Drug Trends

2006-2012

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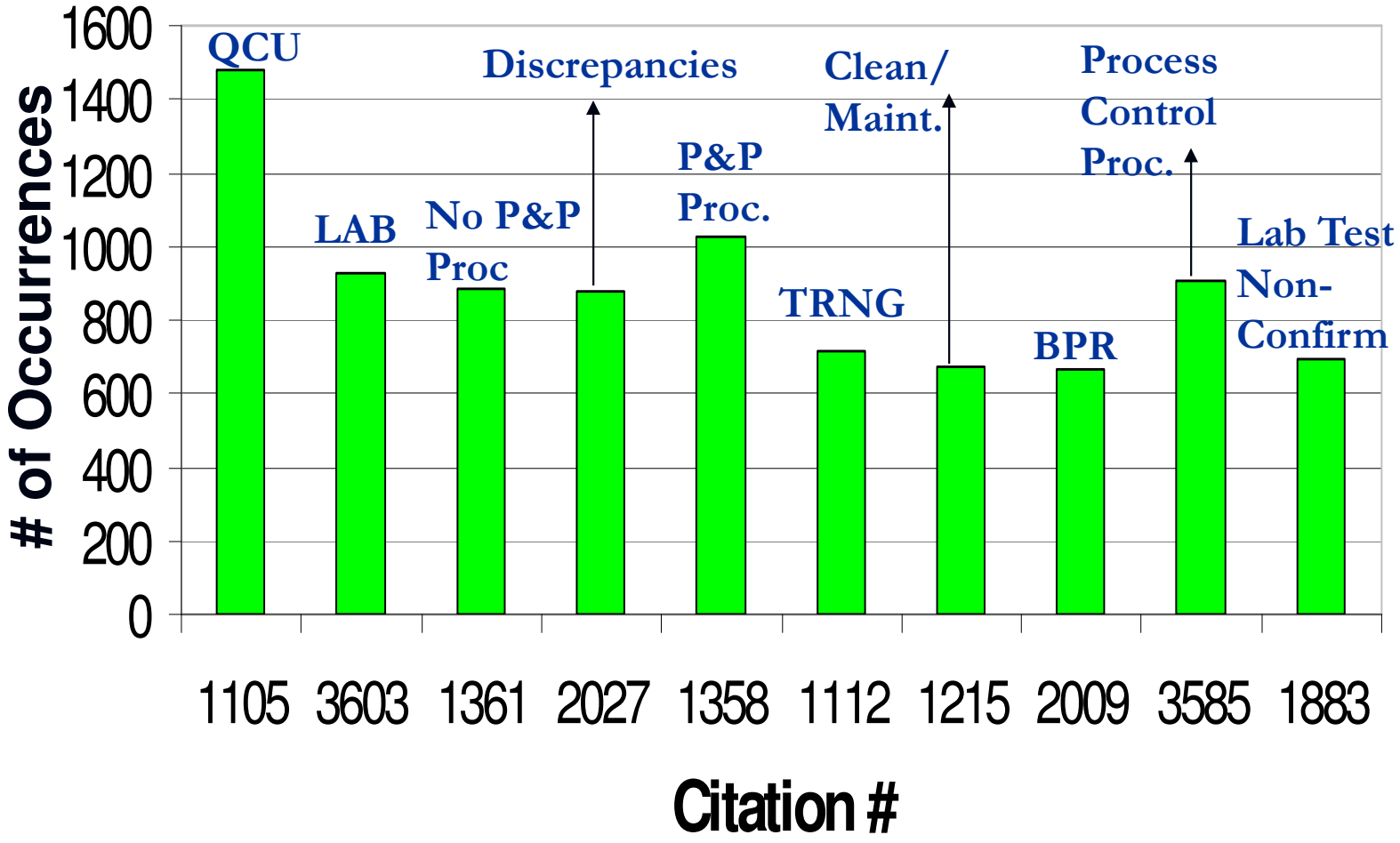
Drug Trends

- Inspection Numbers
- Observations
- Trends
- Examples
- Inspection
- Compliance
- Considerations

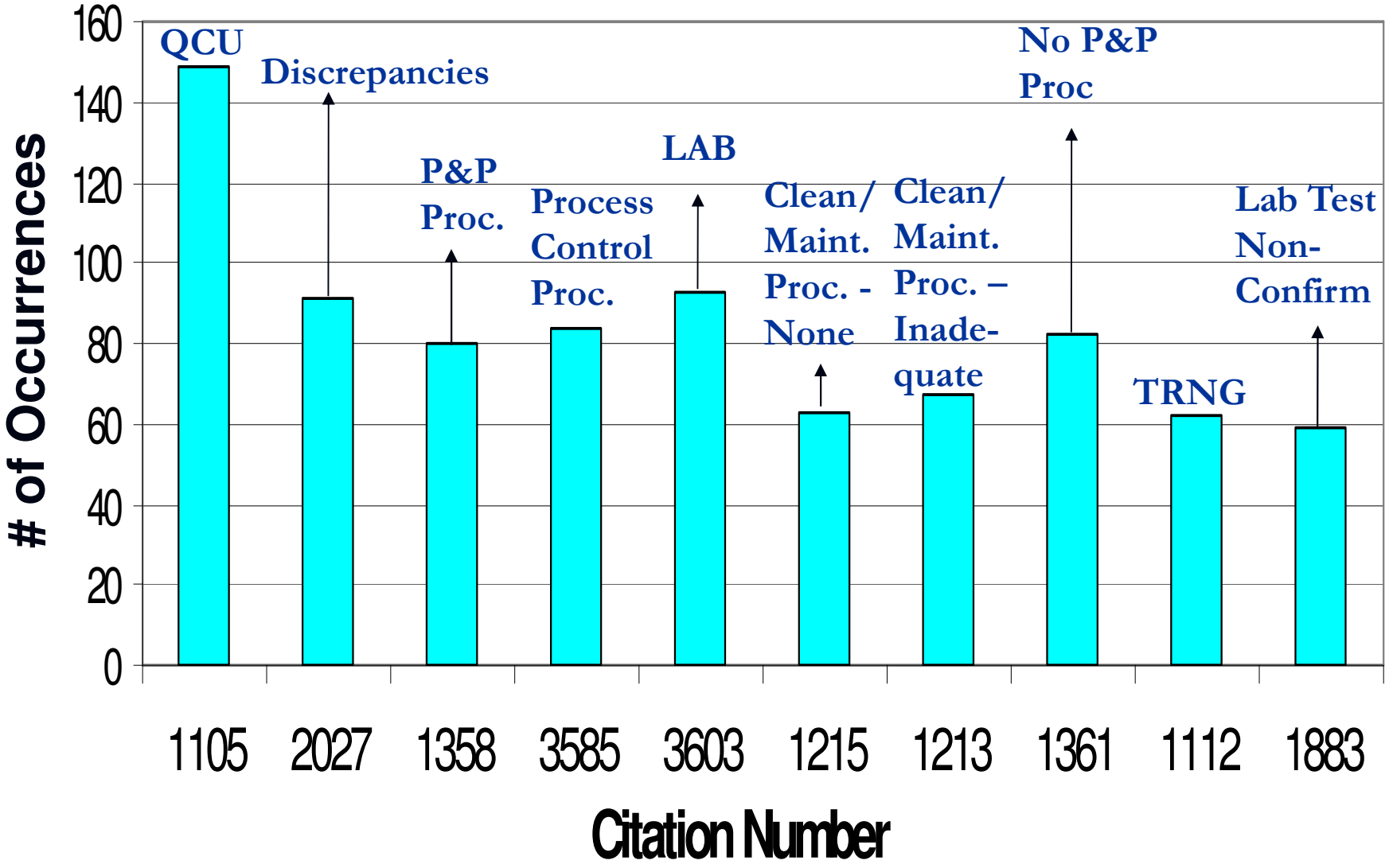
Inspection Numbers

- Calendar Year 2011
  - Approximately 1652 domestic inspections
    - 17 PET Inspections
  - Approximately 607 foreign drug process inspections
    - 296 were Active Pharmaceutical Inspections

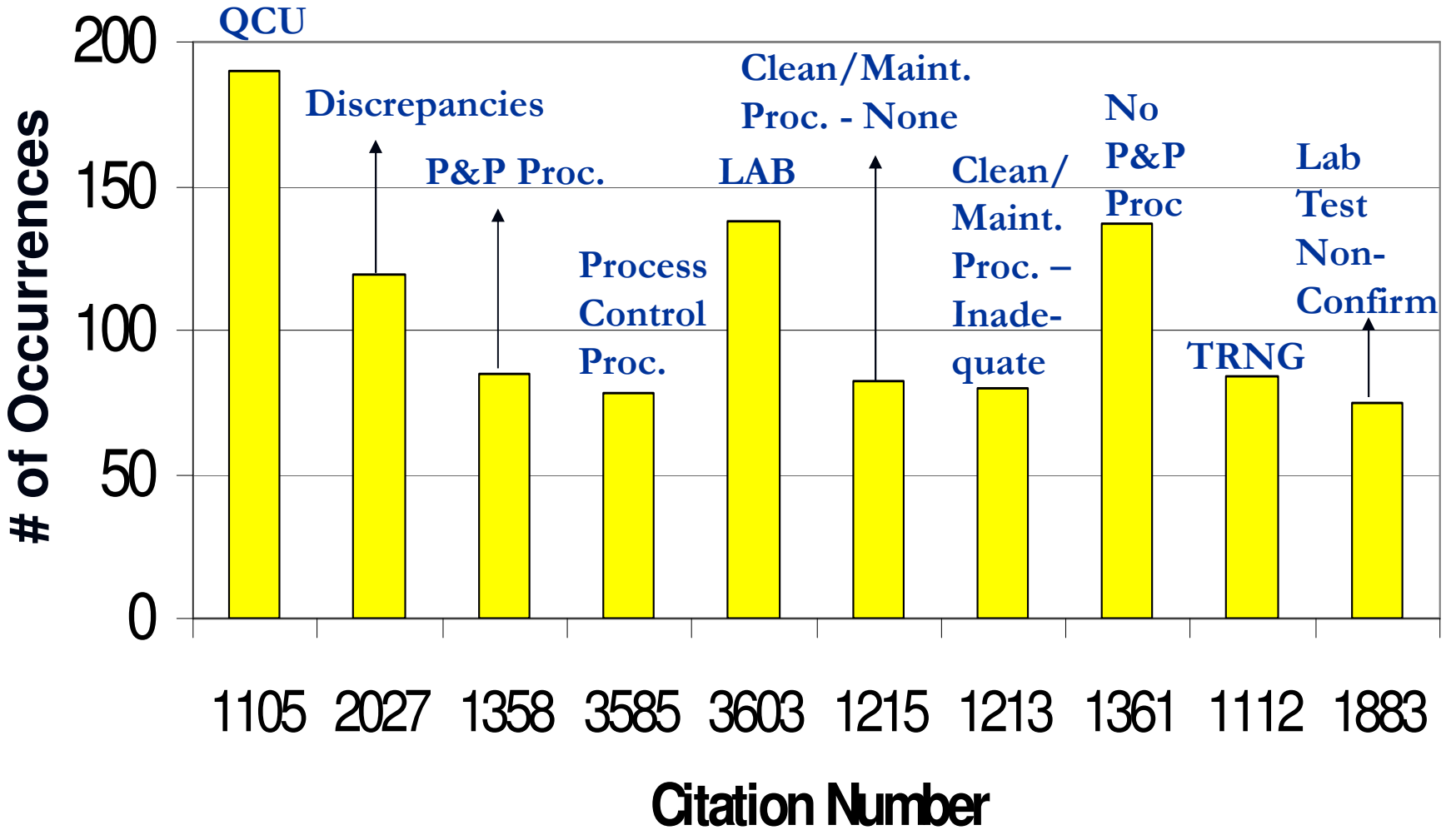
Observations in Turbo Since Implementation



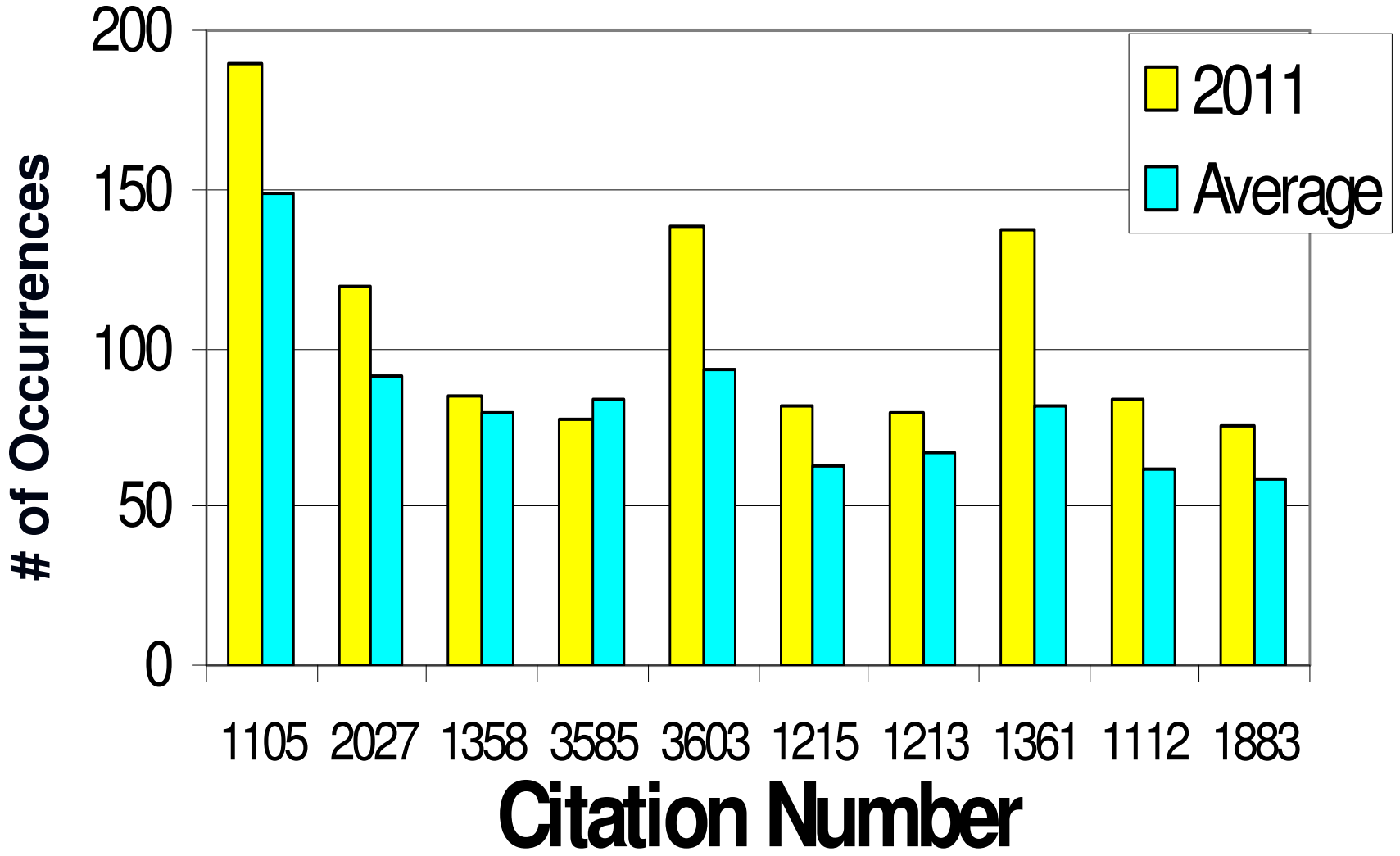
Six Year Average of Turbo Citations



Turbo Citations 2011



2011 vs. 6 Year Average



2011 Top 10 Observations

RANK ORDER	CITE #	21 CFR REF.	RULE	# OF OCCURRENCES
1.	1105	211.22(d)	Responsibility and procedures applicable to the quality control unit	149
2.	3603	21 CFR 211.160(b)	Laboratory procedures do not include establishment of scientifically sound and appropriate…designed to ensure…conform to appropriate standards of identity, strength, quality and purity.	93
3.	2027	21 CFR 211.192	Failure to thoroughly review discrepancies/batch failures	91

2011 Top 10 Observations

RANK ORDER	CITE #	21 CFR REF.	RULE	# OF OCCURRENCES
4.	3585	21 CFR 211.110(a)	Control procedures not established of those manufacturing process which may be responsible for causing variability	84
5.	1361	21 CFR 211.100 (a)	No written procedures for production and process control	82
6.	1358	21 CFR 211.100 (b)	Written production and process control procedures are not followed/documented	80

2011 Top 10 Observations

RANK ORDER	CITE #	21 CFR REF.	RULE	# OF OCCURRENCES
7.	1213	21 CFR 211.67(a)	Written procedures for cleaning and maintenance of equipment are not established/followed	67
8.	1215	21 CFR 211.67(b)	Written procedures for cleaning and maintenance of equipment are not adequate	63
9.	1112	21 CFR 211.25(a)	Employees are not given training in…	62
10.	1883	21 CFR 211.165(a)	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance	59

Quality Control

- Responsibility and procedures related to the Quality Control Unit (QCU)
    - This observation is consistently the number 1 observation issued during drug inspections
    - This can involve complete or partial failure to identify the functions of the QCU
    - 21 CFR 211.22 defines the responsibilities of the QCU

Laboratory Procedures

- Laboratory procedures do not include establishment of scientifically sound and appropriate…designed to ensure…conform to appropriate standards of identity, strength, quality and purity.
  - Lack of procedures, inappropriate procedure for characteristic, non-validated lab procedures.
  - 21 CFR 211.160(b) describes the requirements for lab procedures

Discrepancy Review

- Failure to thoroughly review discrepancies/batch failures
  - Review for discrepancy, investigate where necessary or justify, pre-release or post, inclusion of other batches and written record of such
  - 21 CFR 211.192

Process Control

- Failure to establish control procedures for those processes which may introduce variability
  - This observation includes failure to perform process validation activities, in-process control and testing activities
  - 21 CFR 211.210(a)-(d) discuss in-process and drug product testing

Production/Process Procedures

- Written production and process control procedures are not followed/documented
  - Procedures shall be followed, documented contemporaneously and deviations from procedure documented
  - 21 CFR 211.100(b)

1 - 21 CFR 211.22(d)

Procedures not in writing, fully followed

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, "Standard Operating Procedure ***", eff. 05/24/2010, specifies the responsibilities and authority of the Quality Unit … However, upon review of production records, the sole Quality Unit employee was observed both executing and/or approving various steps in manufacturing and laboratory testing operations.

2 - 21 CFR 211.160(b)

Scientifically sound laboratory controls

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

The following four lots of ***, USP, 250mg were analyzed (Assay by HPLC) using non-compendial reference standard: Aminosidina (Paromomycin Free Base) that had not been qualified as specified in written protocols and/or written procedures at the time of use, namely, Qualification Protocol ***

3 - 21 CFR 211.192

Investigations of discrepancies, failures

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically,

The firm failed to assure that corrective actions were taken following the discovery that incorrect labels had been used for *** between September 2006 and October 2009.

4 - 21 CFR 211.110(a)

Control procedures to monitor and validate performance
Control procedures are not established which monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,
A) Complaint investigation report *** was received by your firm and reported a product mix-up for lot *** with product code ***. Your firm's investigation concluded that the reported product mix-up was attributed to a line clearance failure. No discrepancies in relationship to the reported product defect were documented during the manufacturing process of this lot and the lot was released with satisfactory results.

5 - 21 CFR 211.100(a)

Absence of Written Procedures

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

Your firm did not validate your current manufacturing process for *** following changes to the production process effective 5/24/2011, which included changes to the formulated batch size.

There is no documented assessment on the impact of these process changes on the quality of the drug products, nor is there an assessment of the need for revalidation of the production processes following these process changes.

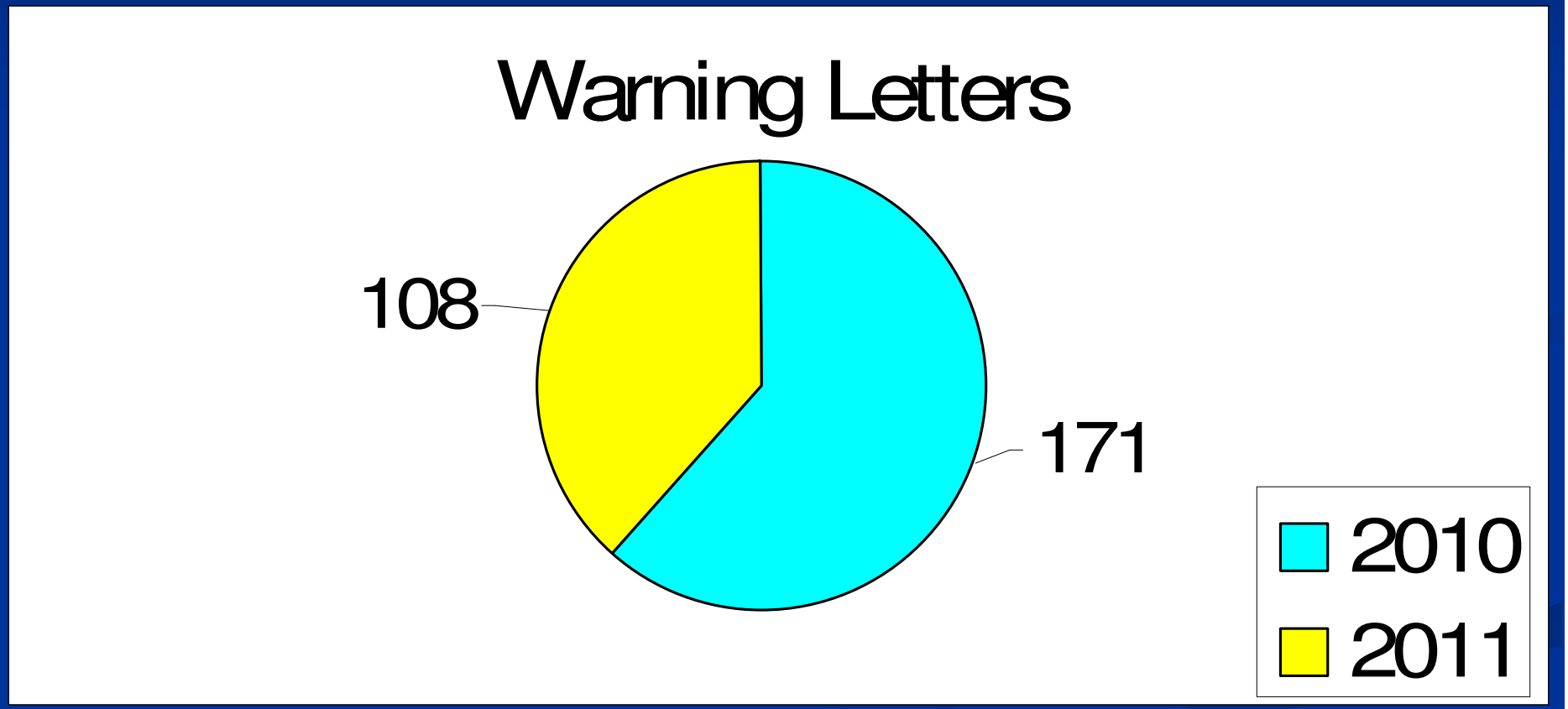
Inspections

- Risk-based analysis determines the direction of the inspection – product/process reviewed
- QCU will always be reviewed
- Continued concern over foreign manufacturing, suppliers and cross-contamination issues

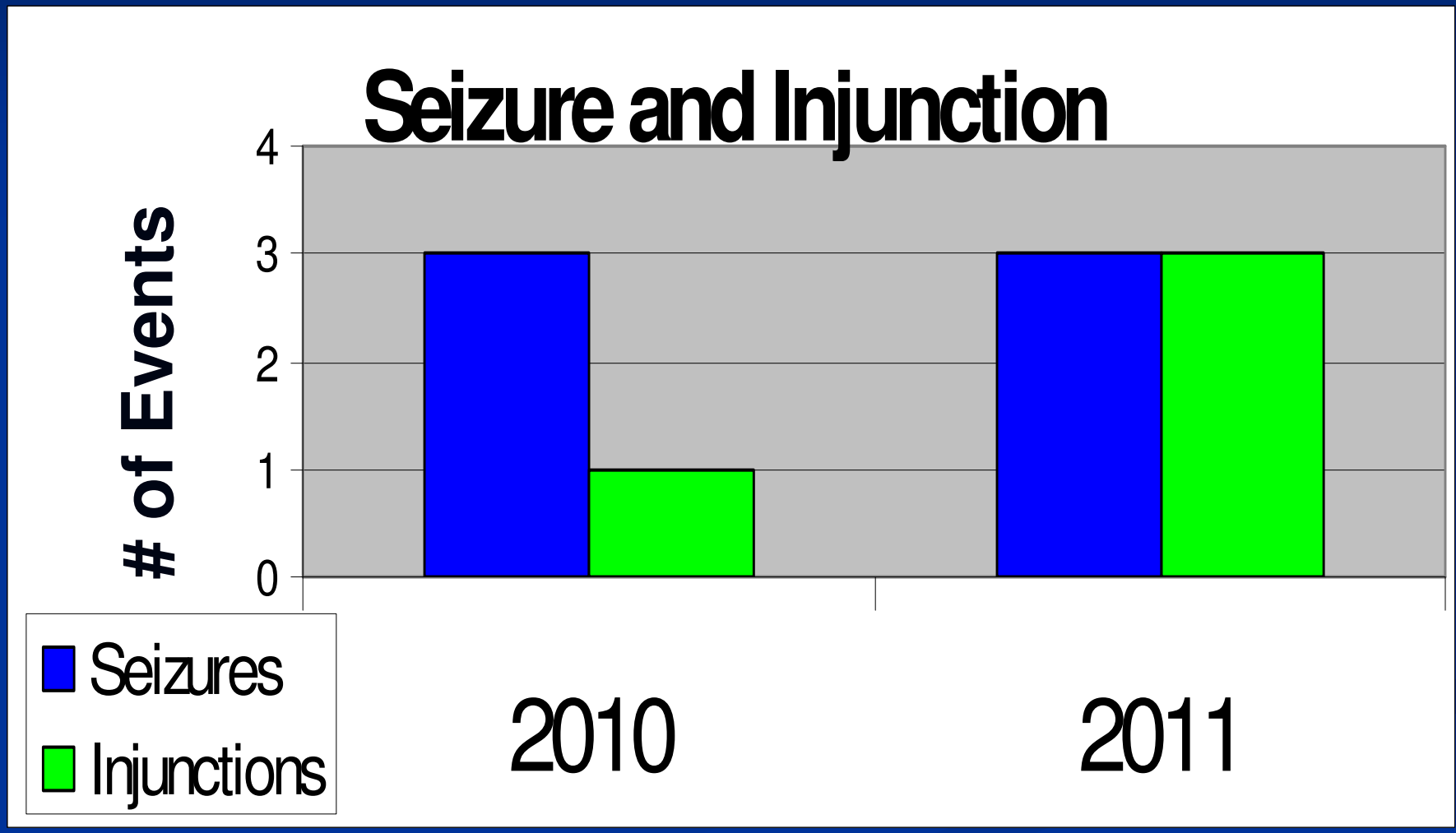
Inspections

- The number of foreign drug inspections continue to increase each year
- Foreign Posts have been established
- Development of the Pharmaceutical Inspectorate and highly skilled investigators

Enforcement – Fiscal Year 2010 vs. 2011



Enforcement – Fiscal Year 2010 vs. 2011



Considerations

- The QCU is the basis for control of the manufacture and handling of drug products
- Process validation and/or verification activities are still not well understood or are improperly applied

Considerations

- Discrepancies are either not detected or when detected are not appropriately addressed – commonly dismissed and batches approved

- Laboratory tests and procedures are not being designed and validated as appropriate for the attribute being tested and/or are not being documented as appropriate

Questions