PDA- PIC/S Q7 Training
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Commonly Identified Deficiencies Found at API Manufacturing Sites– A Regulatory Perspective

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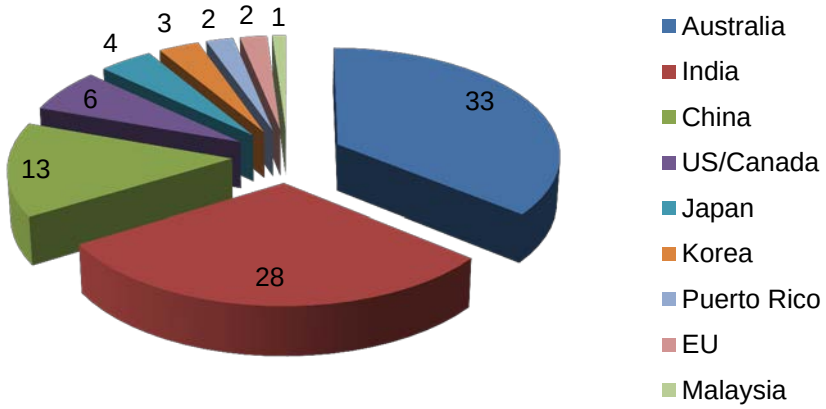
TGA API Inspections 2013-2015

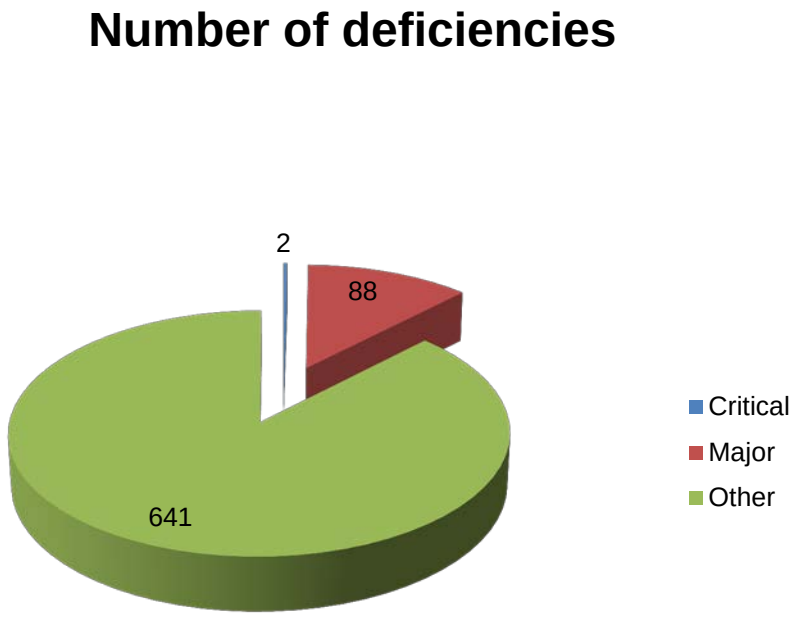
- TGA conducted 92 API inspections in the period June 2013 to August 2015
  - Includes sterile and non sterile APIs, small-molecule synthesis, recombinant biotechnology, fermentation and radiochemical production facilities
  - Average inspection duration of 3.5 days
  - Typically 1 inspector in attendance for non-sterile molecules, 2 inspectors for complex and/or sterile APIs

Total number of inspections = 92

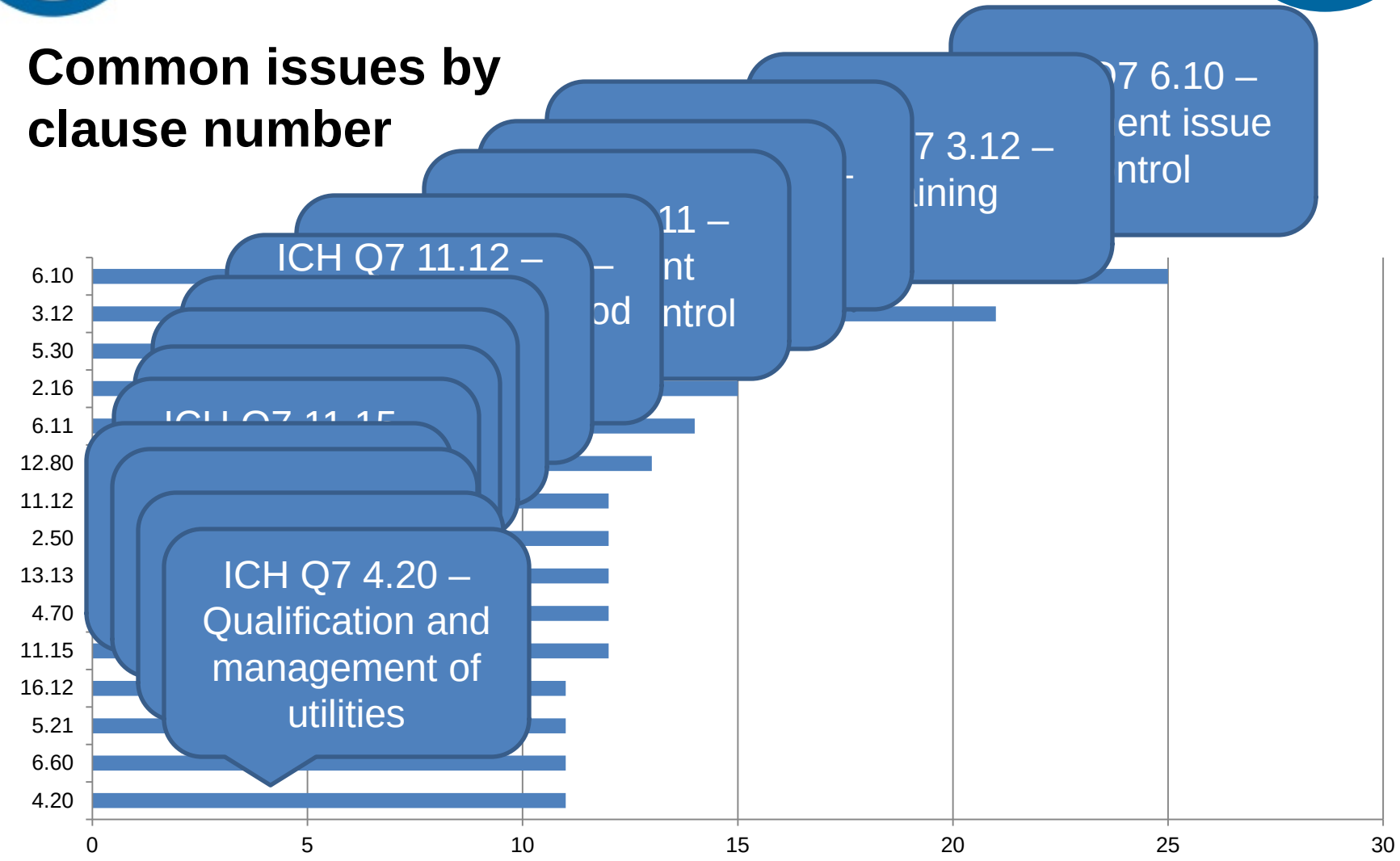


TGA API Inspections 2013-2015

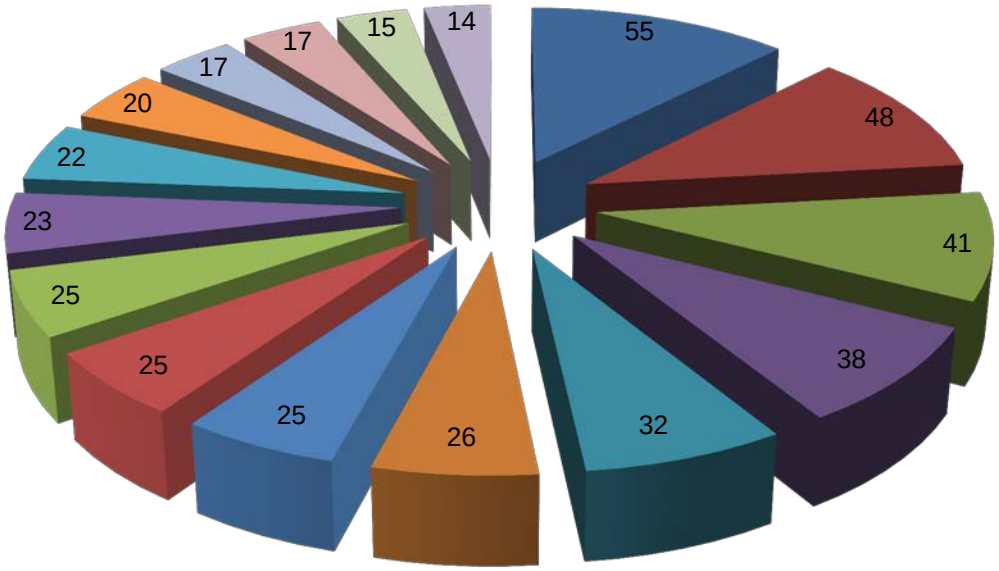
- 37 of the 91 inspections resulted in Major or Critical deficiencies
  - 2 critical deficiencies were reported in the period
  - 2.2% of all 91 inspections raised Critical deficiencies
  - 88 Major deficiencies were reported in the period
  - 40.6% of all 91 inspections raised Major deficiencies



Common issues by clause number



Common issues – by subject



Common issues by significance 1

Validation	•12.22 – Validation reporting •12.30 – Equipment Qualification •12.70 /71/72 – Cleaning Validation •12.80/81/82 – Method Validation & Analytical equipment qualification
OOS result management	•11.15 – Investigation and recording of out-of-specification results
Laboratory control records	•6.60 – Comprehensive QC control records
Utilities	•4.20 – Qualification of utilities, monitoring of utilities and response to deviations from set limits. •4.21 - Adequate ventilation, air filtration and exhaust systems – cross contamination

Common issues by significance 2

Maintenance and Cleaning	• 4.70 – Buildings used should be maintained and cleaned.
Training	• 3.12 – Training to be regularly conducted, assessed and records maintained.
Deviation management	• 2.16 – Any deviation should be documented and explained. Critical deviations should be investigated and documented.

Examples of deviations

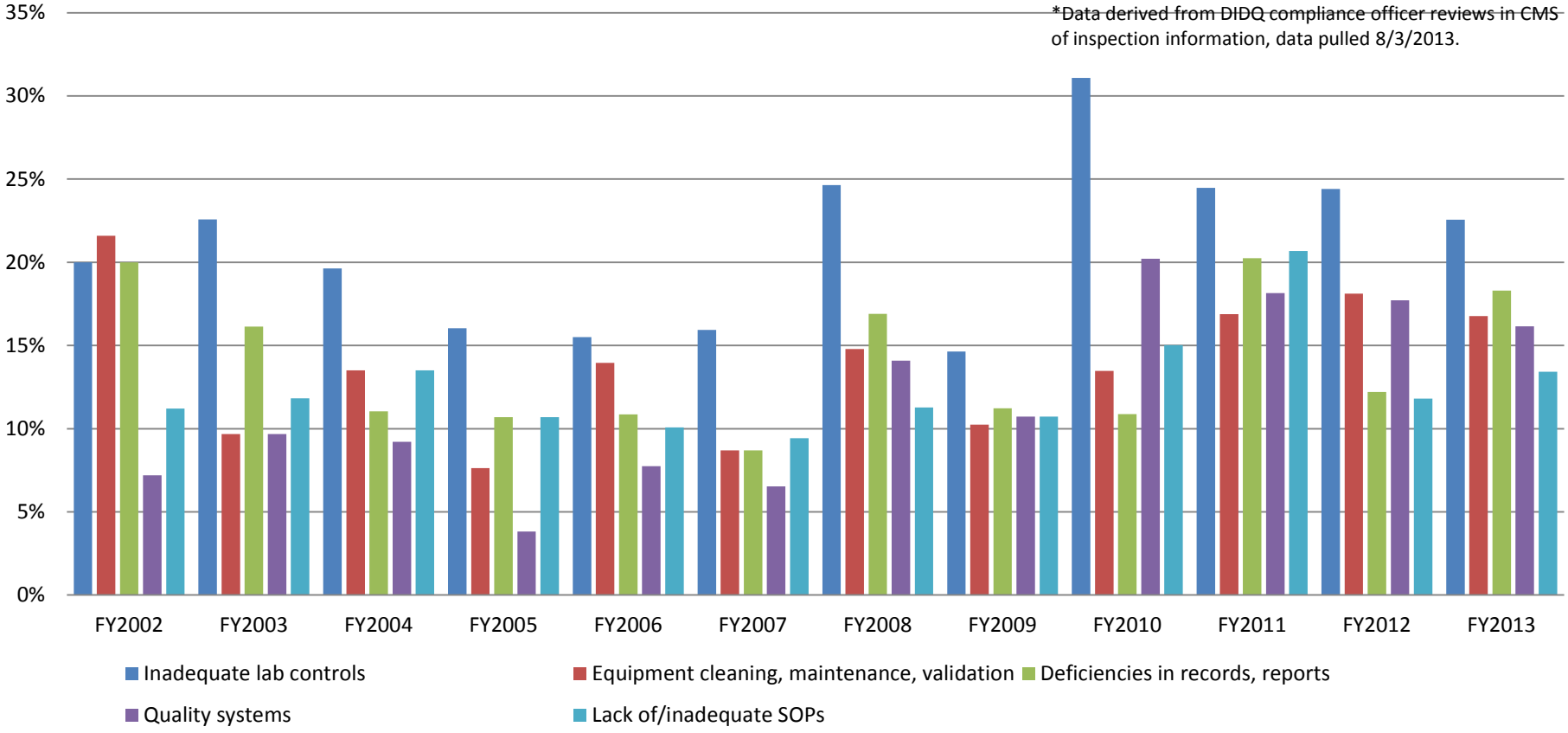
- ***The requirements of Clauses 12.22, 12.30, and 12.60 regarding qualification of equipment, periodic validation review of systems and the generation of related validation documents were not fully met as evidenced by:***
  - *There was no annual or periodic revalidation report, which summarised all aspects of the HVAC system data (e.g. environmental monitoring, particle counts, and pressures) to demonstrate that the system remained within the validated state.*
  - *The stability chamber mapping performed annually by contractors did not detail the mapping procedure or provide a map of probe locations. There was no link identifying that the company mapping procedure was used by contractors.*
  - *The annual maintenance and qualification documentation of stability chambers did not contain sufficient information to ensure that the operation of safety systems checks and alarms were tested.*
  - *The OQ for the rotary dryer (12345) did not challenge the different speed setting of the dryer and only verified the maximum speed as 18rpm. Further, the tachometer used in the OQ was not recorded and identified.*
  - *Temperature mapping of the reference standard fridge (12345) indicated that the hottest position was position 6. The routine monitoring probe was reading from position 3 (coldest) contravening the validation findings.*
  - *The result report and contractors report (ABCDE) for unit A HVAC testing referred to one room as "clean in process – ointment". This room did not exist and there was no way to uniquely identify which rooms had been tested aside from the room name (the room number as per the plans was not referred to).*

- ***The requirements of Clauses 4.20 and 4.21 regarding adequate ventilation and air monitoring to ensure the risk of contamination and cross-contamination is kept to a minimum were not fully met as evidenced by:***
  - *The design of the pressure differentials in the manufacturing area of unit A meant that the centrifuge room and primary packing rooms (connected by a door) were of the same pressure. This design did not provide adequate containment of the powders liberated during packaging.*
  - *The clean air in the packaging areas was not classified and the qualification conducted did not include particulate testing. Although the company was monitoring differential pressures in packaging and conducted smoke test annually, there was no system performance report available for review.*
  - *Unit A plant: The pressure differentials in the plant were out of balance. Most of the 18 magnehelic gauges in the area recorded OOS readings.*
  - *Unit B Plant: A number of magnehelic gauges recorded OOS readings.*

- ***The requirements of Clauses 6.53 and 11.15 that deviations and OOS results should be documented, explained, and investigated especially in relation to an intermediates or APIs failure to meet specifications were not fully met as evidenced by:***
  - *Report 'A' related to lot 12345 "API" in-process check. The UV characteristic test (following PhEur) failed specification but passed the UV test (following the USP). There was no investigation of the cause of failure and the manufacturing process was allowed to proceed on the basis of the USP result, even though both tests were required to pass according to the batch specification.*
  - *Report 'B' related to batch 12345 "API" in-process purity check. The batch failed the in-process purity (the result was 85.94% compared to a minimum specification of 90.0%) and starting material purity was suspected to be the cause of failure. There was no proper assessment of the starting material in the deviation and the process was allowed to proceed without any information regarding how to prevent reoccurrence of the failure, nor any review of changes required to the starting material quality.*
  - *Reports'C&D' related to batch 12345 "API" in-process chiral test failure by HPLC (a result of 92.49% compared to the minimum specification of 94.0%). R&D conducted a trial to correct the issue; however, there was no information documented of the cause of failure and required changes to prevent reoccurrence of the failure.*

U.S. FDA Experiences

GMP problems in all international API inspections over time (% frequency/inspection , FY13 partial)



Common Inspectional Findings (APIs) by FDA

- **Inadequate lab controls**
  - Lack of/inadequate method validation
  - Failure to have scientifically sound and appropriate specifications and test procedures
  - Failure to adequately investigate out-of-specification (OOS) results
  - Failure to document lab controls at the time of performance
  - Failure to have an adequate stability testing program to assess the stability characteristics

Common Inspectional Findings (APIs) by FDA

- **Quality System**
  - Failure of the Quality Unit (QU) to release/reject APIs
  - Failure of the QU to review and approve all quality-related documents
  - Failure to ensure that quality-related complaints are investigated
  - Failure to conduct regular quality reviews of APIs
  - Failure to evaluate the potential impact of proposed changes on the quality of APIs

Common Inspectional Findings (APIs) by FDA

- **Equipment cleaning, maintenance & validation**
  - Equipment not properly maintained
  - Inadequate cleaning procedures (ex. not detailed)
  - Failure to validate cleaning procedures
  - Failure to clean, store, sanitize or sterilize (if applicable) equipment to prevent contamination or carry-over that would alter the quality of API
  - Inadequate qualification of critical equipment

Common Inspectional Findings (APIs) by FDA

- **Deficiencies in records and reports**
  - Failure to prepare adequate batch production records
  - Failure to include complete data derived from all tests in the lab control records

- **Lack of/inadequate SOPs**
  - Failure to establish written procedures related to: production activities, QU responsibilities, laboratory processes, materials management, laboratory controls etc.

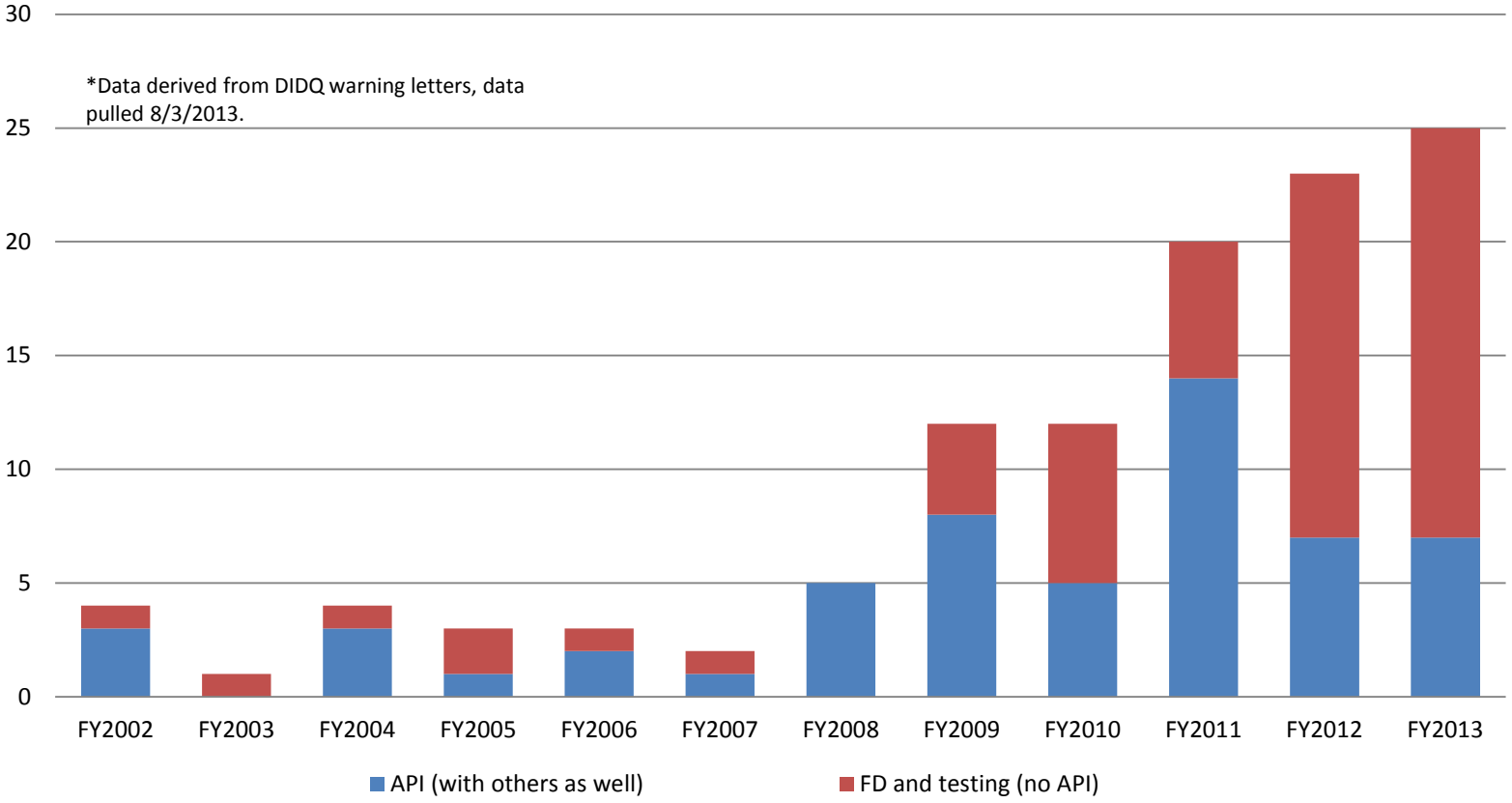
Data Integrity Issues found by PIC/S members:

- False recording of data in logbooks
- Falsification of batch records and test results
- Pretesting samples and ignoring or not investigating out of specification results
- Blending or mixing API batches that failed to meet the established released specifications with batches that met the required final specifications

Data Integrity Issues found by PIC/S members (cont'd):

- Lacking necessary controls in handling and managing critical data
- Entering manufacturing activities on records before occur

GMP Warning Letters (WLs) Issued to International Firms by Manufacturing Type Over Time



Examples of API Deficiencies Cited by FDA on WLs (2014/2015)

- Failure to maintain complete data derived from all lab tests conducted to assure compliance with established specifications
- Failure to document manufacturing operations at the time they are performed (contemporaneously)
- Failure of the QU to review batch production records before the API is released/distributed
- Failure to maintain equipment in a state appropriate for its intended use (cleaning, maintenance, etc.)

Examples of API Deficiencies Cited by FDA on WLs (2014/2015)

- Disregard of OOS results, unofficial testing and trial injections, with no scientific justification
- Failure to document and investigate OOS results
- Inadequate investigations of critical deviations
- Failure to transfer all quality or regulatory information received from the API manufacturer to the customer

Examples of API Deficiencies Cited by FDA on WLs (2014/2015)

- Failure to have dedicated facilities for the manufacture/packaging of penicillin APIs
- Failure to prevent unauthorized access of changes to data and to provide adequate controls to prevent the omission of data
- Deny, Delay, Limit or Refuse an inspection

Acknowledgements

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