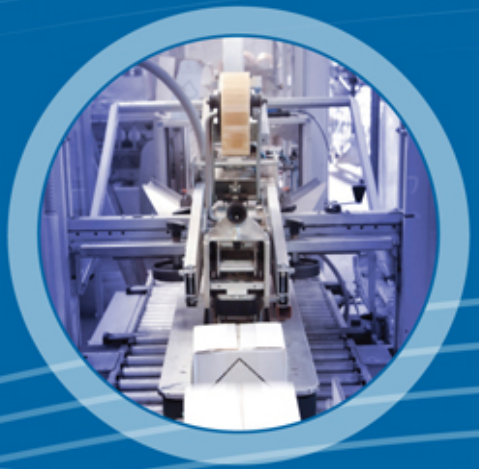
Connecting People, Science and Regulation®

Commonly Identified Non-Compliances Deficiencies Found at API Manufacturing Sites



PDA - PIC/S
ICH Q7 Training

Introductory remark

Disclaimer: the views expressed herein are those of the speaker, and should not be taken as made on behalf of the AEMPS or PIC/S.

Inspection is not validated...

- Results cannot be predicted (multiple uncontrolled inputs, uncertainty).
- Findings vary with inspection's scope, approach, carrying out of the inspection, inspectors' training or areas of particular expertise of the inspector…
- And of course also dependent on the inspected company level of compliance and quality-commitment, openness transparency…

Inspection approach

- Influence of factors attributable to the inspector- inspection process is reduced by the implementation/maintenance of a quality management system in the inspectorate:
  - Inspectors qualification and training (initial and continuous), including inspections (observer/observed).
  - Use of inspection checklists or Aide Memoires, templates for reports.
  - SOP for conducting inspections, review of inspector's performance and inspection results.
  - Joint inspections with other fellow inspectors (within the same authority and from different authorities).

Commonly indentified non compliances

Sources of information are inspections made by AEMPS inspectors, both nationally and abroad.

Selected based on frequency or by relevance/singularity.

Biotech / Sterile APIs not included.

Listed by sections of ICH Q7A:

- Quality Management
- Personnel
- Equipment,
- Premises.
- Documentation and Records.
- Materials management
- Validation and change control.
- Quality control
- Production
- Rejection, re-use and recovery.
- Warehousing, packaging, distribution

Quality Management

- Product Quality Review: not comprehensive, trending not performed, conclusions not supported by data.
- Inconsistencies in release procedures (paper/computerised systems)
- Inadequate qualification of persons authorized to release.
- Underreporting of deviations, quality incidents.
- Inadequate investigation (risk based) / invalid conclusions.
- Abuse of “human error” explanation.
- CAPAs: absence/incomplete evidence, inadequate follow up.
- Internal audits: independence, coverage, corrective action plan.

Personnel

- Qualification of personnel involved in the manufacturing of API or intermediates.
- Lack of training.
- Gowning level not proportionate to degree of product exposure and risks of contamination.

Building and facilities; equipment.

- Poor housekeeping and preventive maintenance: not performed or records absent, discrepancies with suppliers' manuals.
- Cleaning procedures, weak verification of cleaning e.g. by visual inspection (flashlight, mirror…).
- Equipment qualification: nor proportionate to production stage, lack of evidence/documentation, not all critical parameters tested.
- Water quality suitability for intended use.
- Qualification of utilities.
- Containment level/dedicated facilities.

5.21 “[...] Inspection of equipment for cleanliness immediately before use […]”

5.14 “[...] Wherever possible, food grade lubricants and oils should be used.”

Documentation and Records

- Information missing in batch production records: critical steps, deviations, critical process parameters.
- Activities not recorded at the moment that are performed.
- Amendment of data (hiding information, not signed or dated).
- Controlled documents: revision, formal approval of changes.
- Specifications not available for all materials which could impact quality (e.g. lubricants, gaskets, materials…).

Materials management

- Unsound definition of API starting material
- Evaluation of suppliers: manufacturers/suppliers identified, complete data (address), evidences.
- Examination upon reception.
- Cross-contamination in bulk deliveries in non-dedicated tankers: sampling and acceptance, cleaning records.
- Reduction of in-house testing without a valid justification.
- Clear labeling and status identification (IT system validation).
- Sampling procedure and strategy.
- Maintenance of containers stored outdoors.
- Re-evaluation of materials (retest/expiry)..

7.41 Stored off floor, suitably spaced for cleaning / inspection.
7.42 Storage conditions no adverse effect on quality, FEFO

7.20. Materials should be held under quarantine until they have been sampled,[…] and released for use.
7.35 […] be marked to indicate that a sample has been taken.

Validation and change control

- Validation Master Plan: scope, planning.
- Not all quality aspects subject to validation: e.g. holding times for intermediates.
- Risk based approach to validation: quality attributes, process knowledge.
- Changes not appropriately managed/controlled.
- Cleaning validation: strategy, sampling method.
- Computerised system validation.

Quality control

- Samples identification and tracking.
- Unsound OOS investigations, unjustified retesting.
- Availability of raw data.
- Integrity of electronic records.
- Records of review of analytical data.
- Sampling tools.

Production.

- Failure to record deviations.
- Sampling for in-process controls: procedures, records.
- Blending of batches: SOPs, validation, traceability and expiry date assignment.
- Criterion for inclusion of additional batches in stability studies.

Rejection, reprocessing, re-use of materials.

- Procedures for reprocessing /reworking and regulatory filings.
- Records of reprocessed batches (e.g. in PQR).
- Recovered solvents not appropriately controlled /tested.
- Management of returned materials.

Complaints and recalls

- Complaints investigations and records.
- Periodic revisions and trending of complaints.

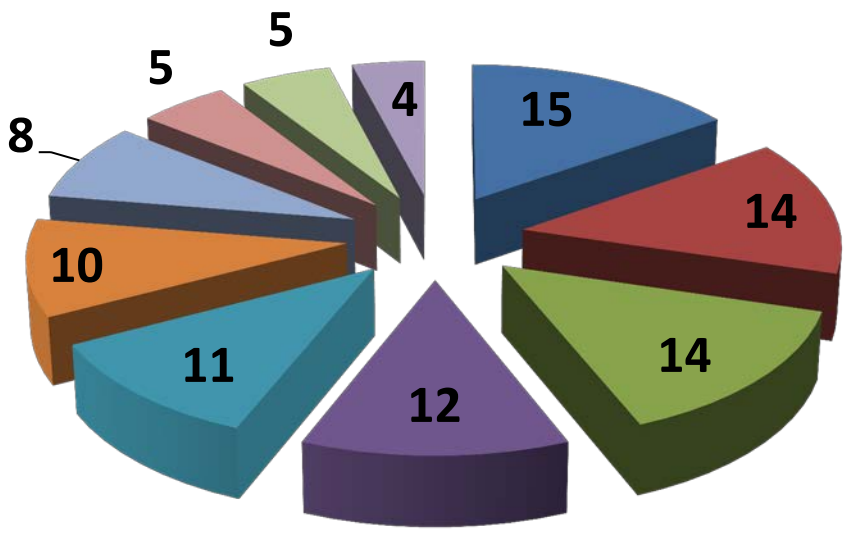
Packaging and labelling.

- Control of packaging materials.
- Control of printed labels. Destruction and reconciliation.
- Segregation of labelling operations.

Storage and distribution.

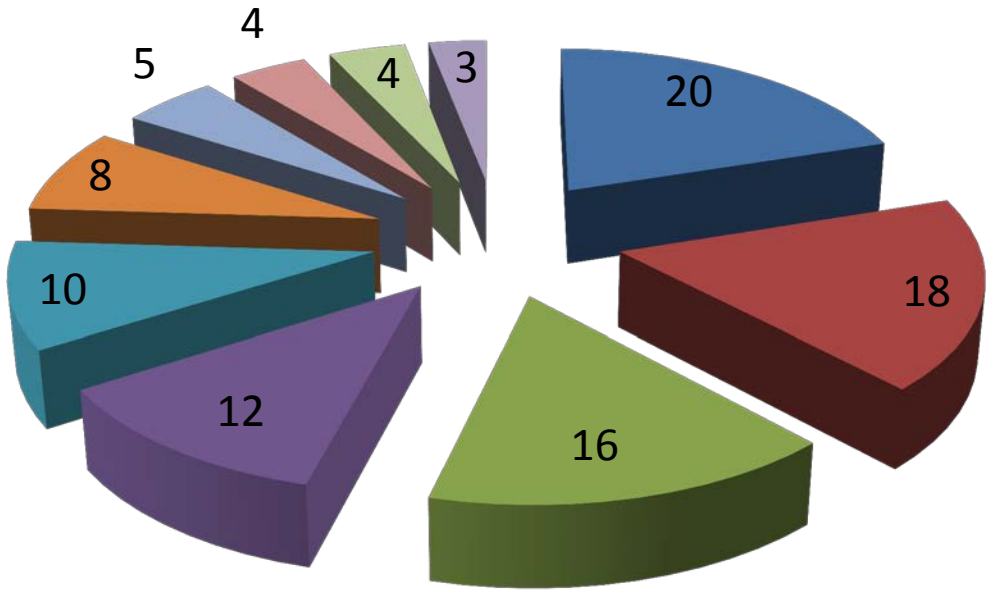
- Conditions for storage and during transport.

Frequent deficiencies (%): API National inspections 2010-2012



Quality Management, premises and equipment, documentation and materials management represent

Frequent deficiencies (%): International inspections 2010-2012



Quality Management, premises and equipment, documentation and materials management represent 76% of deficiencies.

Thank you