Pre-Approval Inspections

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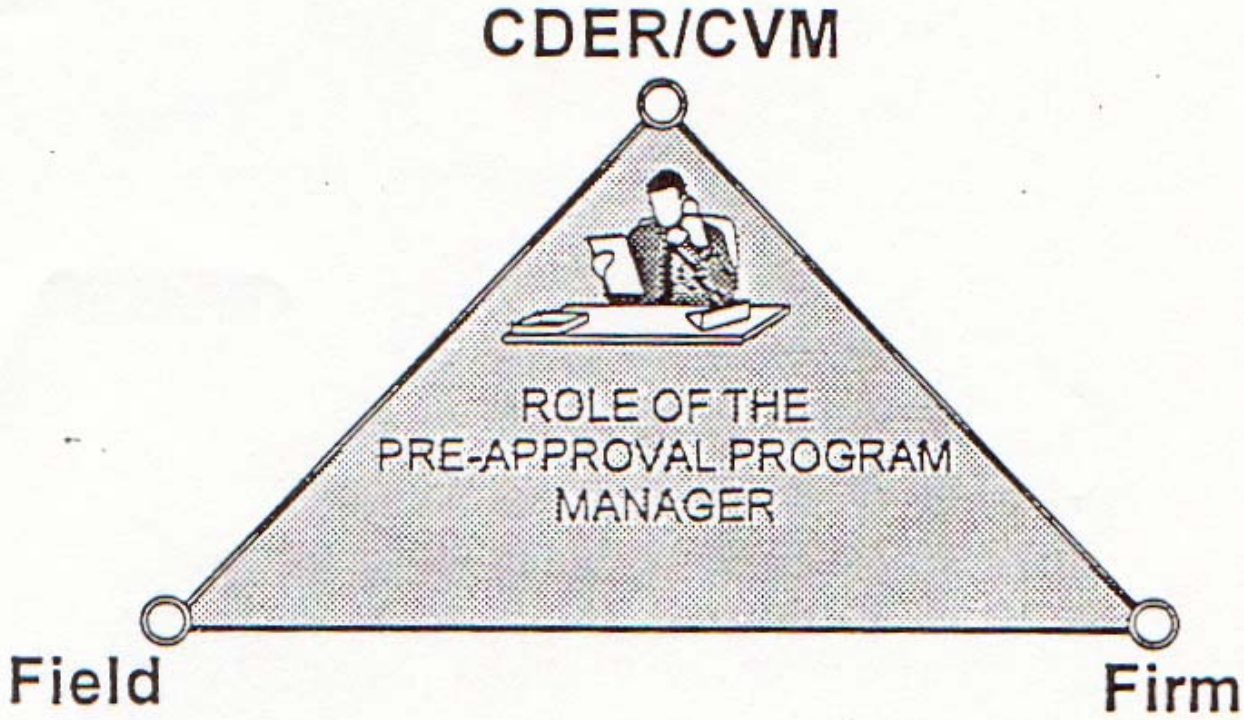

CDER/CVM
ROLE OF THE
PRE-APPROVAL PROGRAM
MANAGER
Field
Firm

Role of the PAI Manager
Primary Responsibilities

- **Liaison between Centers, Field & Applicant**
- **Physically manages 3rd copy of CMC & Correspondence**
- **Conducts Inspections**
- **Provides/Receives Training**
- **Process Validation Review/Scheduling**

Role of the PAI Manager
Acts as Liaison

- Receives assignments from CDER/CVM
- Review firm's history
- Schedule PAI if needed (CP7346.832)
- Contact firm and reviewer as necessary
- Respond to Center with District recommendation
- Prepare correspondence to firm

The Pre-approval Inspection Program District Responsibilities

- **Assure CGMP compliance.**
- **Verify data authenticity and accuracy.**
- **Determine the firm's ability to mfr. the product in accord with all application commitments.**
- **FDA sampling and analysis of the biobatch.**

Pre-Approval Inspections

- **Focus on pre-approval product**
- **Covers the GMP systems employed by the firm impacting the pre-approval product.**
- **Reviews compliance with application commitments.**
- **Evaluates the firm's "State of Control".**
- **Often utilizes team approach.**

PAI Inspections -What We Audit

- **Evaluate** specific product and process
  - Review Biobatches
  - Compare biobatch to filed commercial process
  - Is there data to justify the process?
- **Audit** raw data for integrity
  - raw material, in-process, and finished product testing records
  - stability testing records

Pre-Approval Critical Issues

- Equivalence must be evaluated between the biobatch and proposed commercial production batch. Whether in a validation document, or in some type of development report, the firm must make a correlation between the two. Any differences must be discussed with regard to potential impact on product bioequivalence.

Pre-Approval Critical Issues

- Therefore, it is important that the development and scale-up of the manufacturing process be well documented so that a **LINK** between the bio/clinical batch and commercial batch can be established.

Pre-Approval Inspectional Flags

- No raw data or missing data to support the application or the development report.
- No justification for changes being made between the pivotal clinical/biobatch and the proposed manufacturing batch record.
- No investigations of batch failures or OOS results.

Pre-Approval Inspectional Flags

- Failing stability data not submitted in NDA/ANDA.
- Discovery of batches which were not discussed in the development report.
- Lack of characterization of the drug substance or discussion of why some characterization may not be important.

Pre-Approval Inspectional Flags

- **Analytical methods are not validated or stability indicating.**
- **Manufacturing procedures are not specific**
  - **lack mixing times**
  - **equipment and settings not specified**
  - **temperatures**
  - **hold times**
- **Failure to comply with application commitments**

Pre-Approval Inspections

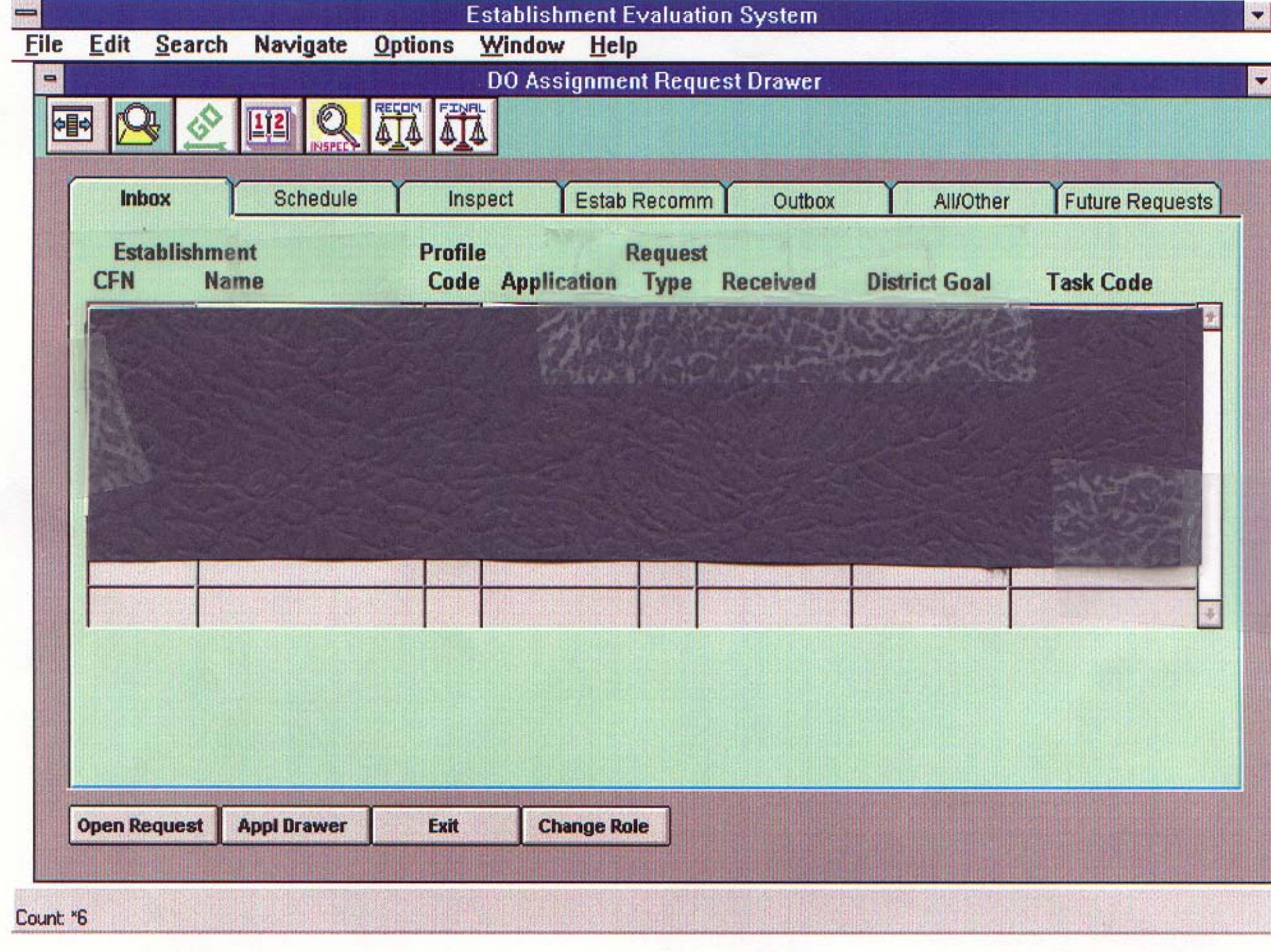
- Administrative actions are taken on pending products
- District recommendation made to CDER/CVM to withhold approval
- This is not a regulatory action

Establishment Evaluation System

- NDA's, ANDA's & supplements
- FDA-wide data base
- 40 Field withhold recommendation categories
- Summaries by calendar year

INSPECTION TRIGGERS

- New Molecular Entity
- Priority NDAs
- First application filed for establishment
- For cause inspection
- Treatment IND
- No qualifying GMP inspection in past 2 years
- Narrow Therapeutic Range (deleted)
- Top 200 Drug (deleted)


Establishment Evaluation System
File Edit Search Navigate Options Window Help
DO Assignment Request Drawer
RECOM
FINAL
INSPECT
Inbox
Schedule
Inspect
Estab Recomm
Outbox
All/Other
Future Requests
Establishment CFN
Name
Profile Code
Application
Request Type
Received
District Goal
Task Code
Open Request
Appl Drawer
Exit
Change Role
Count: *6

40 Withhold Recommendation Categories in EES

1. AIP Firm	Pending regulatory actions:
2. Drug not made here	6. Warning Letter
3. Facility withdrawn from application	7. Seizure
4. Firm not ready	8. Injunction
5. Inadequate firm response	9. Previous deviations persist

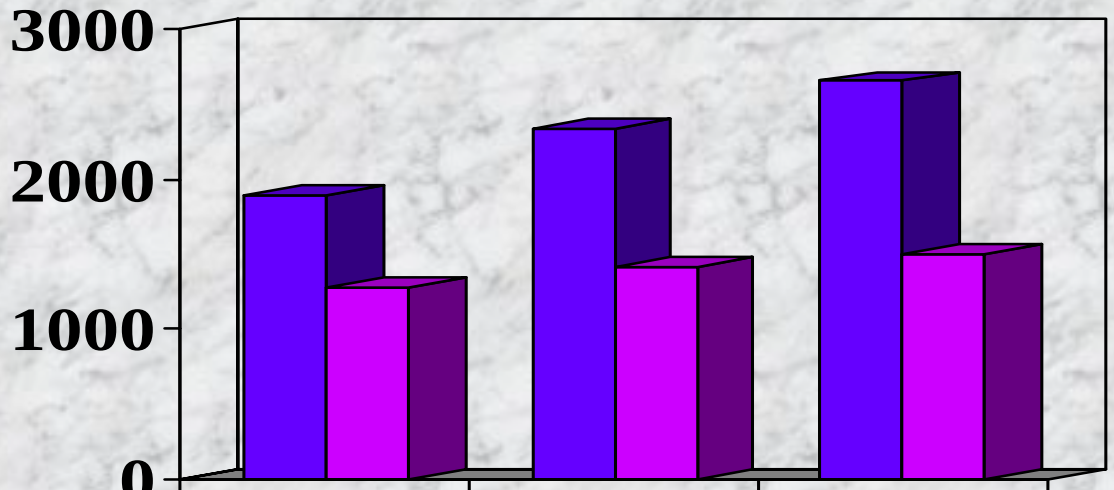
40 categories continued…

18. Holding & distribution
19. Lab controls
20. Master record non-specific or deficient
21. Packaging and labeling controls
22. Production & process controls
23. QA functions
24. Organization
25. Records/reports
26. Reprocessing
27. Specifications
28. Stability program
29. SOPs lacking or inadequate
30. Training

40 categories -Validation Issues

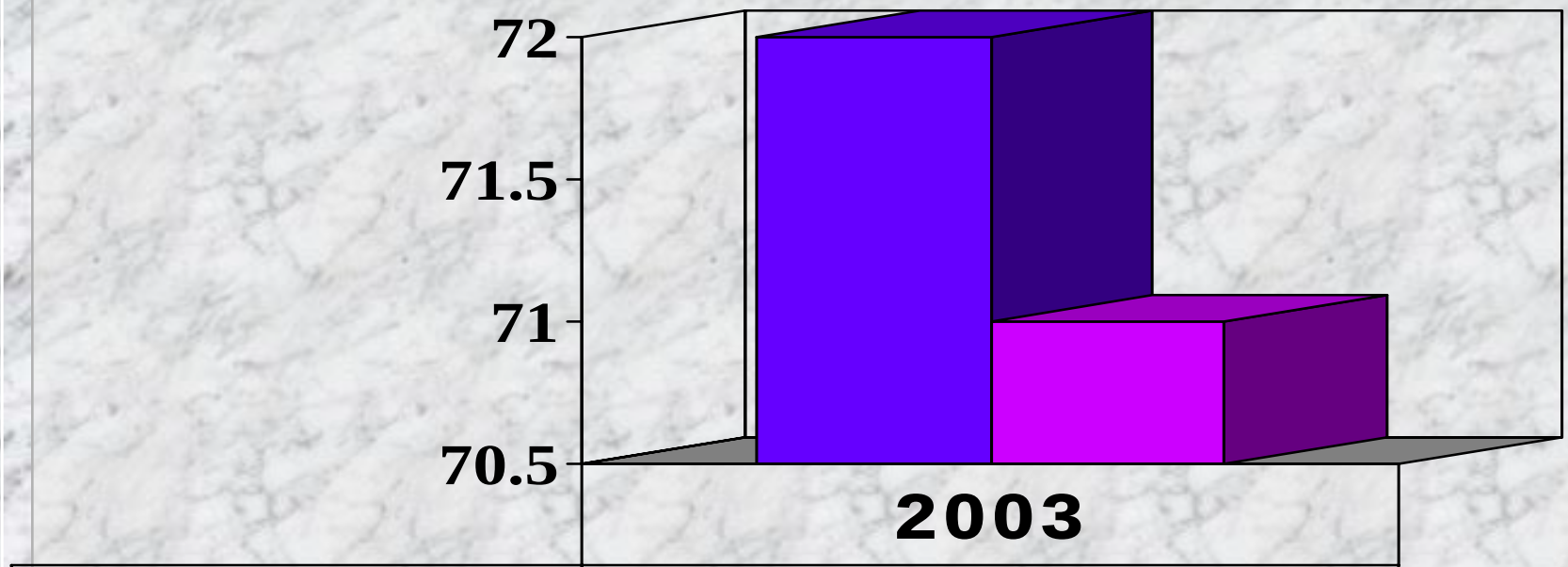
31. API Process validation	36. Media fills
32. Computer validation	37. System IQ/OQ
33. Equipment cleaning validation	38. Scale-up validation failure
34. Equipment qualification	39. Validation protocol inadequate
35. HVAC validation	40. Water system validation

CDER Pre-approval Inspection Requests



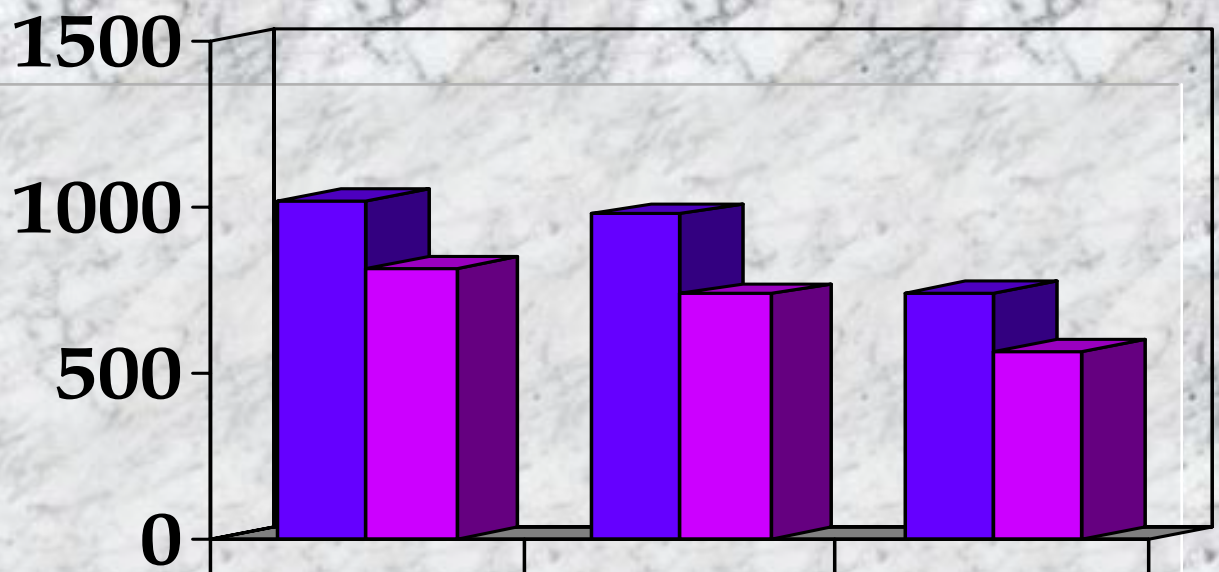
	1998	1999	2003
CDER Requests	1896	2328	2648
Applications Covered	1282	1418	1499

CDER Pre-approval Inspection Requests Downstate New York



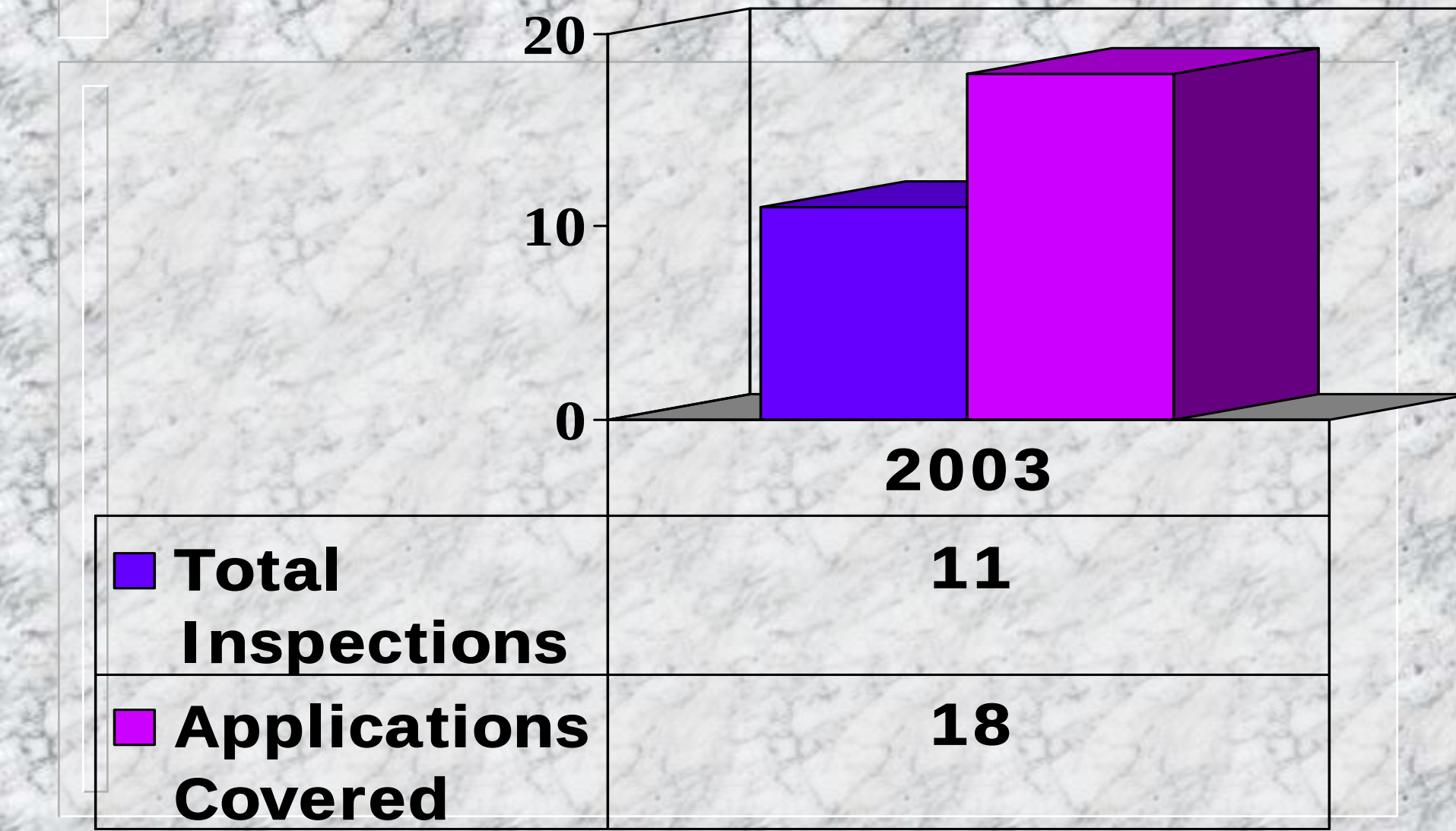
	2003
CDER Requests	72
Applications Covered	71

Inspections vs Applications

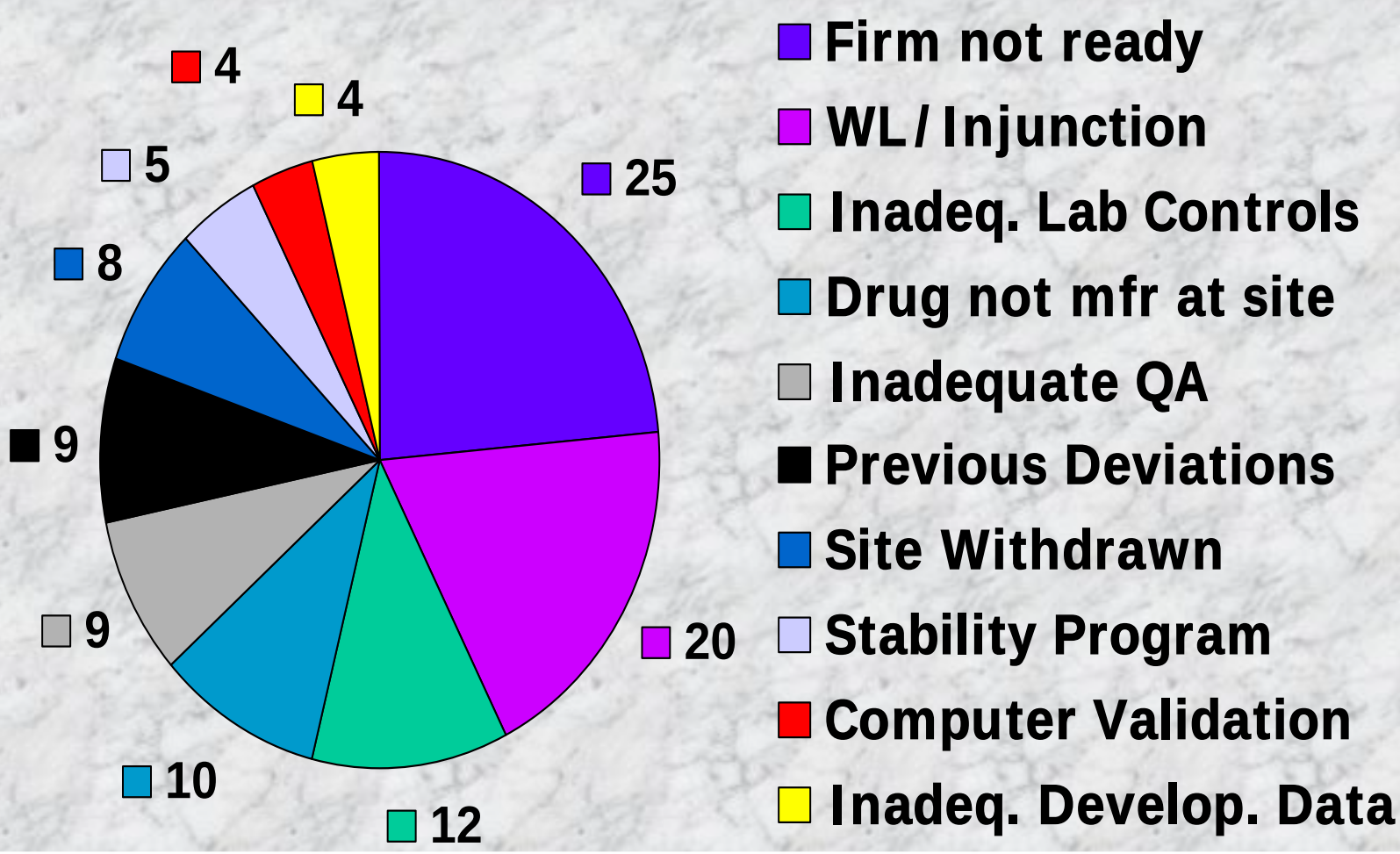


	1998	1999	2003
Total Inspections	1016	977	741
Applications Covered	813	736	566

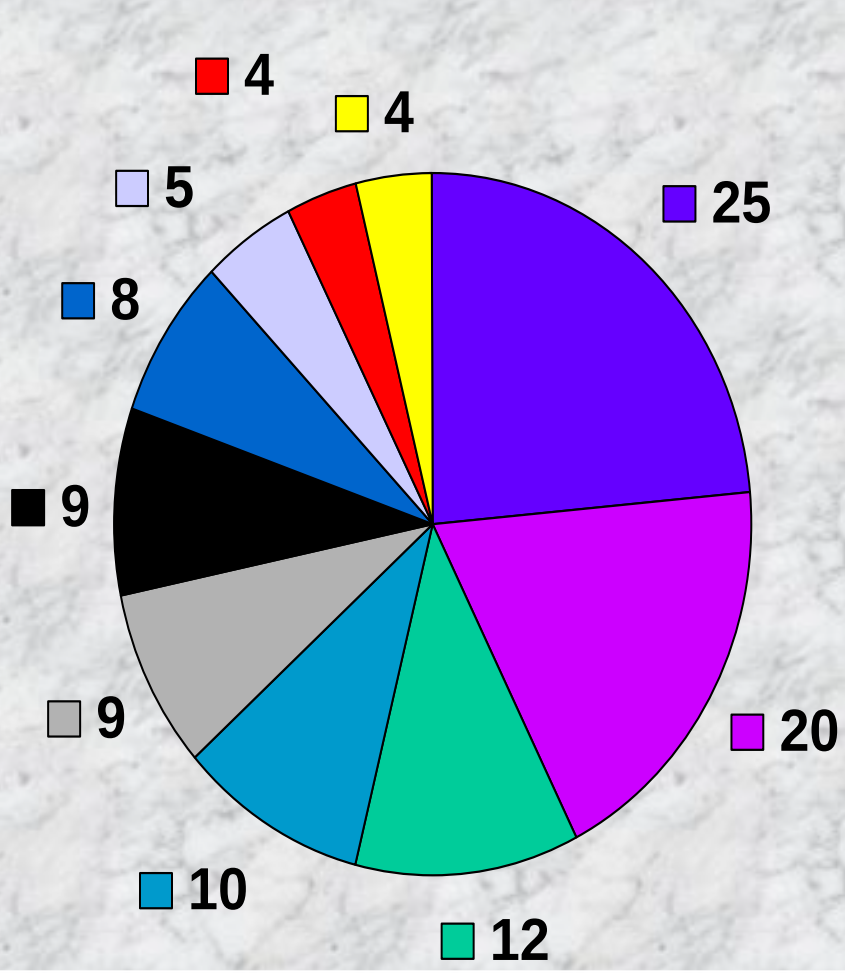
Inspections vs Applications Downstate New York



Top 10 NDA Withhold Recommendations FY2003



Top 10 ANDA Withhold Recommendations FY2003



- Firm not ready
- WL / Injunction
- Inadeq. Lab Controls
- Drug not mfr at site
- Inadequate QA
- Previous Deviations
- Site Withdrawn
- Stability Program
- Computer Validation
- Inadeq. Develop. Data

Firm Not Ready

Quote from Form 356h, Application to Market a New Drug, Biologic, or an Antibiotic for Human Use,

"Please indicate **whether the site is ready** for inspection or if not, when it will be ready" ….for all manufacturing, packaging, and control sites in the application

Applicant Certification on 356h

The data and information in this submission have been reviewed and to the best of my knowledge are certified to be true and accurate.

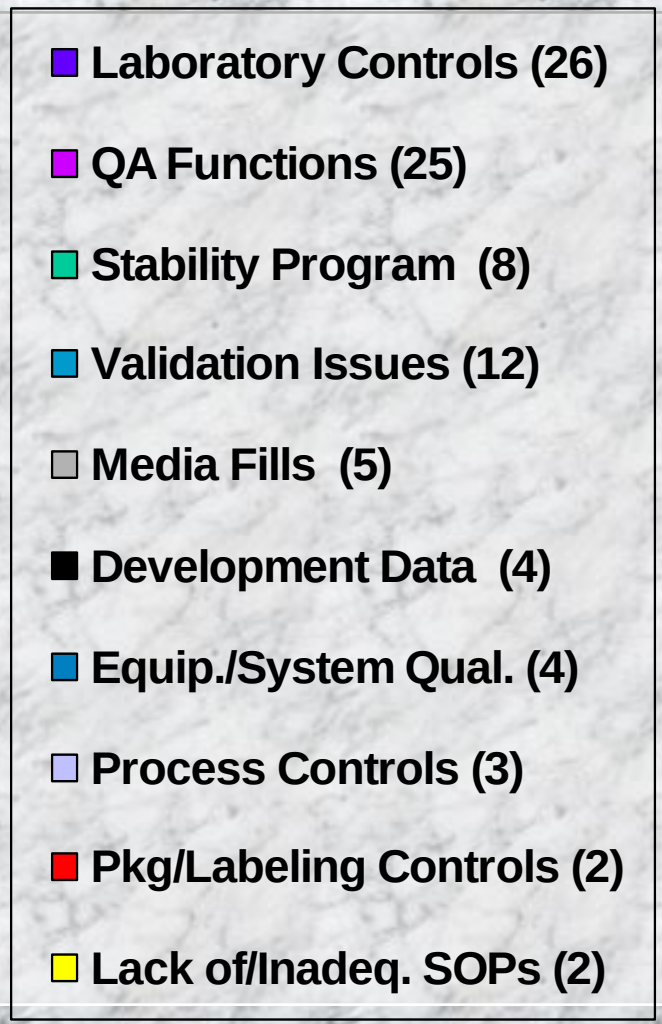
Warning on Form 356h:

A willfully false statement is a criminal offense, U.S. Code, Title 18, section 1001

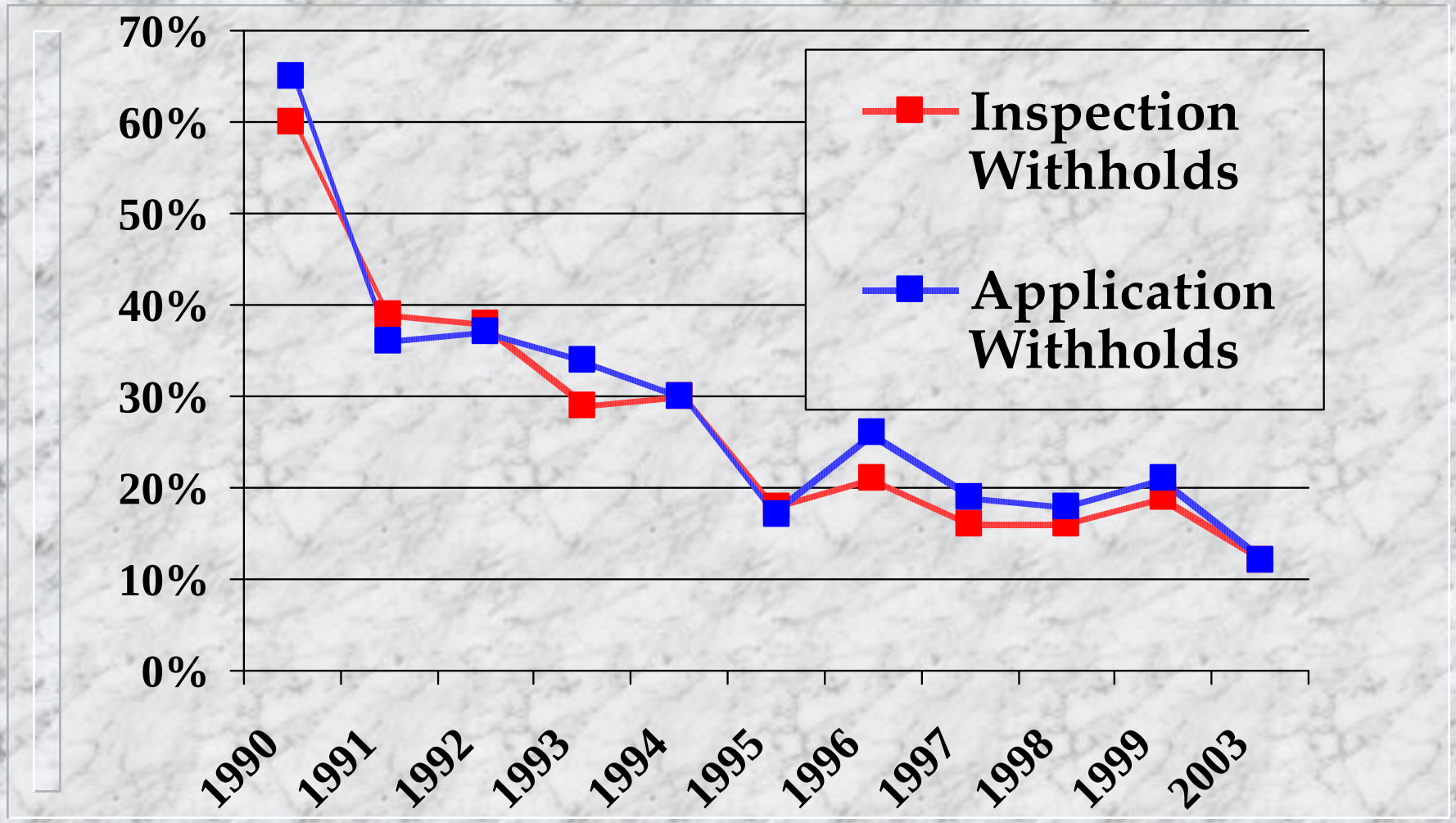
“Firm Not Ready” Policy

- Firm advises FDA they are not ready
- If District enters “firm not ready” in EES as final recommendation, a Not Approvable Action letter may issue from Center

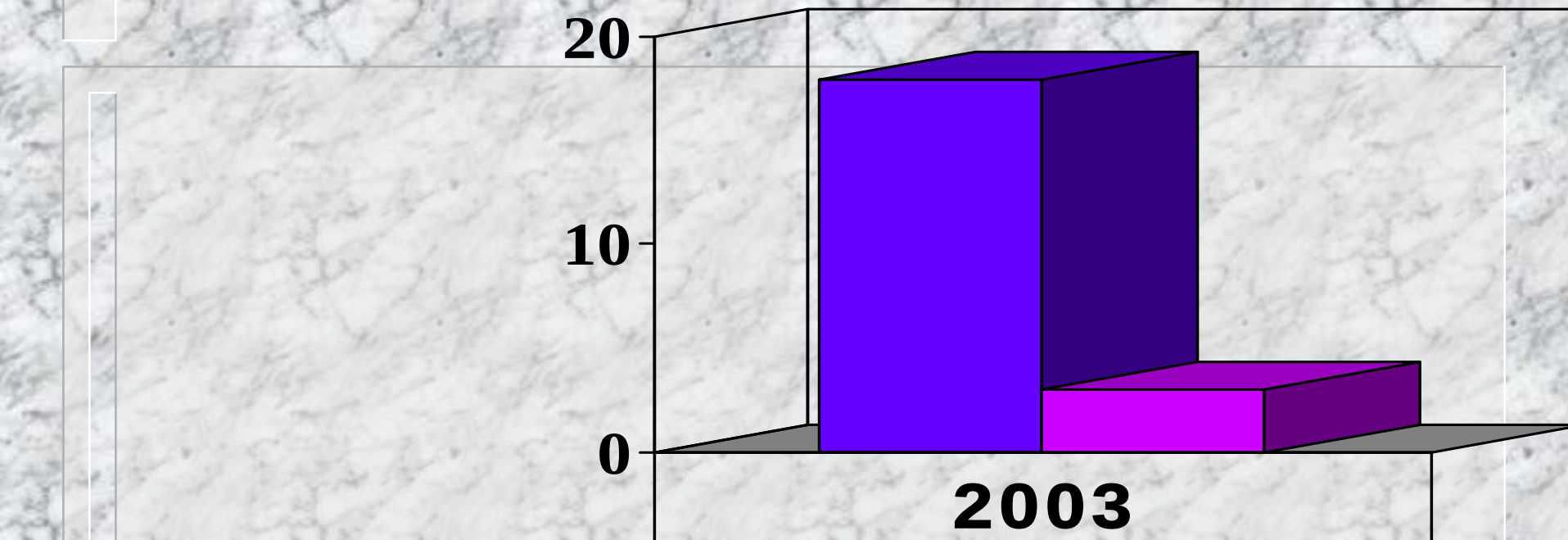
FY2003 Most Common CGMP withhold recommendations for NDAs/ANDAs



Withhold Recommendation Trends



Application Approvals Withheld FY2003 Downstate New York



	2003
Applications Covered	18
Approval Withheld	3

Summary

Keys to a successful PAI:

- Internal PAI
- Documentation
- Changes Justified/Documented
- Integrity of the Data

483 Items- APIs

- No physical specifications such as particle size and bulk/tapped density have been established and filed for the active pharmaceutical ingredient.
- No stability data on finished product manufactured with active material from the filed commercial API source have been submitted to this pending new drug application.

483 Items- APIs

- The NDA XXX states that firm's method XXX will be used as an alternate analytical procedure for assay and HPLC purity of the active drug substance. It was noted that method XXX is actually a procedure for testing the finished product. The firm has no written in-house method specific for assay and purity testing of the active drug substance.

483 Items- Instrument/Testing

- The firm has not validated the method for XXX which was modified from the USP compendial method.
- For the product XXX system suitability for related substances can be met using only one particular lot of column packing material from one supplier.

483 Items- Instrument/Testing

- The method for known impurities XXX lacks any system suitability parameters typically found in an HPLC assay method (i.e. RSD, Tailing, Resolution etc).

483 Items- Instrument/Testing

- The NDA for XXX states this firm does all release testing of the API. The drug substance test for crystal form requires the use of X-ray diffraction. The firm does not have the instrumentation necessary to perform this testing.

483 Items- Instrument/Testing

- HPLC assay for XXX included no injections of standards between samples or at the end of analysis. A total of 14 sample injections were made after the initial 5 standard replicates… over 8 hours of analysis was completed without any assessment of instrument performance.

483 Items- Instrument/Testing

- Peaks are not properly attenuated in the chromatograms relating to the HPLC assay analysis of XXX. The peaks of interest in the chromatograms are off scale, and only half of each peak is apparent. The peak should be scaled in the 50-75% FSD range as per the USP.

483 Items- Ref. Stds/Calibration

- Reference standards used for analysis are not dried prior to weighing nor are loss on drying or water factors used to correct the weights.
- The firm failed to follow SOP XXX in that many of the 50 reference standards on hand lacked required identification such as name, lot number, expiration date, date qualified, etc.

483 Items- Ref. Stds/Calibration

- The firm's SOP for reference standards does not include acceptance criteria for standards obtained from sources other than in-house or the USP. The SOP does not include information on the expiration date for reference standards, how they will be dried prior to weighing or use of purity factors.

483 Items- Ref. Stds/Calibration

- The firm lacked data for the setting of expiration dates for in-house standards, internal standards, special standards, etc.
- There are no written calibration procedures or evidence of calibration for the polarograph test instrument.

483 Items- Ref. Stds/Calibration

- The Potentiometric pH instrument was not properly calibrated for XXX pH determinations. The observed pH value for XXX was 11.0 … the pH meter was calibrated with buffers 7 and 10.

483 Items- Ref. Stds/Calibration

- Working standards were not qualified against USP reference standards.
- Non-compendial reference standards used by the firm for analysis are accepted and used as 100% pure, although certificates of analysis do not always contain adequate purity or potency data to make such as judgment.

483 Items- OOS

- There is no record of investigation into 3 repeat potency stability failures of XXX at the 9-month test station. New stability samples were analyzed which yielded passing results, and the product was deemed acceptable based solely on the re-sample results.

483 Items- OOS

- When OOS stability results for XXX occurred from March 1999 through November 1999, there was no documented investigation or corrective action to identify and remedy the cause of the problem.
- There is no SOP for handling OOS results obtained during product stability testing.

483 Items- OOS

- Purified water test records showed a point-of-use sample with a positive test result for coliforms. Although firm's specs have a zero tolerance for coliforms, with follow-up requiring system sanitization and re-sampling, the referenced test report was annotated "very low count, no action taken".

483 Items- Record keeping

- Raw data for all analytical work performed in-house is recorded on individual loose sheets of paper. These work sheets are not pre-numbered or otherwise strictly controlled to ensure the originality and traceability of the data.
- There were numerous examples of cross-outs and overwrites in lab notebooks that weren't annotated/explained.

483 Items- Record keeping

- There were a number of examples where the analyst rounded test values to zero or reported results as meeting NMT limits without reporting the actual test results obtained.
- There are no entries in lab notebooks of raw data for the sample, standard and mobile phase preparations or other preparatory work for the stability testing of XXX.

483 Items- Microbiology

- No preparatory testing as required by the USP has been conducted by the firm for XXX which is currently being analyzed for microbial limits.
- Product samples are not weighed or measured to ensure delivery of the specified amount of sample to media as required by USP test procedures.

483 Items- Microbiology

- Firm's SOPs for growth promotion testing of in-house prepared media do not specify the quantity of organisms to be inoculated. Per management, a loopful from an overnight culture is used for such testing
- Firm’s SOPs call for media to be autoclaved at sterilization parameters for 30 minutes, however records show these media are routinely autoclaved for 60 minutes.

483 Items- Microbiology

- In-house prepared media are not checked prior to use for compliance with required final pH specifications following their preparation and autoclave sterilization.
- The firm has not validated the aseptic compounding operations involved in the production of ophthalmic ointments.

483 Items- Microbiology

- Media fills do not mimic conditions of actual production operations including duration of filling and movement of personnel during interventions such as equipment adjustments, environmental sampling, etc.

PAI Manager

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