Safeguarding public health

Deficiency Data Review April 2010 to March 2011

Name Di Morris
Date August 2011

Relevant Inspections Performed:

= 353

Critical Observations:

= 23

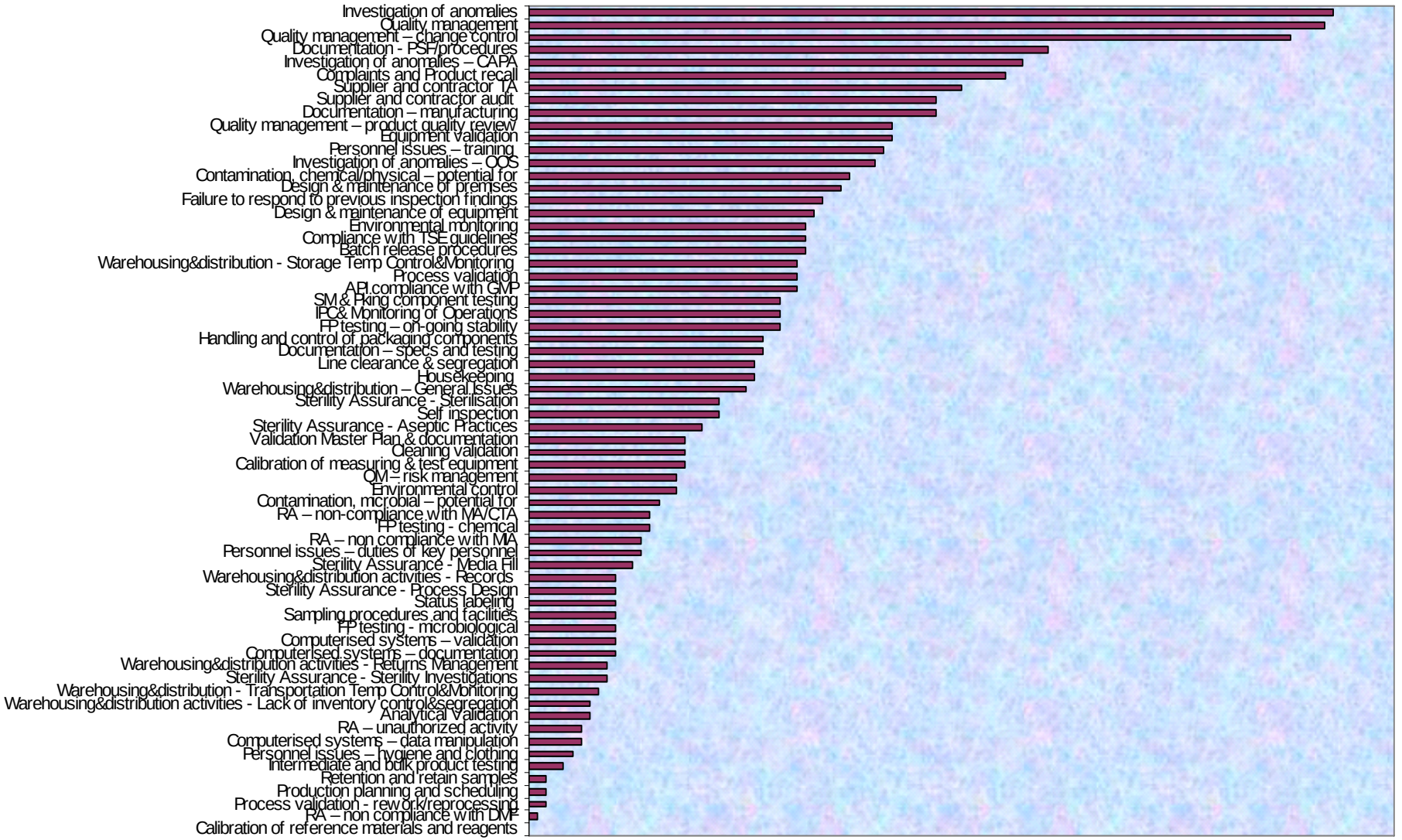
Major Observations:

= 749

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

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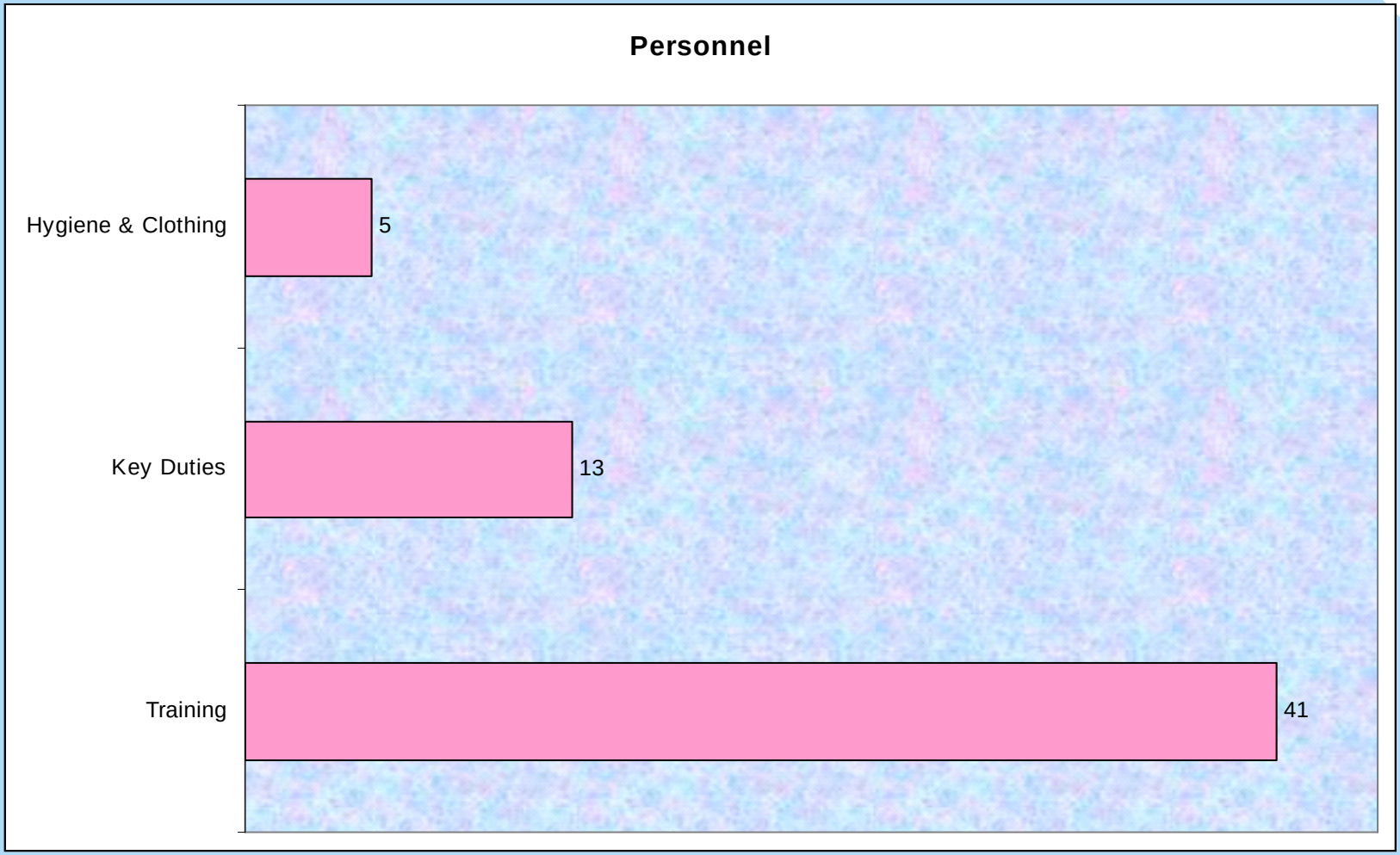
Personnel
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5
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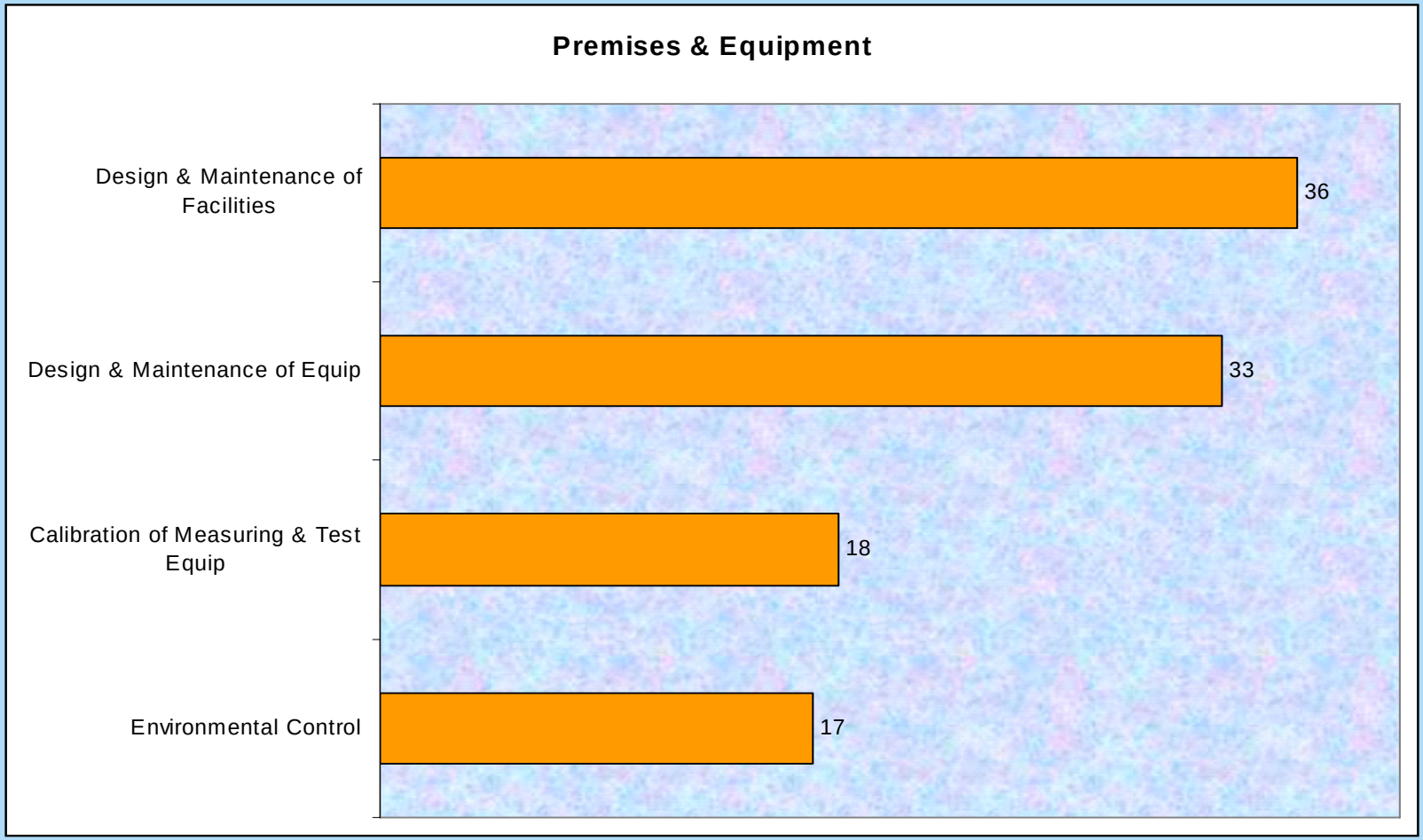
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Design & Maintenance of Facilities
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Design & Maintenance of Equip
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Calibration of Measuring & Test Equip
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Environmental Control
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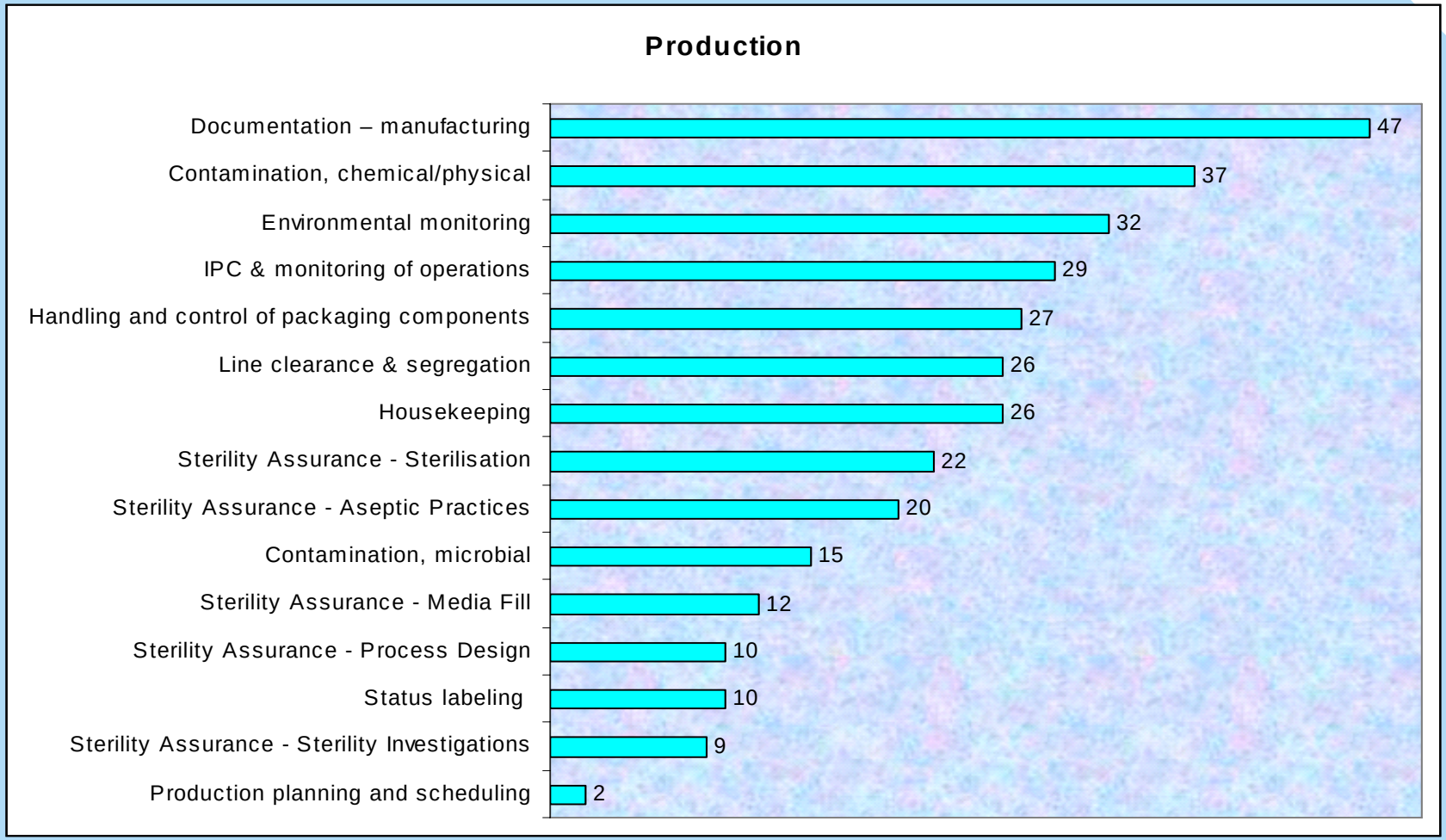
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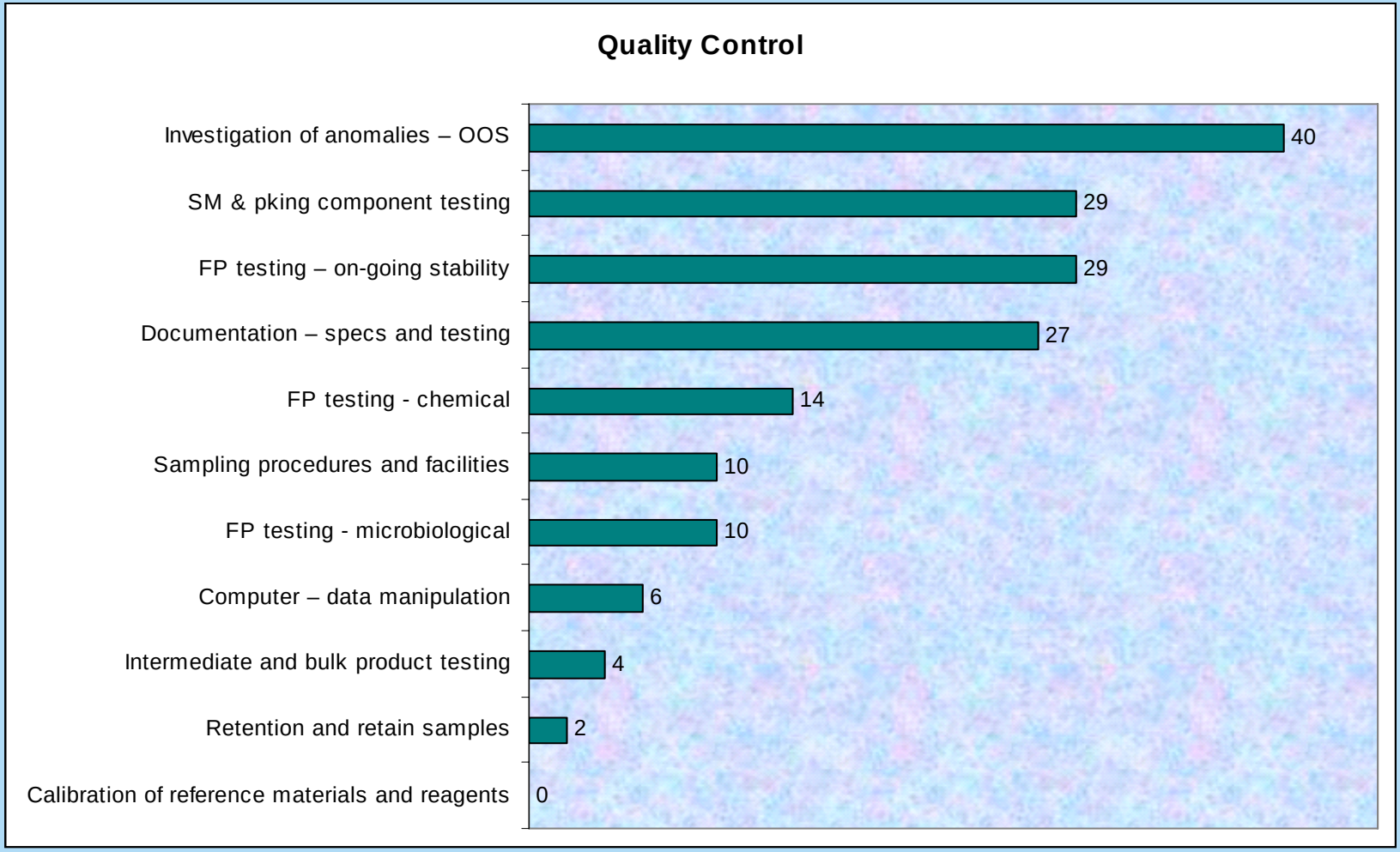
2


Quality Control
Investigation of anomalies – OOS
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Warehousing & Distribution - Transportation Temp Control&Monitoring
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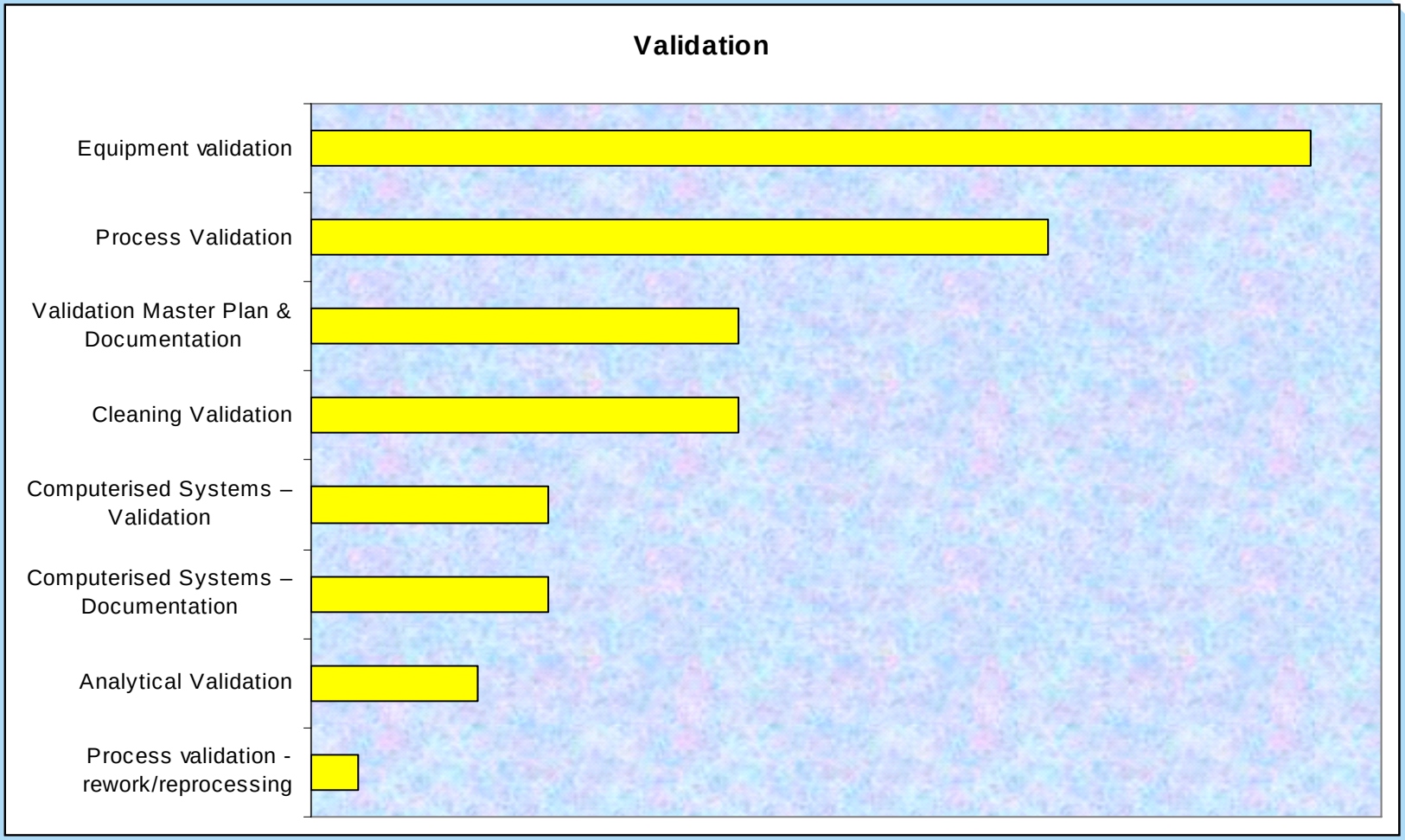
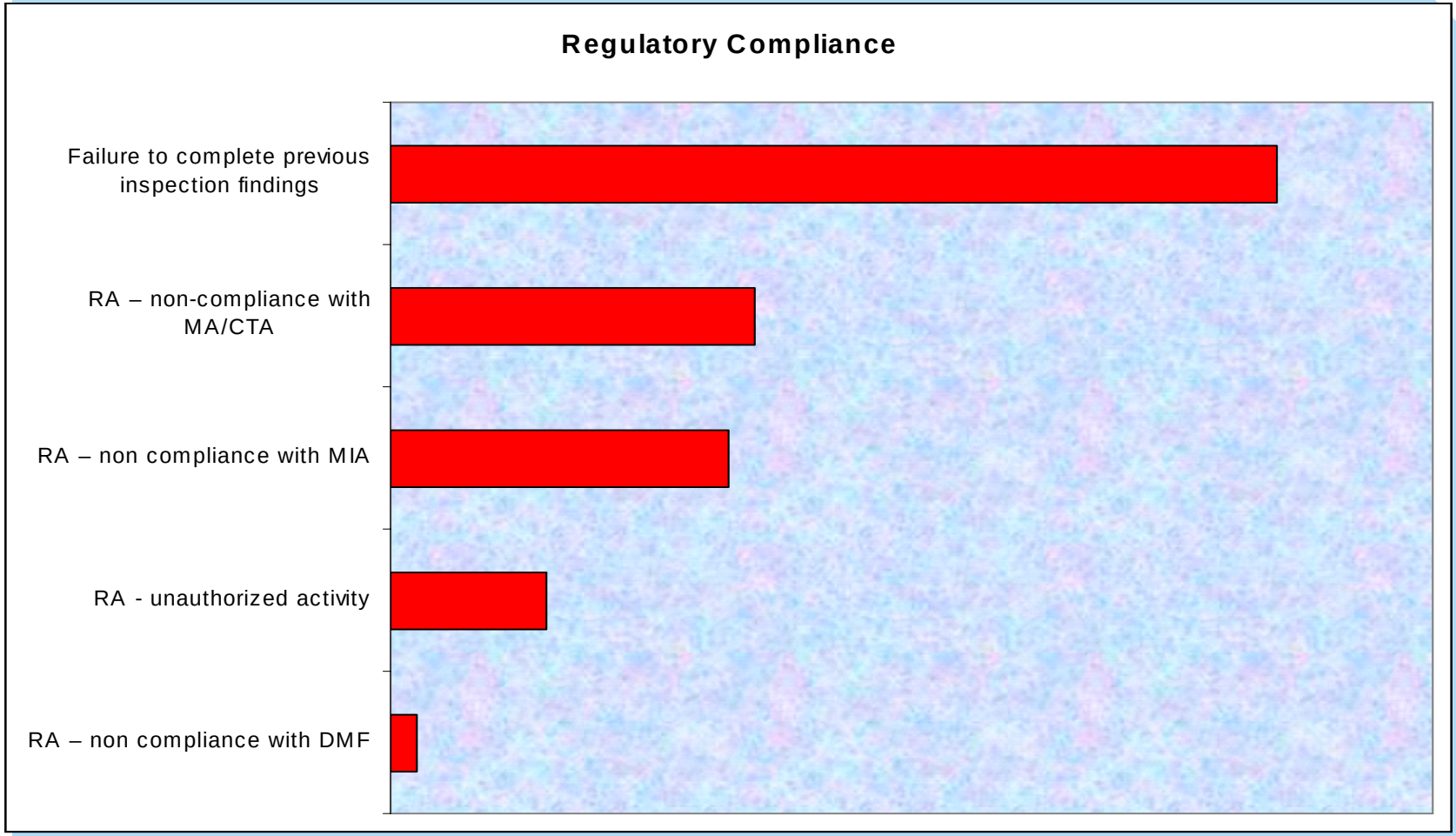

Validation
Equipment validation
Process Validation
Validation Master Plan & Documentation
Cleaning Validation
Computerised Systems – Validation
Computerised Systems – Documentation
Analytical Validation
Process validation - rework/reprocessing


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

INSPECTION FINDINGS – Top 10 Categories

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1. Investigation of anomalies
2. Quality management
3. Quality management (Change Control)
4. Documentation – PSF and Procedures
5. Corrective action/preventive action (CAPA)

INSPECTION FINDINGS – Top 10 Categories

6. Complaints and Product Recall
7. Supplier and Contractor Technical Agreement
8. Supplier and Contractor Audit
9. Documentation – Manufacturing
10. Quality Management – Product Quality Review

1 Investigation of Anomalies

Number 1 in 2008-2009 top five and number 1 in 2009_2010 and 2010_2011

Examples:

There had been no deviations raised to formally investigate and record the impact on product identified as having been exposed to -5C temperature in one of the recent ambient temperature shipping studies for product from EEA.

A significant number of deviations had been recorded for errors in the packing record and label generation processes yet there was no recognition of this trend and as a result there had been no concerted root cause analysis and corrective/preventative action identified.

Overall the investigation reports into deviations and OOS did not follow a logical process and lacked detailed in the documentation of all the actions and justifications taken during the investigation.

1 Investigation of Anomalies

The investigation into the rejection of batches did not examine the reasons why the supplier admitted having to recalibrate equipment and other errors that occurred during analysis. Good practice would have been to perform an immediate audit of the facility to ensure the laboratory was under control.

The control of non conformance investigations was weak in that:
The Quality Event Reporting (QER) procedure lacked detail.
A number of QER investigations did not robustly address the root cause;
They were not raised in a timely manner; CAPA was not tracked to completion.

There was no specified period to complete incident reports to ensure that issues were resolved to an appropriate timescale.
A significant number of deviations were open for extensive periods. The inspector noted that since January 2009, 457 deviations were open including a number that stretched back over 6 months.

1 Investigation of Anomalies

Numerous deviations were identified relating to OOS low and high results . The manner in which these investigations and subsequent CAPAs were handled was deficient in that:

The investigations were not progressed in a timely manner.

There was no definitive root cause identified.

Numerous batches had been produced which had been released after partial rejection of the batches in question on customer request e.g. from middle to end of lot due to an end low result. There was no scientific rationale or justification documented for such an approach and it was not clear how the middle of the batch was determined.

The significance of the results and the possibility that the process was no longer in control was not taken into consideration.

2 Quality Management (systemic issues across all systems) examples:

Not in 2008-2009 top five and number 2 in 2009-2010 and 2010_2011

The quality of investigations performed was not of the required standard to consistently identify the root cause of the issue and suitable corrective and preventative actions, including a robust assessment of the impact of the findings on other batches or systems.

Investigation of complaints, rejects, deviations and out of specification data was unsatisfactory. The quality of investigations performed was not to the required standard to consistently identify the root cause of the issue and suitable corrective and preventive actions, including a repost assessment of the findings and other batches or systems.

2 Quality Management (systemic issues across all systems) examples:

The control of the Quality Management system was deficient in that:

Risk assessment and categorisation were weak with the lowest impact risk appearing to be selected for every investigation.
The change control system was not used despite a number of significant changes having taken place e.g. new fridge and new isolator.

The control of documentation was weak as demonstrated by the use of Ditto marks, pencil and missing information.
Procedures did not reference other relevant procedures
There was no requirement to perform periodic test of the recall system

2 Quality Management (systemic issues across all systems) examples:

The control of the Quality Management system was deficient in that: cont'

The PQR report did not review all of the items detailed in the procedure e.g. Technical Agreements and equipment validation status.

Training records had not been completed for the new starter (March 08) until 2009.
The training reassessment for domestic staff had not been performed in a timely manner with the assessment for January 2010 still being overdue.

There was still no procedure to cover the scheduling and performance of self inspection. The informal schedule shown to the inspector could not be used to demonstrate any schedule, with apparently scheduled inspections not performed or moved with no clear justification.

3 Investigation of Anomalies – CAPA

Number 3 in 2008-2009 top five and number 3 in 2009-2010 number 5 2010_2011

Investigations often lacked detail and adequate consideration of related issues, for example:

Investigation X lacked adequate justification for invalidation of the original corrective action, and lacked consideration of training issues identified by subsequent investigations.

Investigation X did not adequately detail the events involved in a cleaning sampling failure, and did not sufficiently support the assumption that the sample was invalid.

Out of Trend into a cleaning conductivity sample failure, did not lead to a full investigation into the CIP process even though it was decided to re-run the CIP cycle.

3 Investigation of Anomalies – CAPA

Investigations often lacked detail and adequate consideration of related issues, for example: cont'

> Investigations X and Y were not completed in a timely manner, contained inadequate consideration of the microbial risk of contamination presented by the incident, and a lacked of consideration of the re-occurring nature of this issue (it had occurred three times in close succession).

Recurrent issues were not effectively captured, tracked or trended. CAPA where included was not effectively prioritised to ensure a future compliant operation.

The investigations for a number of quality systems (QIRS, Complaints, OOS) were reviewed and they were not sufficiently detailed, they did not consider the full impacts and as a result did not include appropriate corrective and preventive actions. No clear instructions on root cause analysis were included in any of the associated procedures.

3 Investigation of Anomalies – CAPA

Non-conformance x failure of the positive displacement pump on IWKA filling line did not adequately describe the nature of the issue or corrective action to be taken.

- There was no reference to the failure in the batch record.
- No assessment was made of the overall risk to the batch and there was no rationale for the subsequent destruction of Pallet 20 only.
- The Qualified Person was not made aware of the incident.

There was no defined system for monitoring the effectiveness of the Quality Management System including the closeout of identified actions for example there was no trending performed on complaints.

Investigation for complaints and incidents did not consistently identify root cause and hence corrective and preventative actions designed to minimise the probability of reoccurrence. For the reviewed empty blister complaint it was noted that the current procedure did not include details of the required checks after engineering set up.

4 Quality Management – Change Control

Number 2 in 2008-2009 top five and number 4 in 2009-2010 and number 3 2010_2011

Provisions for the management of Change are insufficiently robust as exampled by:

- No change control was raised for the replacement of the X vacuum pump
- No change control was raised for the replacement of the X generator and the temporary provisions for sanitisation were not defined in a deviation.
- Change Control is not used as part of the Artwork revision procedure, refer to other issues identified during the inspection.

4 Quality Management – Change Control

Change Control xx for the change of material from X to Y did not include a detailed list of required actions before authorisation to use in commercial batches.

- There was no statistical comparison between the two raw materials or the finished product produced by each.
- Product X was manufactured and released to European markets before documented verification that there was no regulatory impact had been received.
- There was no data or justification to support the decision not to revalidate the process following the change.

Although a commitment was made to include more documentation within the change control for those reviewed insufficient documentation have been included were approved as being satisfactory.
No change control was raised to assess the impact on product on sourcing 300 ml X bottles from new supplier.

4 Quality Management – Change Control

The process for implementing change controls was not clear.
The change controls reviewed did not consider all aspects of the impact of the change for example X agreed to the reconstitution end of shelf life stability study but no consideration had been given to the number of samples and whether the existing study would have enough samples left to complete it.
There did not appear to be a final approval step after approval to implement the change had been given.

5 Documentation – PSF & SOPs

Number 5 in 2008-2009 top five and number 5 in 2009-2010 and number 4 2010_2011

Approved procedures and documents were not available for the following activities:

- Operation, control and cleaning of isolators
- Operation, control and cleaning of compounding and repeater pumps
- Equipment, room and cleaning logs
- Sterility testing requirements
- Stability testing requirements
- Specifications, methods and worksheets for routine analytical testing
- Out of Specification results and laboratory investigations
- Batch records
- Customer returns
- Critical instrument list and calibration schedule
- Procedure for introduction of new products and processes
- Self inspection procedure and plan.

5 Documentation – PSF & SOPs

Whilst stage omissions within batch records had been recorded through the deviation procedure, there was insufficient additional data available within the record to demonstrate a compliant process.

The prioritisation of batch record changes was not effectively managed
There was no effective system to account for superseded copies of procedures
Unapproved documentation was observed within GMP areas.

The site did not have access to key documents such as the clinical trials authorisation and ethics committee approval to ensure that the relevant conditions were satisfied
There was no assessment of compliance with the CTA during certification
The methods employed to capture changes in the CTA and ECA were not robust.

5 Documentation – PSF & SOPs

Document control and completion was weak in the following respects:
Uncontrolled instructions were noted (including but not limited to) on the feeder in Aerosol suite,
The Injection configuration on the Agilent and inconsistent instructions to not use some of the control buttons on some of the Agilents.
A number of forms were uncontrolled including temperature chart log book and all equipment log books.
The Temperature chart log book reviewed gave comment that the incorrect charts had been used when the company management indicated that this was not the case.
Inappropriate documentation practices such as overwriting, use of post it notes, non permanent pen and use of ditto marks were noted.

5 Documentation – PSF & SOPs

The reviewed procedures consistently failed to describe the steps required to perform an operation in sufficient detail both as instruction for established staff and as a training aid for new staff. There was no evidence that such discrepancies were being reported by users.

The procedure for the batch release of inspected tablets did not reflect the stated practice as described by the company including the relevant QA checks on documentation and checks on the inspection process. The label applied to denote release was not consistent with the production label in terms of processing stage. The batch documentation is not designed to follow the chronological processing order and therefore presents the risk of non compliance with the required sequence and steps. For example the check on overprint correctness on cartons precedes the line clearance of the packaging line.

Complaints and Recalls

The recall records for Capsules, 20mgs from July 2009 were inadequate in that:
The file did not contain a list of all affected customers supplied with the product to allow full reconciliation. This was required by the SOP (X).
There was no notification letter in the file indicating the reason for the recall or which organisation or company had requested this.
The returns forms used indicated that the lots were 'Back to location' *i.e.* returned to stock. It is noted that the company provided evidence that the affected batches had been returned to the manufacturer.
The form used to notify the customer of the recall was an uncontrolled version of a previous form used for recalls.

Complaints and Recalls

The investigation conducted for recall of Y injection was completed prior to documented review of the response received from the API manufacturer which challenged the proposed root cause of the initial investigation.

The impact of the recall on future supply was not documented.

The failure to conduct an audit at the API manufacturer based on apparent refusal by the API site had not changed the status of the supplier on the approved vendor system or the status of the Batch Manufacturing Record naming material from this supplier.

Investigation into the Z recall had failed to consider variables such as shipment conditions and testing methods as part of the investigation.

The complaint investigation concerning sodium benzoate content of oral suspension proposed non homogeneity as a possible cause of the issue. However, there was no consideration as to the impact of this hypothesis on the assay results obtained for other batches supplied.

Supplier and contractor audit

The postal audit questionnaire did not consider materials of animal origin
No process to ensure notification from suppliers of changes to their site /process that might affect the purchased product.
There was no process in place for periodic review of the TSE certificates to ensure they were still current.
The procedure did not specify API audits would take place and who was responsible.
There was no approved supplier list.
Repeat issues where identified with starting materials on receipt (damaged bags of sodium chloride) but not corrected and associated documentation was not complete.

Supplier and contractor audit

There is a backlog of audits against the required frequency in procedure 010D. It was accepted that for API that this was not directly impacting products for European supply but, given the commonality of equipment utilised in the factory, consideration of secondary risks should be evaluated and built into the plan.

Brokers or agents are not currently included as part of the plan.

There is no process for confirming with site Quality Assurance that the required audit programme has occurred and the issuance of an immediate confirmation if significant issues are observed.

The procedure for site audit does not include a review of previous supplier performance as appropriate.

Supplier and contractor audit

The supplier approval procedure differentiates the requirement for audit based on geographical location - this is not an acceptable GMP position. Checks performed by warehouse and sampling staff do not confirm the correct site of manufacture of the starting material. The subsequent release process does not confirm correctness of manufacture and site.

The approved vendor list was found to contain erroneous (Head Office?) addresses as opposed to the required site of manufacture.

There were numerous examples where material descriptions for a given material on controlled documentation were not consistent between documents. In addition, the use of material or item codes was not consistent on both documentation and labels.

Supplier and contractor audit

There was no listing of Transmissible Spongiform Encephalopathy (TSE) certificates available to warehouse staff at the time of the inspection as required in the TSE procedure.

The absence of a confirmation of a check on TSE certificate had not prevented batch release for dispatch.
The use of an Excel spreadsheet for pre-dispensing material checks is not included as part of the procedure.

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