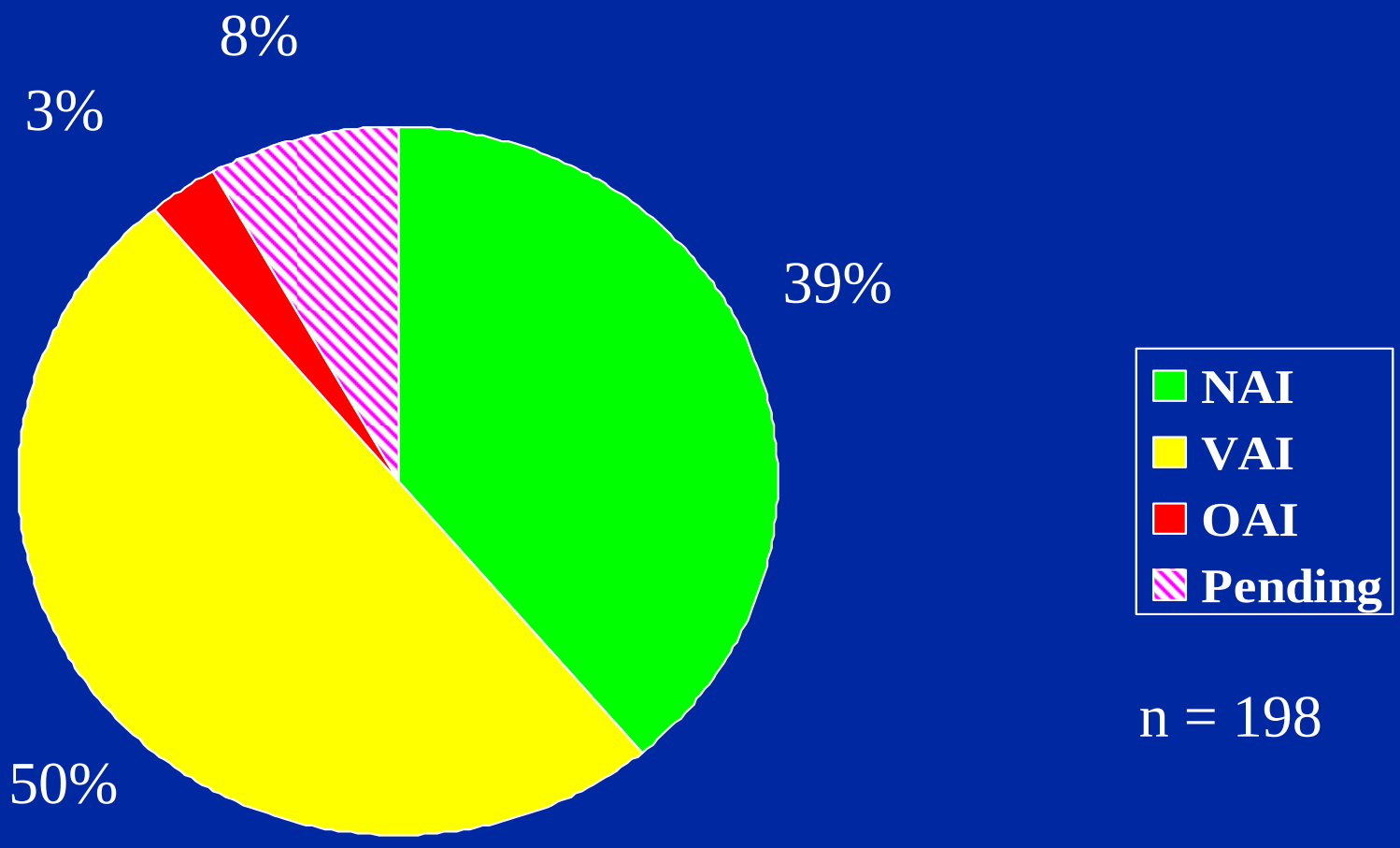
Common Deficiencies Found in Informed Consent Documents

- 50.25(a)(7)
  Identification of person to contact regarding research, rights and injury
- 50.25(a)(4)
  Incomplete description of alternative procedures
- 50.25(a)(5)
  Inadequate confidentiality statement
- 50.25(a)(1)
  Incomplete description of research procedures
- 50.25(a)(6)
  Incomplete description of compensation and treatment for research-related injury

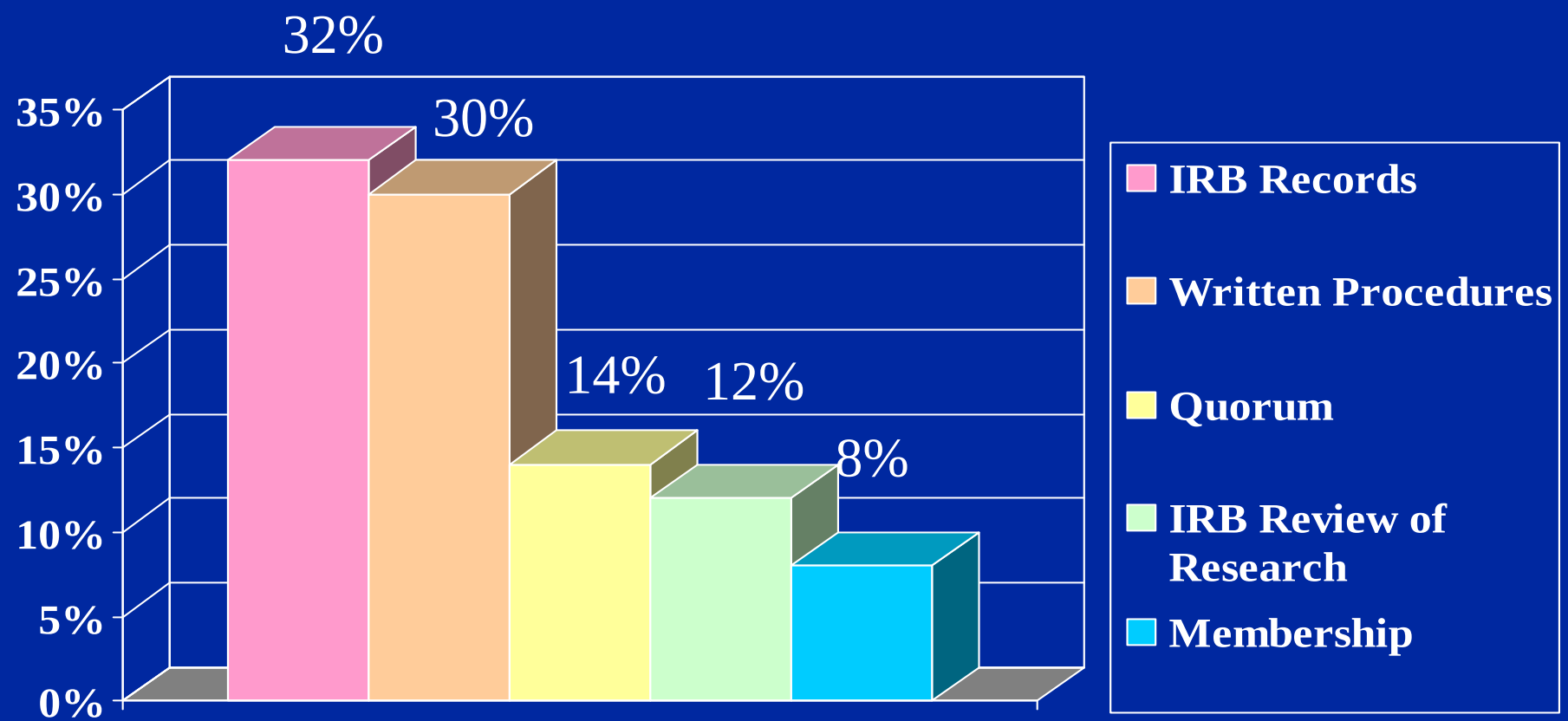
IRB Classifications

FY 2004 – All Centers



IRB Deficiencies

FY 2004



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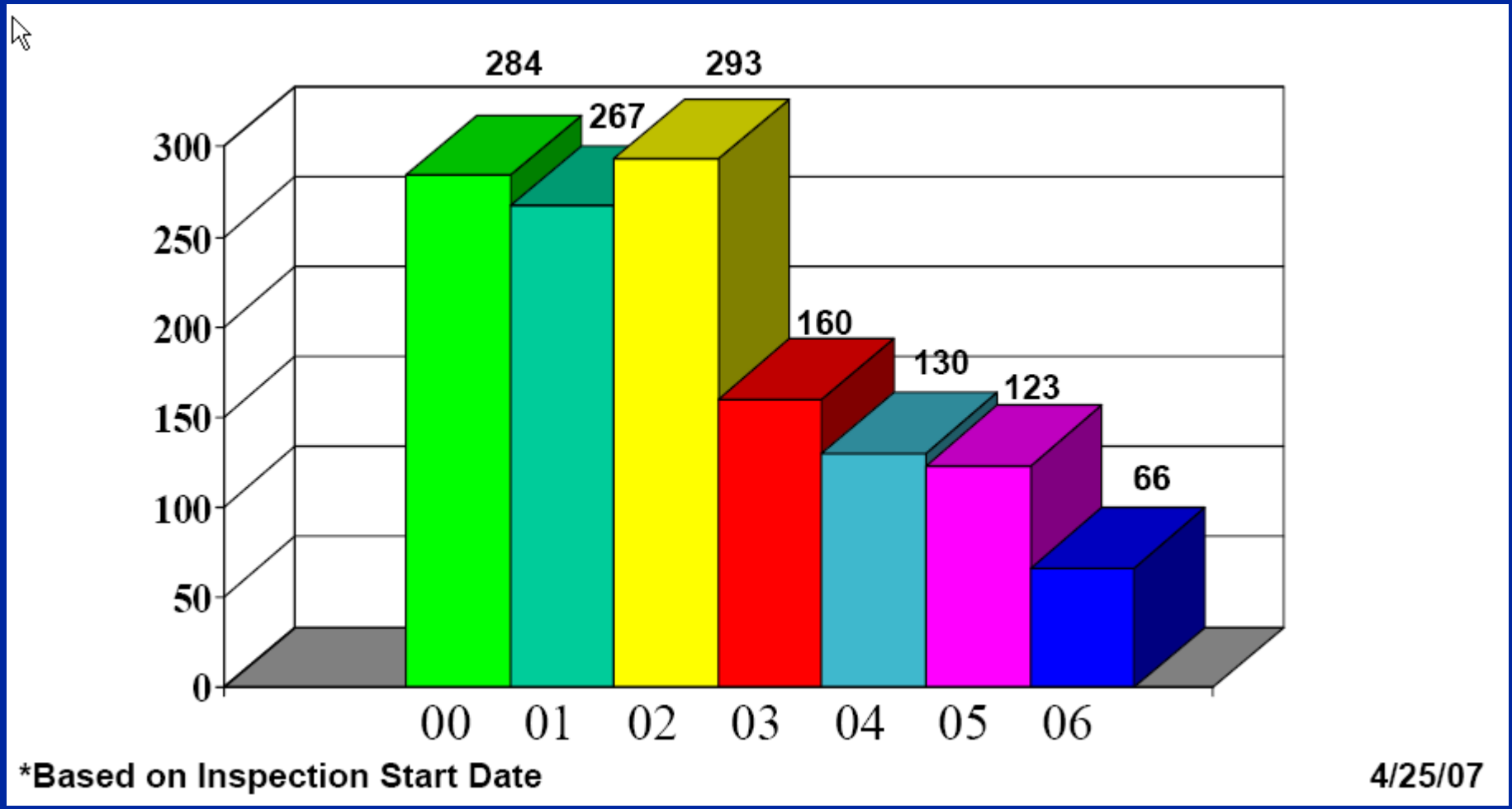
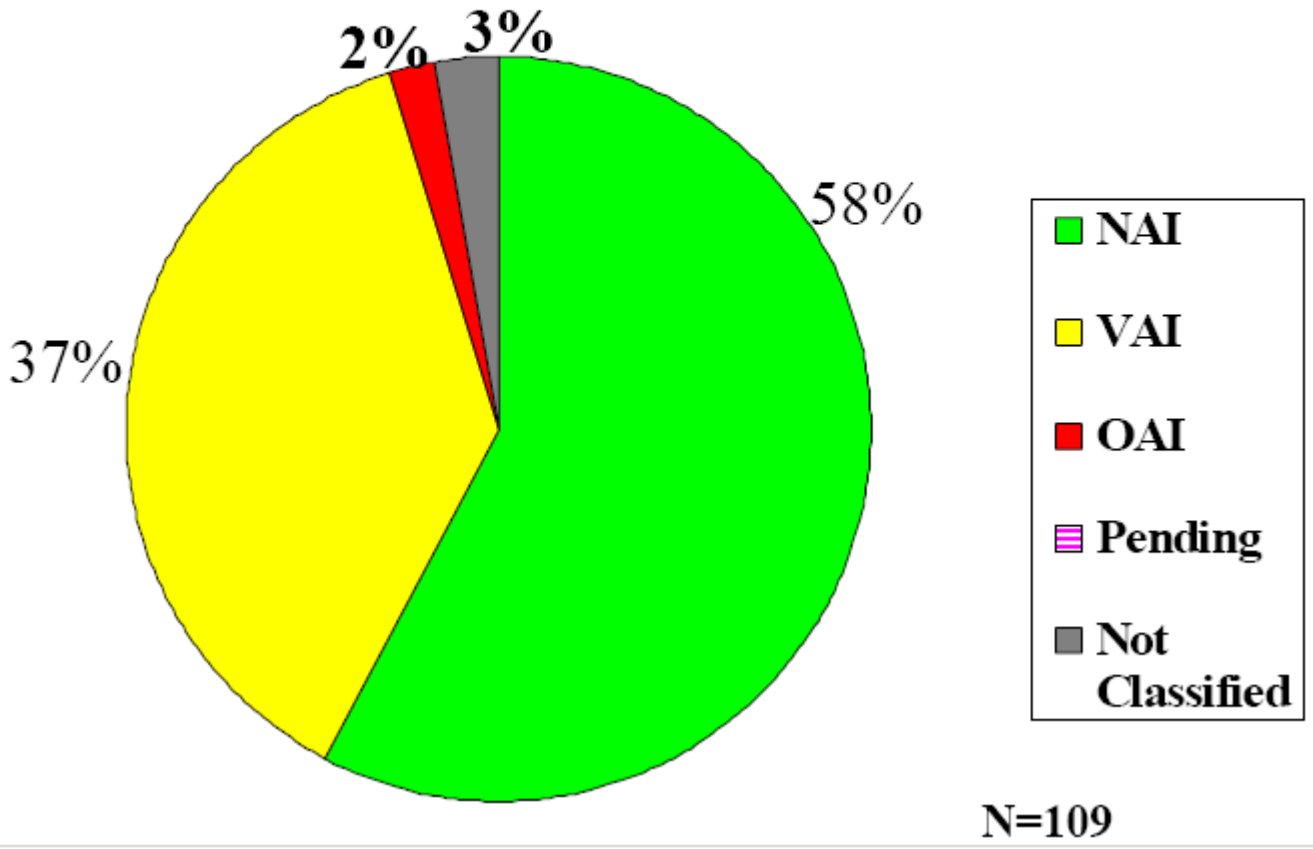
CDER Assigned Inspections

IRB Inspections*- FY 2000 - 2006
Center for Drug Evaluation & Research



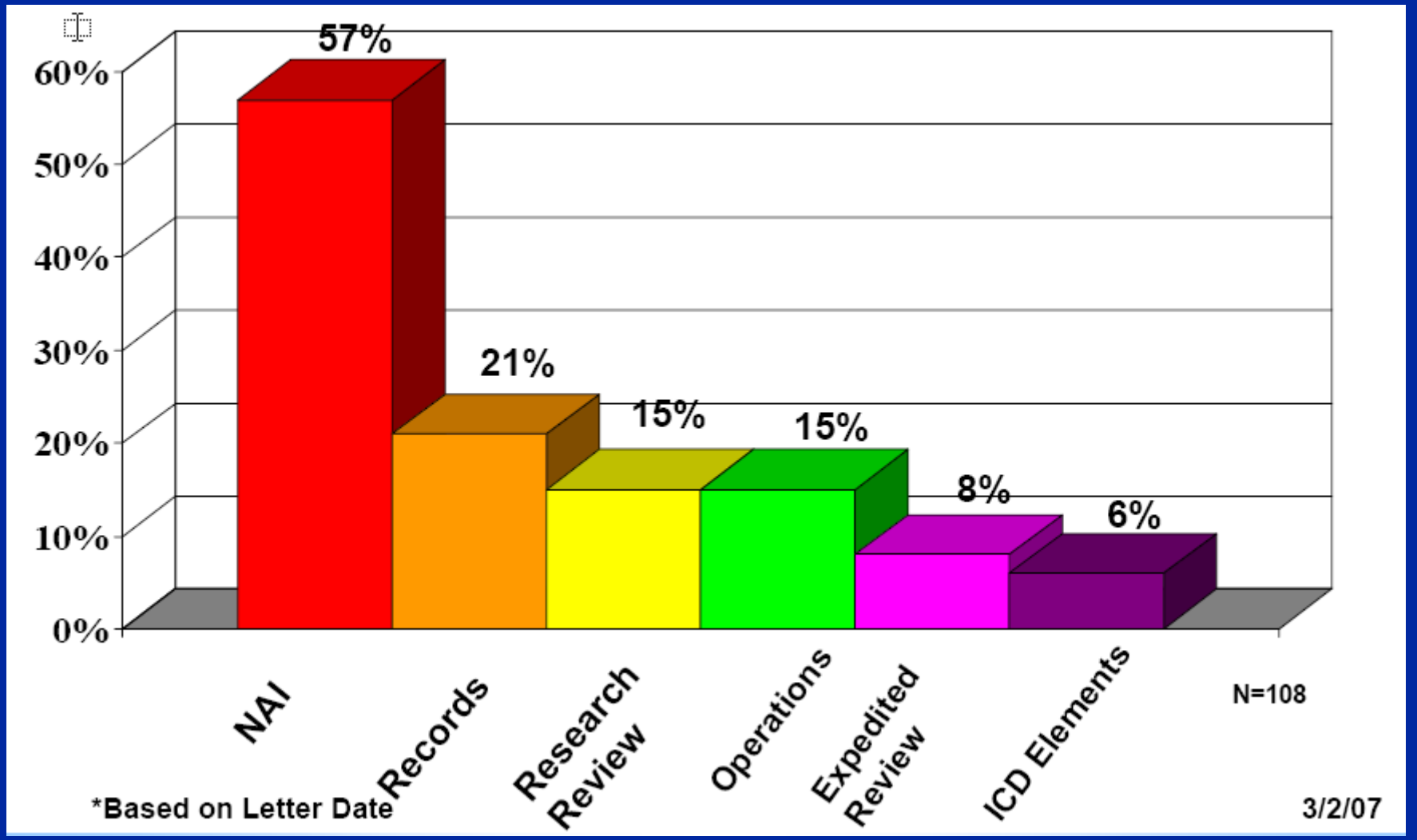
IRB Classifications

CDER Inspections – FY06



IRB Deficiencies*

FY06: CDER



US IRB's: Observations as Symptoms

- Heightened Workload Pressures
  - Adverse event reports
  - Protocol amendments
- Limited Resources
- Limited Useful Feedback on Multi-Site Trials
- Limited Feedback on Problem Investigators
- IRB Membership
  - competing commitments; training

FDA Inspections in Asia Pacific (1)
Roche Experience

- **X-country, November, 2004 (483 was issued)**

  “Failure to assure that an IRB, complying with applicable regulatory requirements, was responsible for the initial and continuing review and approval of a clinical study.

  Specifically, the PI failed to ensure that there was at least an annual review of the clinical study performed by the Research Ethics Committee, IRB, on or prior to initial approval date of 1/24/02. The PI’s annual report dated 6/10/03 was approved by the Research Ethics Committee on 6/30/03”.

FDA Inspections in Asia Pacific (2)

- **Y-country, December, 2004 (483 was issued)**

  "Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others *(delay in months)*."

Criteria for FDA Acceptance of Foreign Non-IND Data

(21 CFR 312.120 (updated as of 27 Oct, 2008) and 314.106)

- **Ethics acceptable to the world community**
- **Protection equal or greater than the ICH-GCP** (no ref to the DoH!)
- Trial well-designed and well-conducted
- Investigators qualified
- **Trial approved by independent review committee**
- Trial may be inspected*

(* only the clinical trial centre, **no** IRBs / IECs inspected outside of the US!)

THANK YOU