Safeguarding public health

Deficiency Data Review April to June 2012

Name Di Morris
Date December 2012

Relevant Inspections Performed:

= 58

Critical Observations:

= 4

Major Observations:

= 106

Top 10 Deficiency Categories:

1 Investigation of Anomalies

2 Supplier and Contractor Audit

3 Design & Maintenance of Equipment

4 Investigation of Anomalies – CAPA

5 Supplier & Contractor Audit

6 Line Clearance & Segregation

7 Design & Maintenance of Premises

8 Quality Management – Change Control

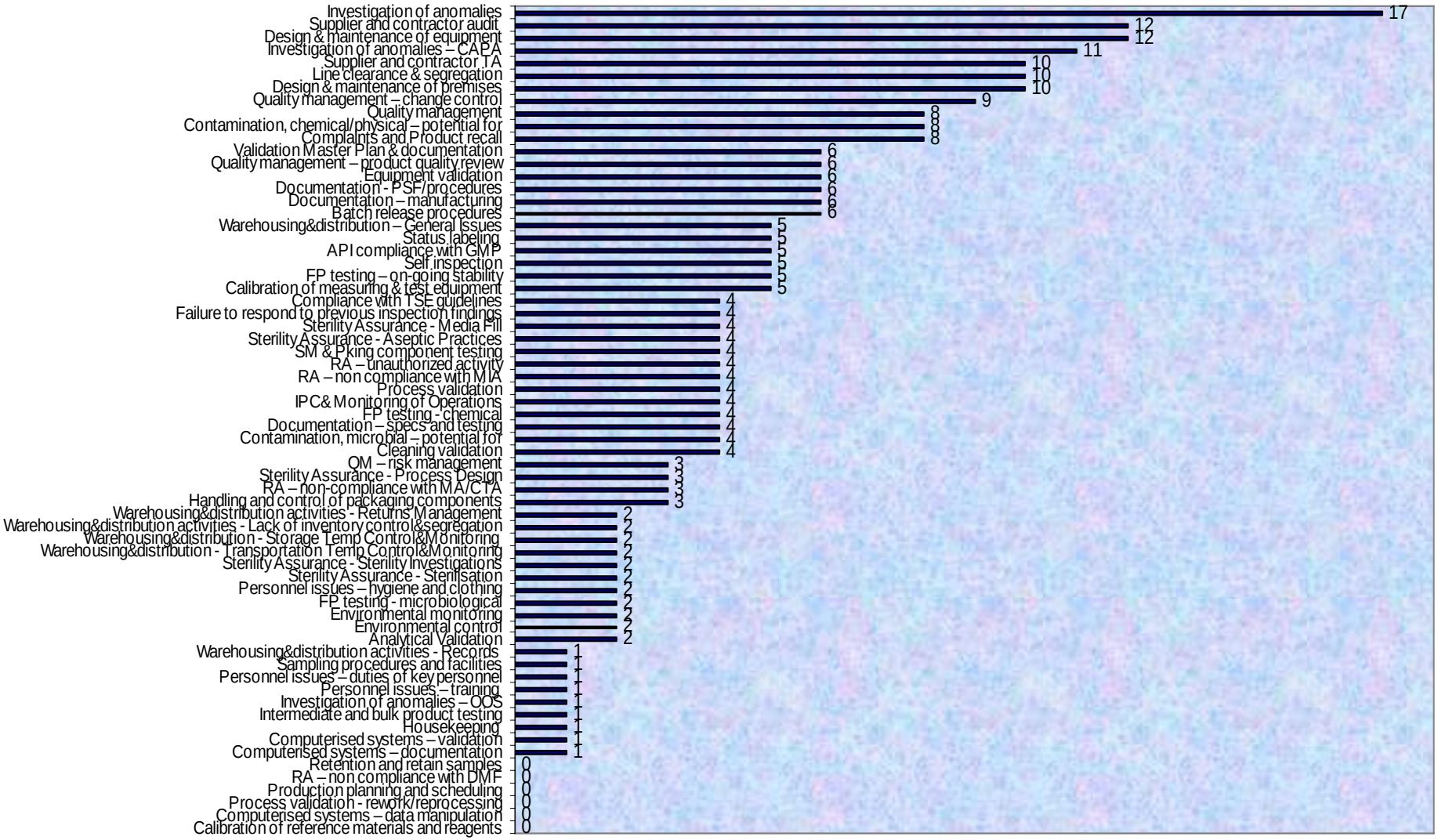
9 Quality Management

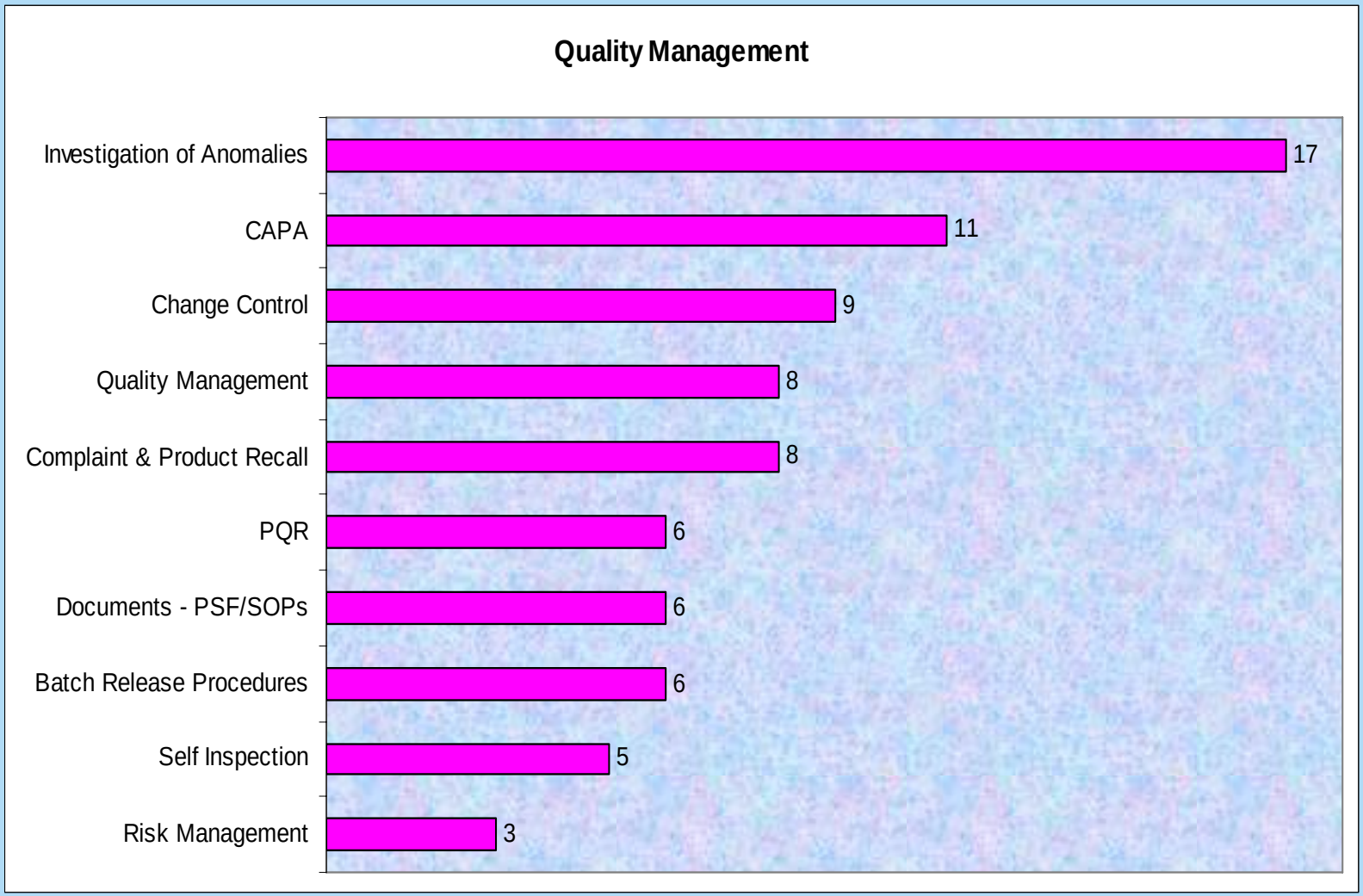
10 Contamination, Chemical/Physical – Potential For

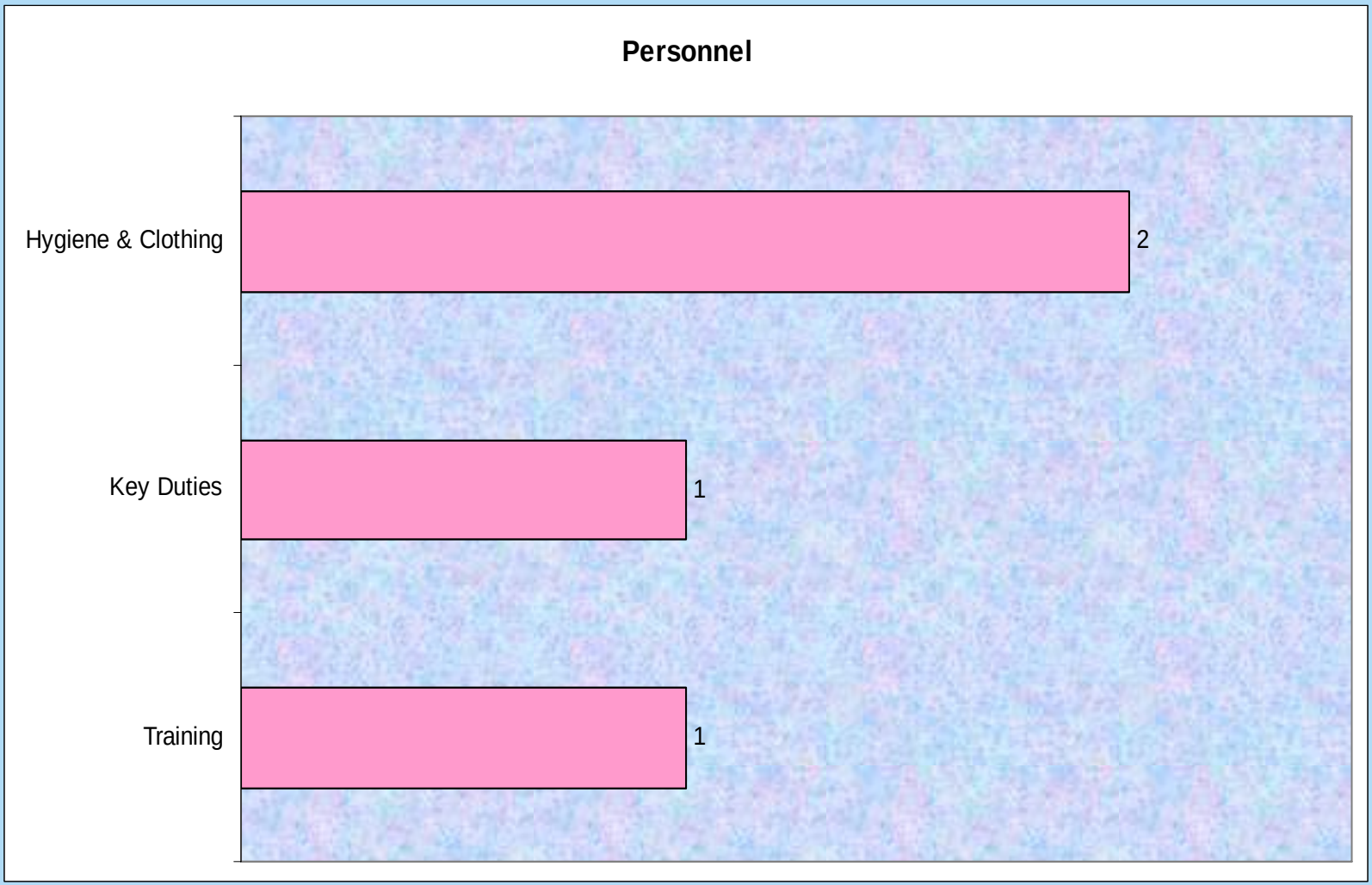
Safeguarding public health

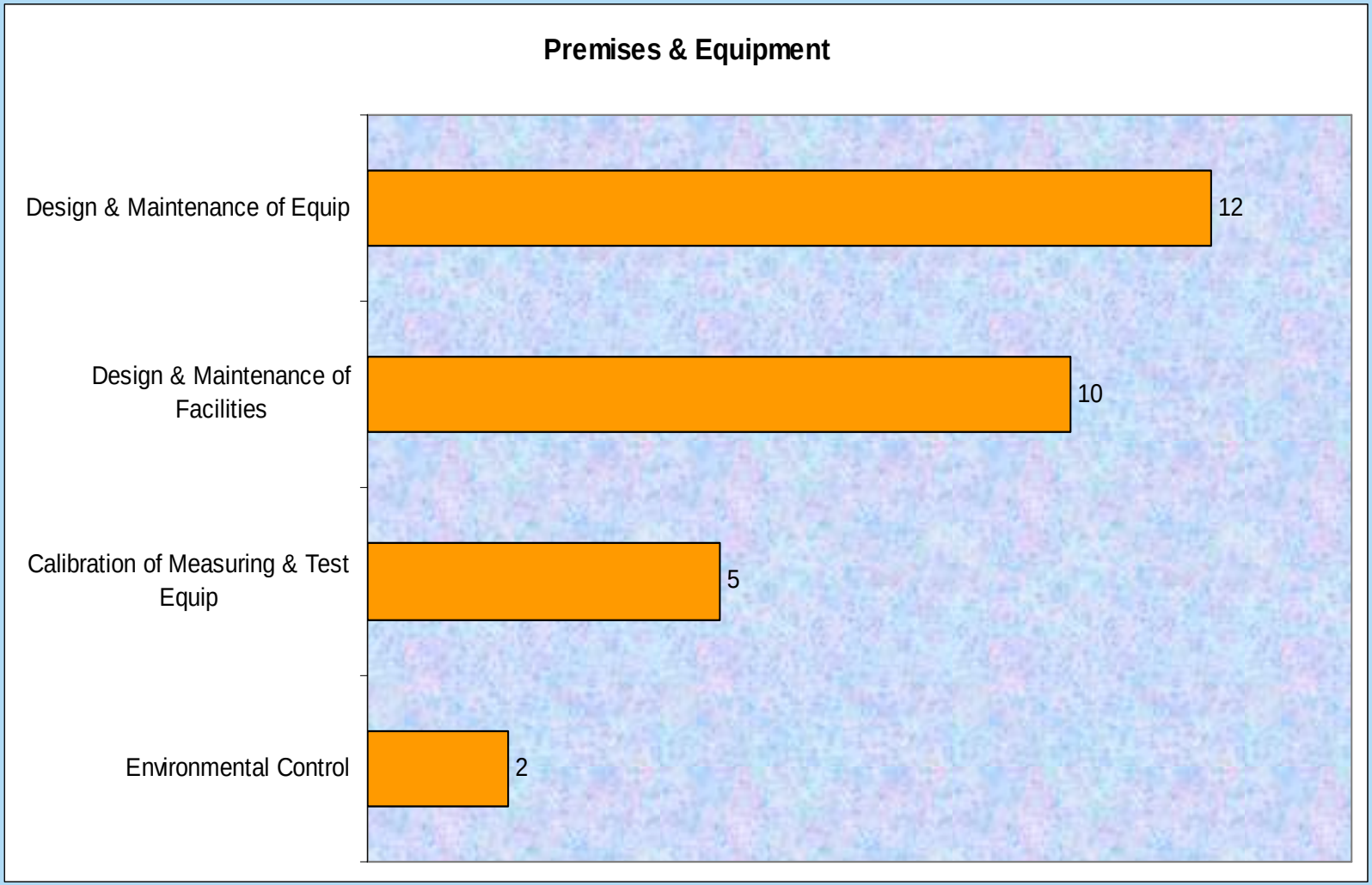
Batch Release	Sterility assurance	Finished product testing – chemical
Complaint and Product Recall	Contamination, chemical/physical – potential	Calibration of reference materials / reagentsCleaning validation
Quality Management	Documentation – manufacturing	Supplier and contractor audit
Quality management – risk management	Production Planning and Scheduling	Compliance with TSE guidelines
Investigation of anomalies – CAPA	Contamination , microbial – potential for	Warehousing and distribution activities
Quality management – change control	Line clearance, segregation and potential for mix-up	Starting material – API compliance with GMP
Documentation- quality systems elements	Housekeeping – cleanliness and tidiness	Supplier and contractor technical agreements
Investigation of anomalies	Handling and control of packing components	Validation master plan and documentation
Self inspection	Environmental monitoring	Equipment Validation
Quality management – product quality review	Status labelling – work in progress, facilities, equipment	Computerised Systems - documentation
Personnel issues – duties of key personnel	Sampling procedures and facilities	Computerised systems – validation
Personnel issues – hygiene and clothing	Sampling procedures & facilities – retention & retain samples	Process validation
Personnel issues – training	Documentation – specifications and testing	Analytical Validation
Design and maintenance of premises	Starting material & packaging component testing	Cleaning validation
Design and maintenance of equipment	Computerised systems – data manipulation	Failure to respond to previous findings
Environmental control	Finished product testing – on-going stability	Regulatory issues – non compliance with MIA
Calibration of measuring and test equipment	Intermediate and bulk product testing	Regulatory issues – non-compliance MA/CTA
In-process control and monitoring of production operations	Finished product testing – microbiological	Regulatory issues – unauthorized activity

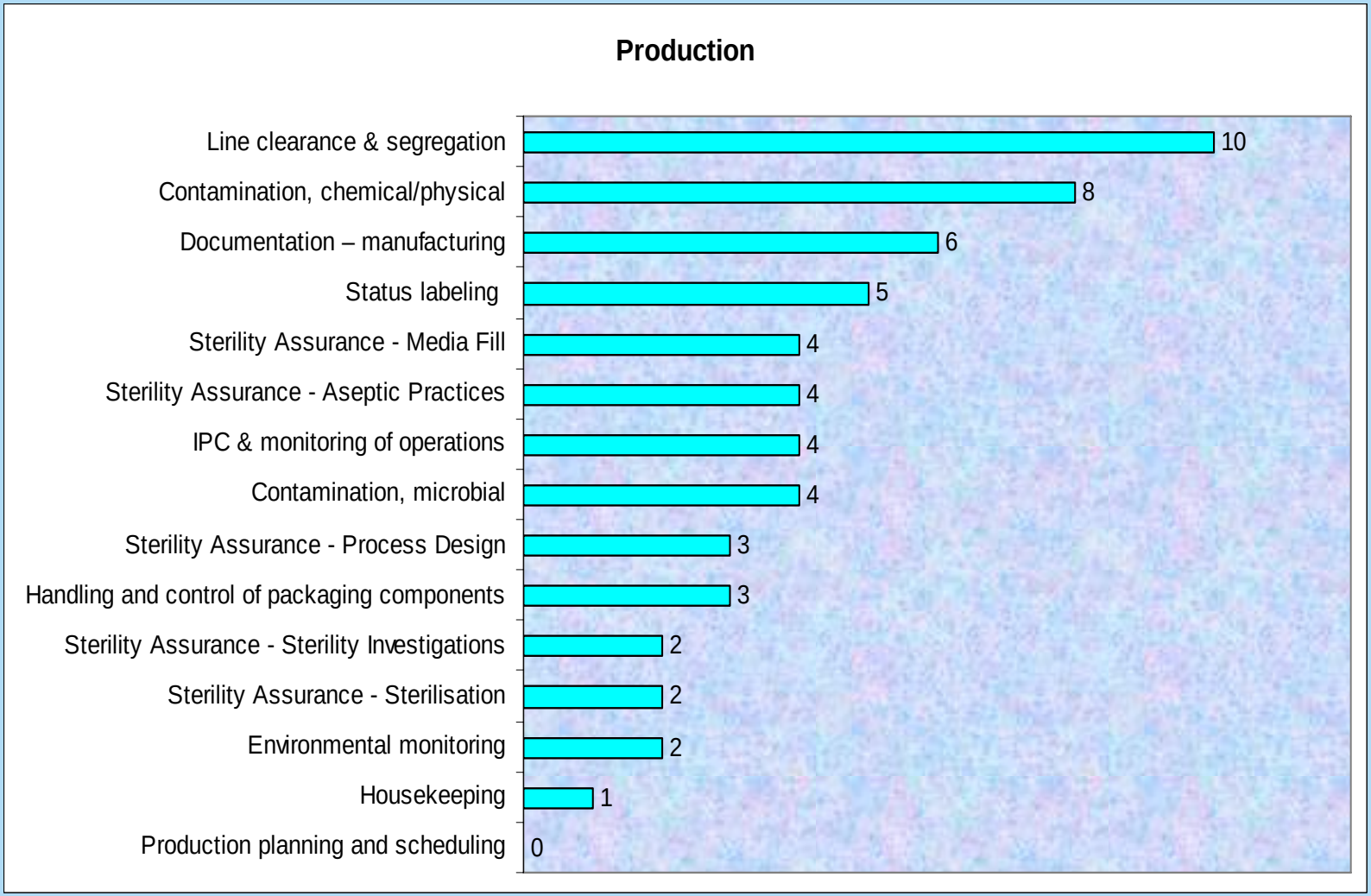
All deficiencies

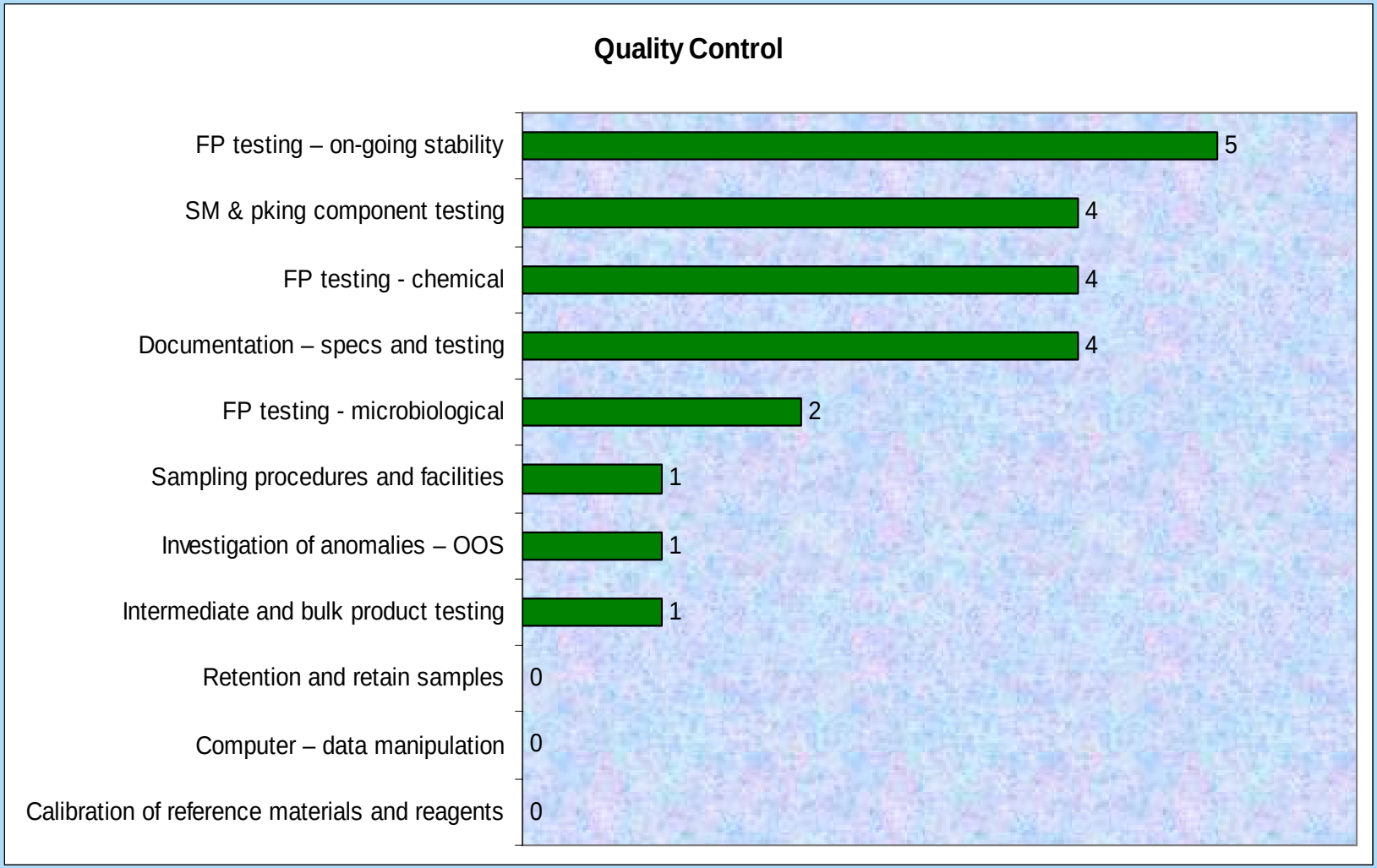


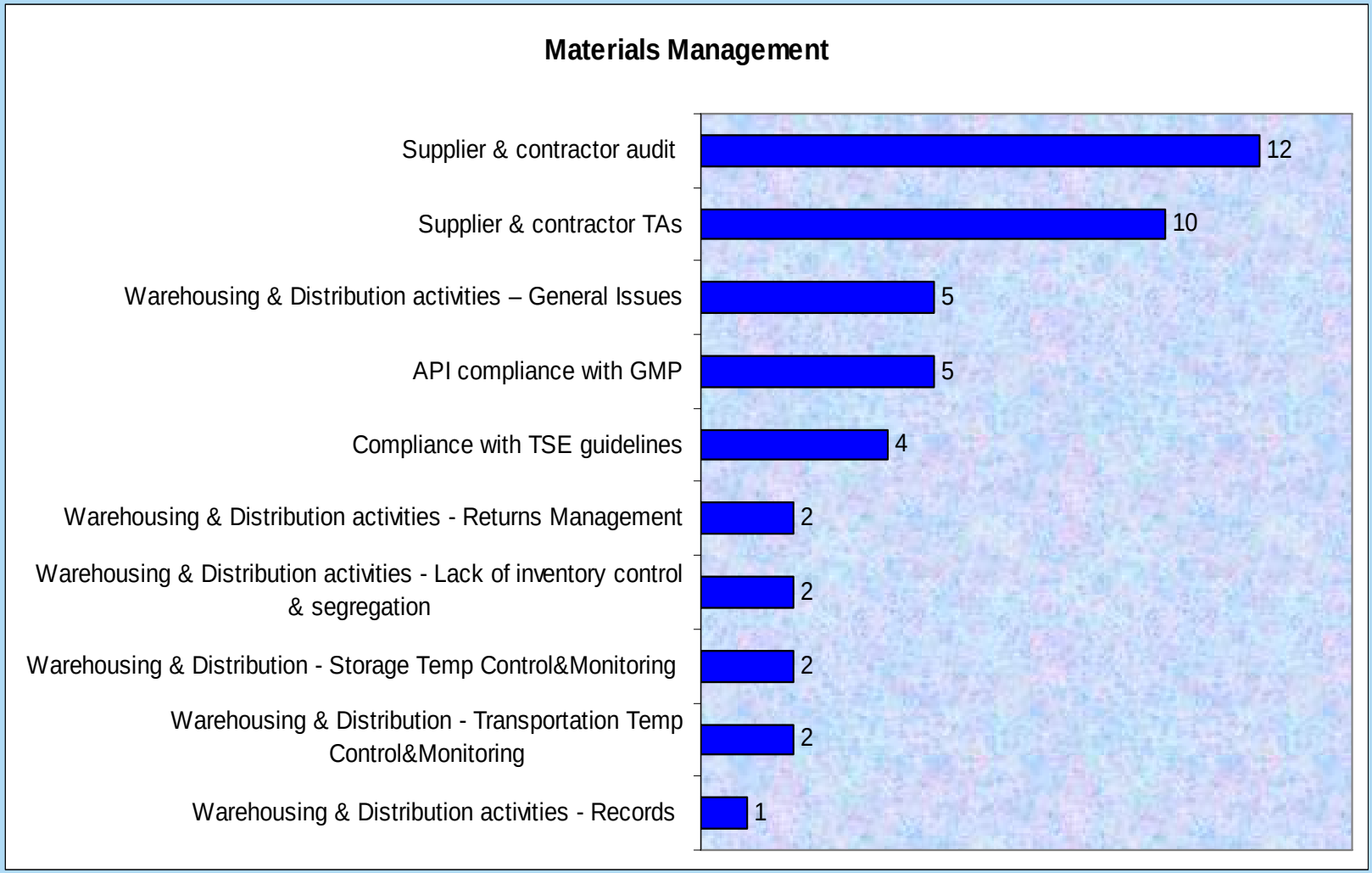

Quality Management
Investigation of Anomalies
17
CAPA
11
Change Control
9
Quality Management
8
Complaint & Product Recall
8
PQR
6
Documents - PSF/SOPs
6
Batch Release Procedures
6
Self Inspection
5
Risk Management
3

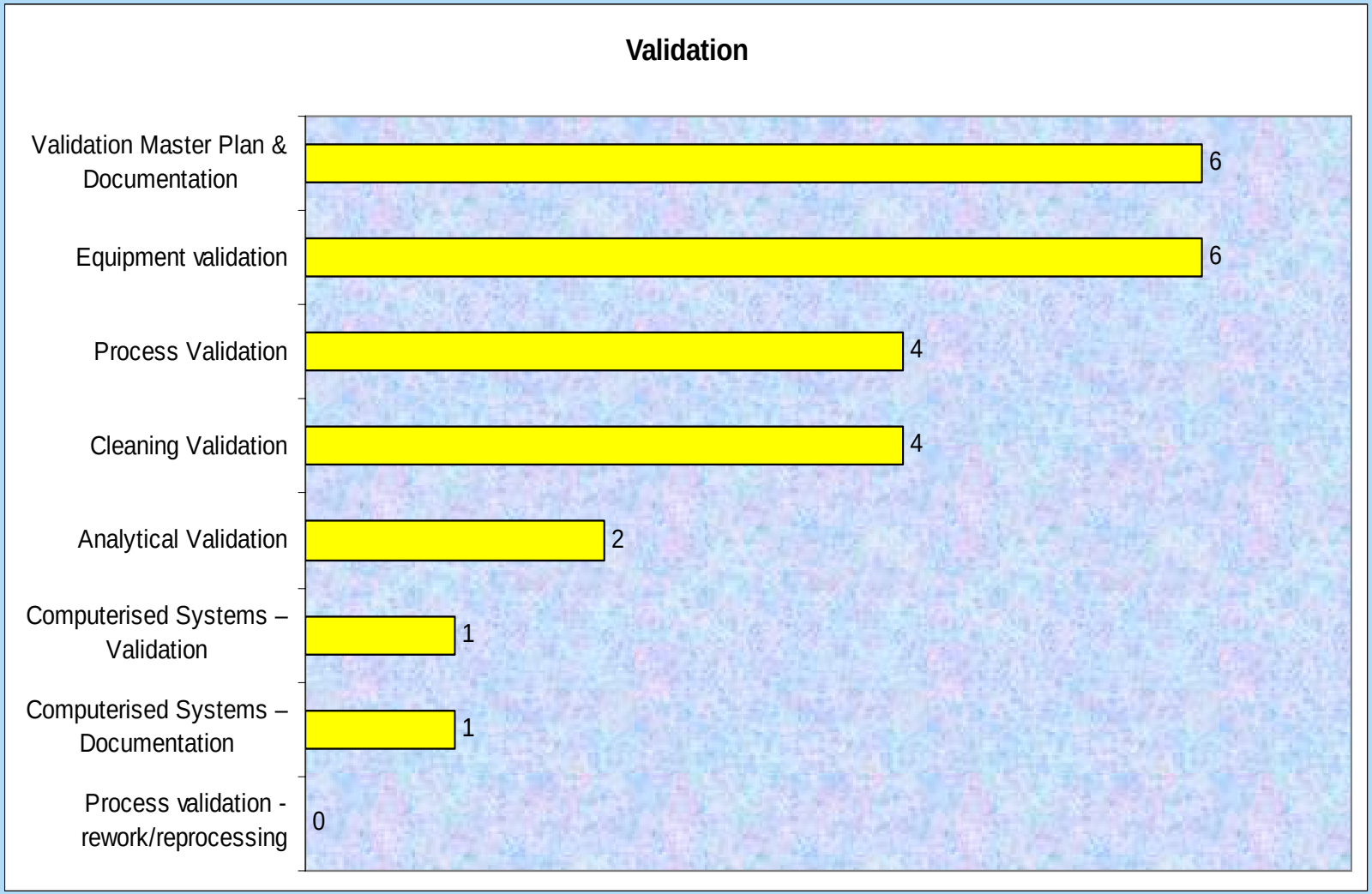

Personnel
Hygiene & Clothing
2
Key Duties
1
Training
1


Premises & Equipment
Design & Maintenance of Equip
12
Design & Maintenance of Facilities
10
Calibration of Measuring & Test Equip
5
Environmental Control
2


Production
Line clearance & segregation
10
Contamination, chemical/physical
8
Documentation – manufacturing
6
Status labeling
5
Sterility Assurance - Media Fill
4
Sterility Assurance - Aseptic Practices
4
IPC & monitoring of operations
4
Contamination, microbial
4
Sterility Assurance - Process Design
3
Handling and control of packaging components
3
Sterility Assurance - Sterility Investigations
2
Sterility Assurance - Sterilisation
2
Environmental monitoring
2
Housekeeping
1
Production planning and scheduling
0


Quality Control
FP testing – on-going stability
5
SM & pking component testing
4
FP testing - chemical
4
Documentation – specs and testing
4
FP testing - microbiological
2
Sampling procedures and facilities
1
Investigation of anomalies – OOS
1
Intermediate and bulk product testing
1
Retention and retain samples
0
Computer – data manipulation
0
Calibration of reference materials and reagents
0


Materials Management
Supplier & contractor audit
12
Supplier & contractor TAs
10
Warehousing & Distribution activities – General Issues
5
API compliance with GMP
5
Compliance with TSE guidelines
4
Warehousing & Distribution activities - Returns Management
2
Warehousing & Distribution activities - Lack of inventory control & segregation
2
Warehousing & Distribution - Storage Temp Control&Monitoring
2
Warehousing & Distribution - Transportation Temp Control&Monitoring
2
Warehousing & Distribution activities - Records
1


Validation
Validation Master Plan & Documentation
6
Equipment validation
6
Process Validation
4
Cleaning Validation
4
Analytical Validation
2
Computerised Systems – Validation
1
Computerised Systems – Documentation
1
Process validation - rework/reprocessing
0


Regulatory Compliance
Failure to complete previous inspection findings
4
RA - unauthorized activity
4
RA – non compliance with MIA
4
RA – non-compliance with MA/CTA
3
RA – non compliance with DMF
0

INSPECTION FINDINGS – Top 5 Categories

Top 5 Deficiency Categories: Example Findings

1 Investigation of Anomalies

2 Supplier and Contractor Audit

3 Design & Maintenance of Equipment

4 Investigation of Anomalies – CAPA

5 Supplier & Contractor Audit

INSPECTION FINDINGS – Top 5 Categories 1 - Investigation of Anomalies

Continuing to be the number 1 deficiency

Examples:

Deviations were lacking in details:-

- Investigation X was in July 2011, however QA did not approve until 12/04/12. No deviation was raised to investigate this failure of the deviation system.
- Investigation Y did not contain evidence to demonstrate that the tooling continued to meet the original tooling specification post modification.

- The investigation did not formally consider the impact on batches made since the rogue tablet was known to be on the packing line.
- No batches were placed on hold pending the outcome of the investigation.
- The deviation was signed off with the statement that the risk to the previous batches was unknown.
- The risk assessment documented was very brief and did not consider the previously packed batches.
- The batch was released on the 8/06/11 despite the deviation being open at that time and the risk assessment not being completed until the 30/06/11.

INSPECTION FINDINGS – Top 5 Categories 1 - Investigation of Anomalies

- Incident Investigation Report Foreign Matter in ABC was lacking in a number of areas:-
  - It was not possible to piece together the events or any accompanying risk evaluation which may have taken place.
  - There was no clear rationale for batch certification.
  - The rationale for bracketing and the inclusion of additional batches was not defined.
  - There was no impact assessment on lots previously certified.
  - The contract manufacturer's investigation was not referred to or detailed.
  - There was no root cause and no preventative actions detailed.
  - There was an inappropriate statement regarding release of the lot, 'A risk assessment will be performed by QA prior to release and distribution'.

INSPECTION FINDINGS – Top 5 Categories

2 - Supplier and Contractor Audit

- The Finished Product had been certified and placed onto the market despite the company documenting that the API had not been manufactured in accordance with EU GMP.
- Vendor Assurance was inadequate in that:-
    - There was no risk assessment in place to support the continued use of the API manufacturers that had not been audited. It was noted that the company had a plan in place to complete the outstanding audits by mid 2013.
    - Deliveries had continued to be receipted from a broker with an unapproved status. It was not clear how purchasing had been able to order stock from a company with an unapproved status.
    - The audit report for XYZ who supply the API was deficient in that:-
        - There was no response to the deficiency or target date for completion.
        - Actions from the audit were not tracked.
        - There was no formal assessment as to the status of the supplier following the audit.
- A number of companies were listed as category A suppliers on the ASL dated 30/9/11 which had not yet been audited, despite being a requirement of the company's SOPs.

INSPECTION FINDINGS – Top 5 Categories 3 - Design & Maintenance of Equipment

Air handling unit:-

- The drain line was broken and the calibration certificates on the equipment to measure the pressure drops over the filters had worn blank.
- The instrument to measure pressure drop over the HEPA filter for Air handling unit, supplying air to the manufacturing area, had not been calibrated since November 2010.
- The equipment is not detailed in the Critical instruments Master list.

- Filling line components such as pumps, filling needles and associated tubing were not cleaned and changed between batches of the same product to reduce the possibility of contamination. It was noted that, as some filling lines are product dedicated the change frequency of such product contact components was driven solely by component failure.

- The water delivery pipe to the filtration systems was not free draining and could be left full over a weekend – the impact of this was not known.

INSPECTION FINDINGS – Top 5 Categories 4 - Corrective action/preventive action (CAPA)

The management of Corrective and Preventative Actions was weak as evidenced by:

- SOP x requires senior management to review repeat CAPA but there was no mechanism to detect or report these.
- The CAPA SOP was due for review on 12/03/12 but this had not occurred.
- Not all CAPA had been entered into the database. This is not in accordance with the SOP.
- There are still a large number of CAPA overdue.
- No CAPA had been generated to retrain the staff following a poor cleaning incident.
- The setting sheet action had been marked as being complete on 20/4/11 on the form; however the setting sheet did not appear to be updated until 12/5/11.
- The CAPA was due in September 2011 but it was not on the CAPA database and had not been done.
- The CAPA actions had been completed, but the date of completing the actions entered on to the database was incorrect.
- The CAPA in response to the rogue investigation of May 2011 did not demonstrate a sustained high performance of line clearance activities.

INSPECTION FINDINGS – Top 5 Categories 5 – Supplier & Contractor Technical Agreements

- There was no technical agreement with Company X to confirm they would inform site of any recalls on stock supplied.
- There was no written agreement in relation to product recall for those companies from which unlicensed products were imported.

- The importation of product was deficient in that:-
  - There was no technical agreement with X who manufacture, test and perform the initial release of product into the EEA.
  - Full testing is not carried out on the product upon re-entry to the EEA.
  - Sampling was not detailed in the Technical Agreement.