Safeguarding public health

Deficiency Data Review April 2011 to March 2012

Name Di Morris
Date April 2012

Relevant Inspections Performed:

= 303

Critical Observations:

= 26

Major Observations:

= 644

Top 10 Deficiency Categories:

1 Investigation of Anomalies

2 Quality Management – Change Control

3 Investigation of Anomalies – CAPA

4 Complaints and Product Recall

5 Quality Management

6 Supplier and Contractor Audit

7 Contamination, Chemical/Physical – Potential For

8 Documentation - PSF/Procedures/Technical Agreements

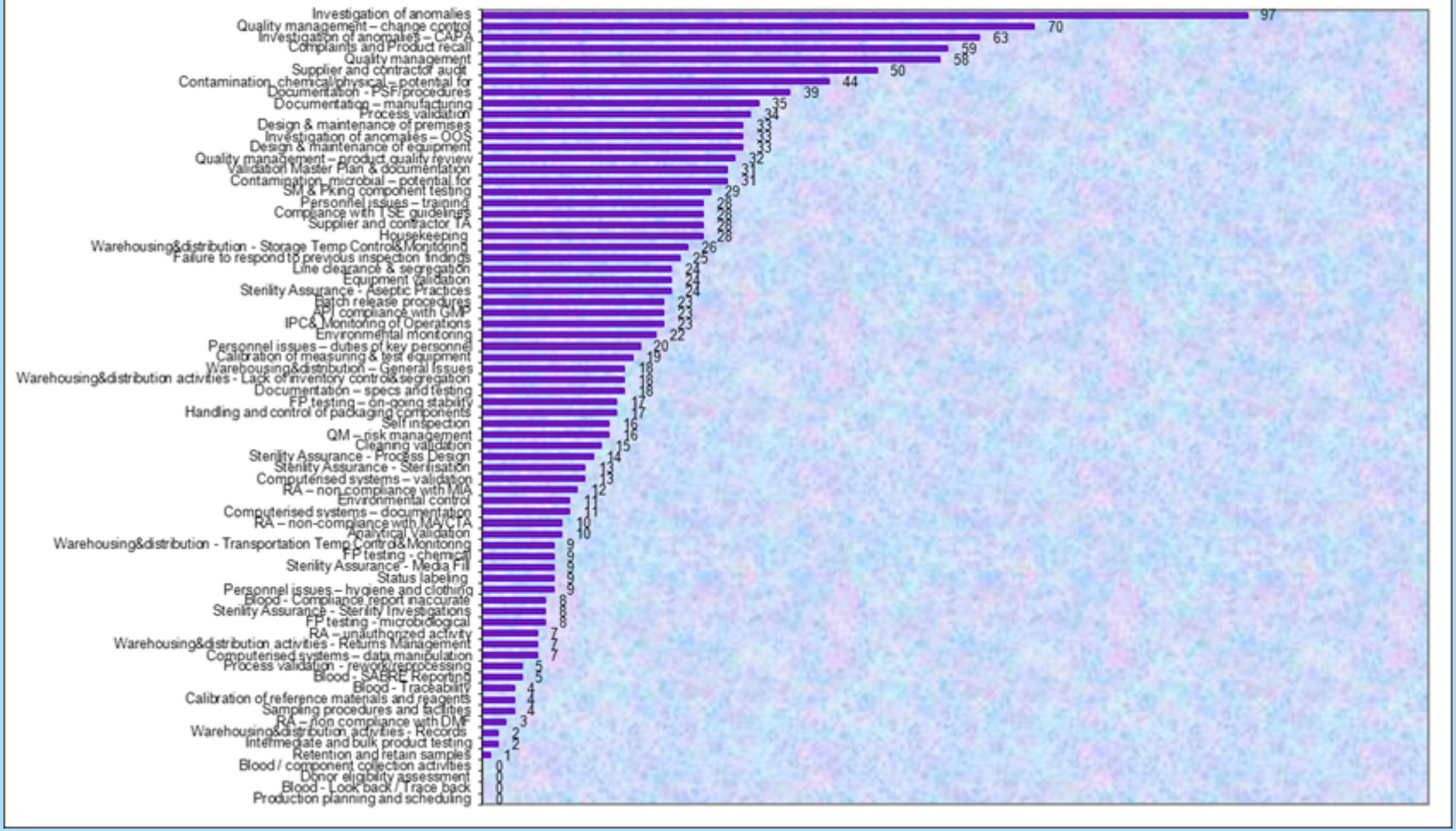
9 Documentation – Manufacturing

10 Process Validation

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 Categories




Quality Management
Investigation of Anomalies
97
Change Control
70
CAPA
63
Complaint & Product Recall
59
Quality Management
58
Documents - PSF/SOPs/Tas
39
PQR
32
Batch Release Procedures
23
Self Inspection
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Risk Management
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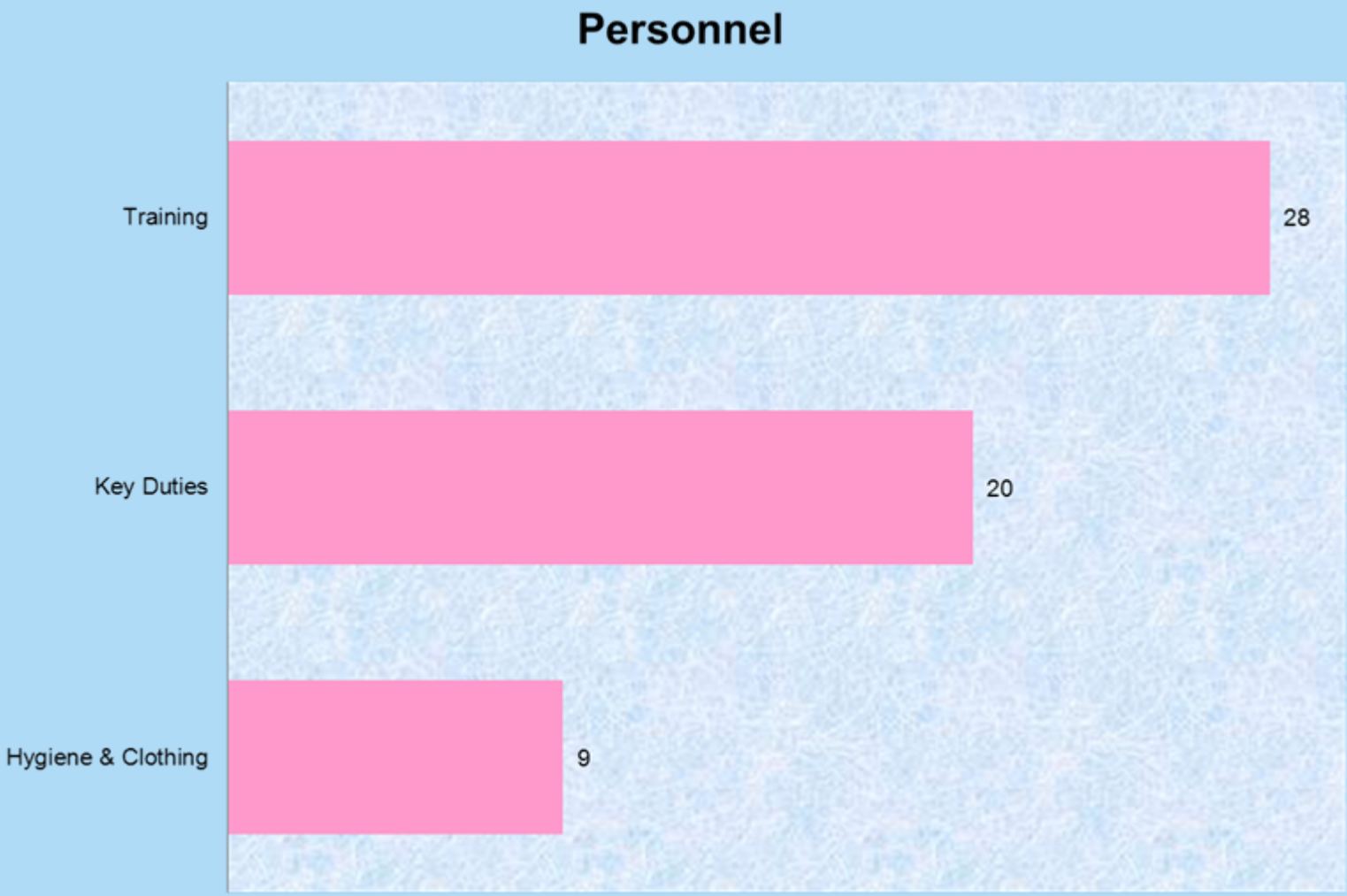
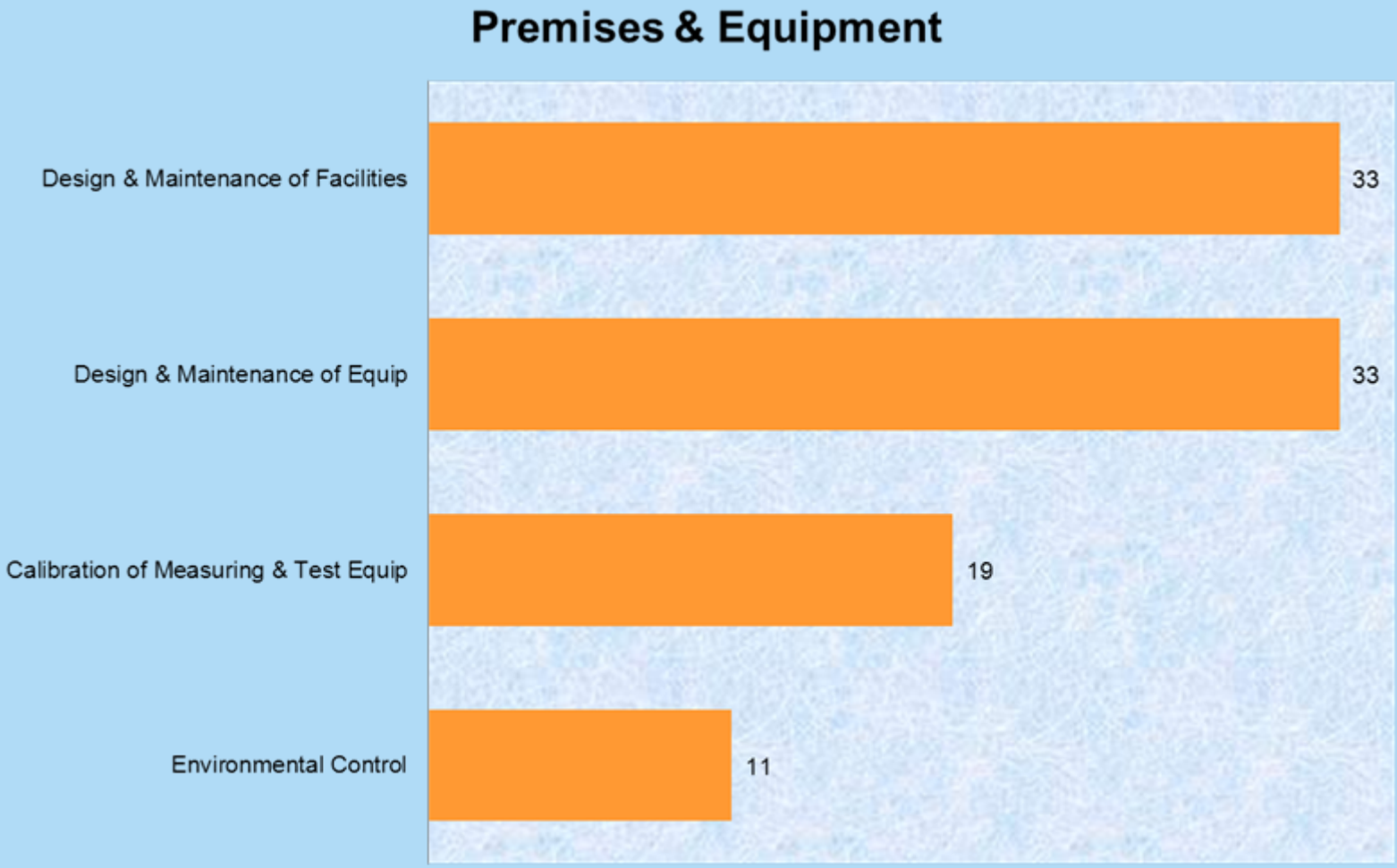
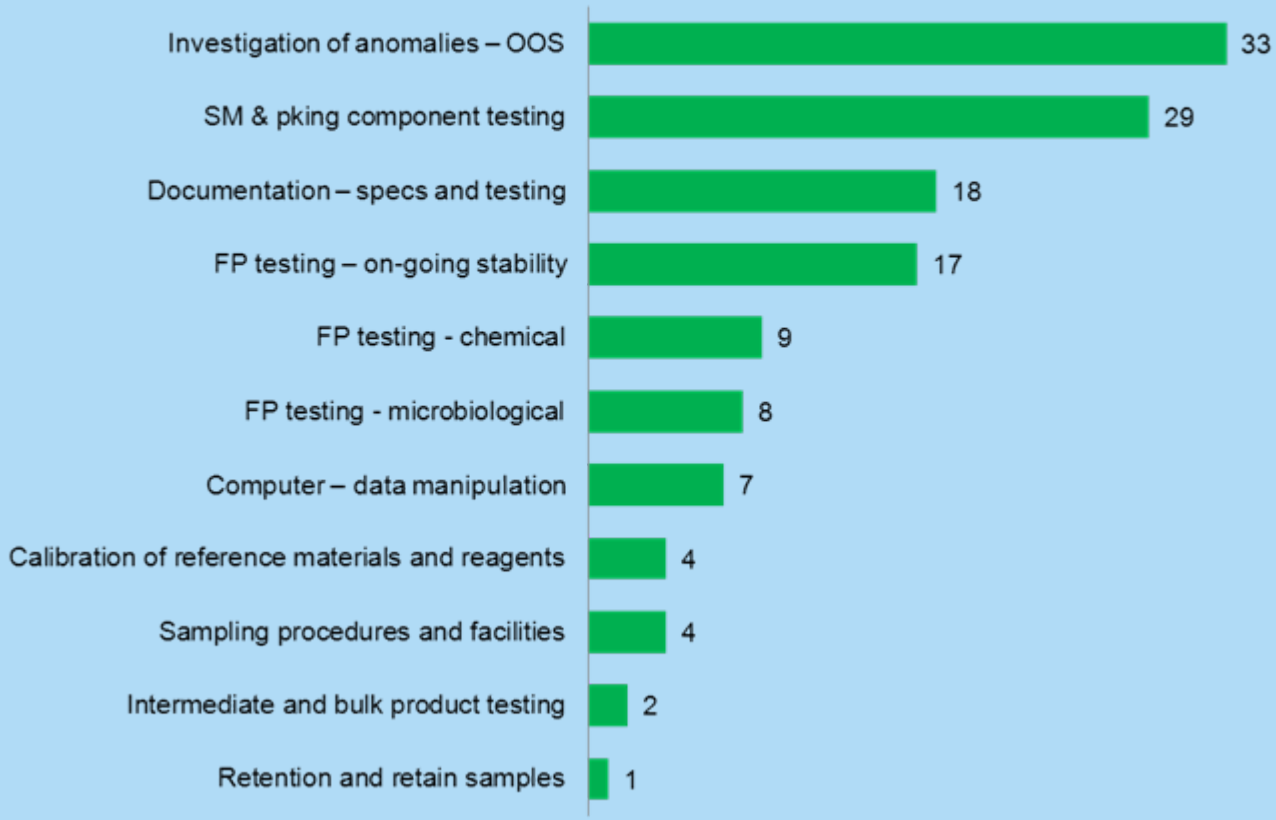

Personnel
Training
28
Key Duties
20
Hygiene & Clothing
9

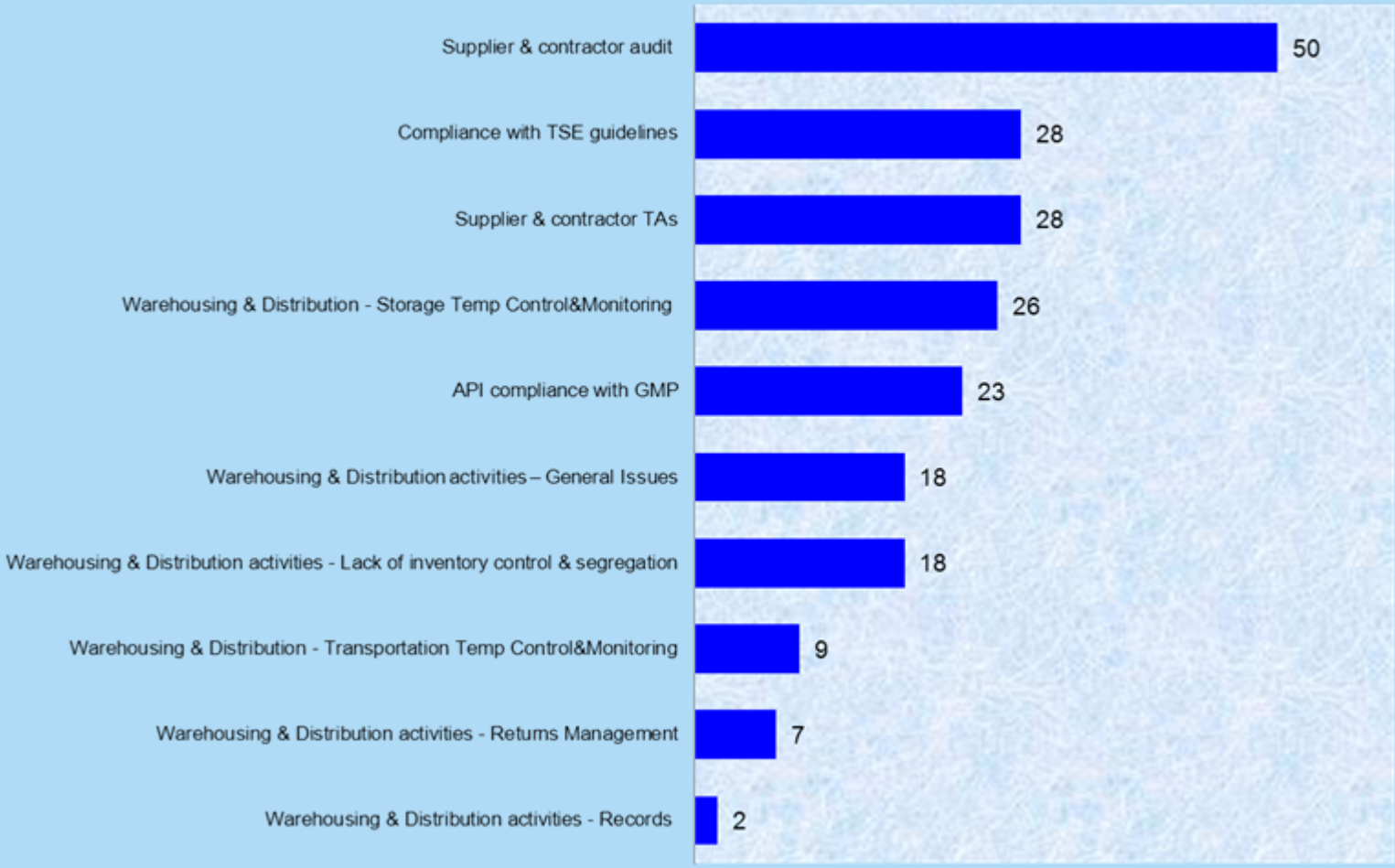

Premises & Equipment
Design & Maintenance of Facilities
33
Design & Maintenance of Equip
33
Calibration of Measuring & Test Equip
19
Environmental Control
11

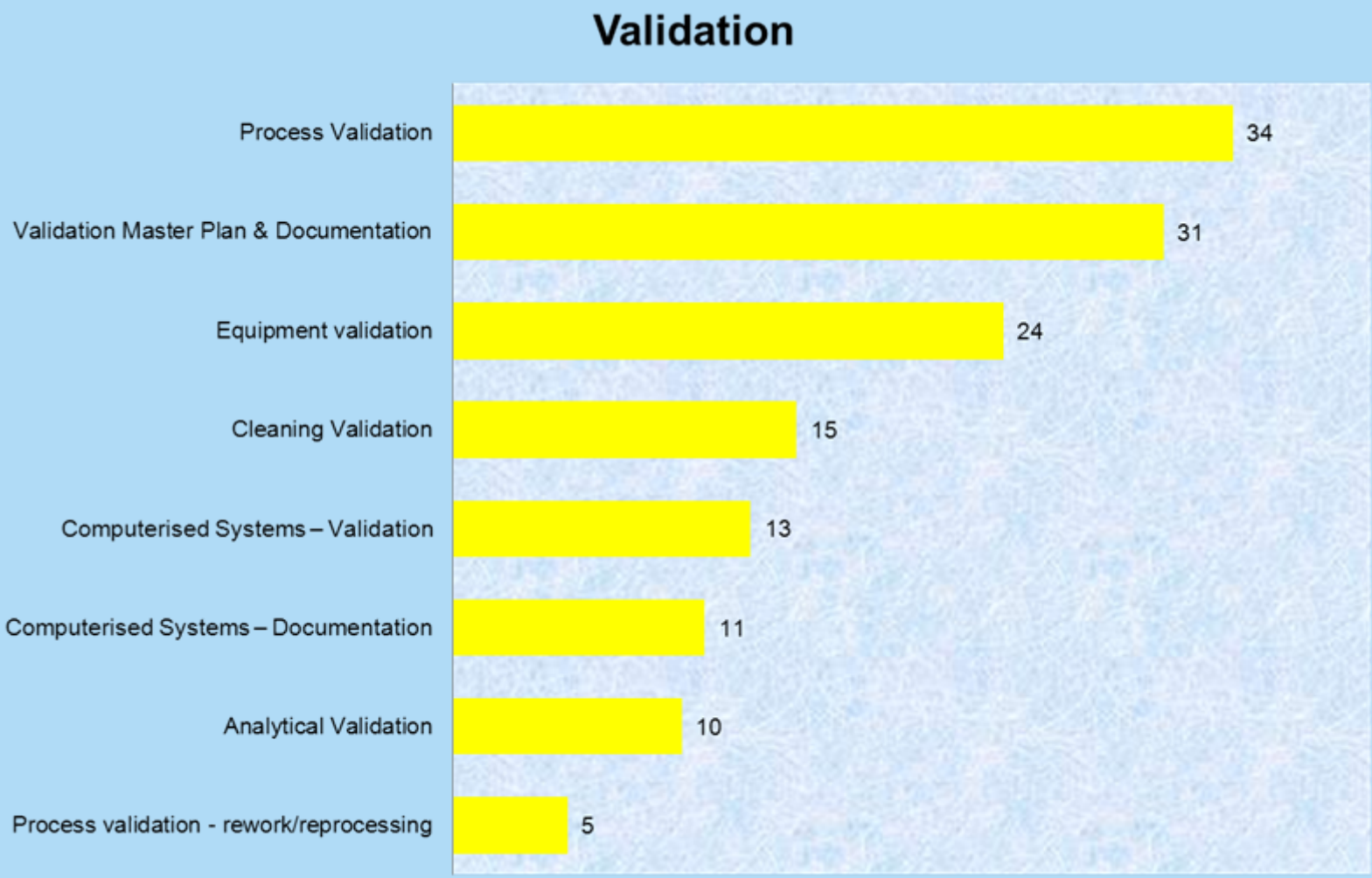

Production
Contamination, chemical/physical 44
Documentation – manufacturing 35
Contamination, microbial 31
Housekeeping 28
Line clearance & segregation 24
Sterility Assurance - Aseptic Practices 24
IPC & monitoring of operations 23
Sterility Assurance - Sterility Investigations 23
Environmental monitoring 22
Handling and control of packaging components 17
Sterility Assurance - Process Design 14
Sterility Assurance - Sterilisation 13
Sterility Assurance - Media Fill 9
Status labeling 9
Production planning and scheduling 0

Quality Control

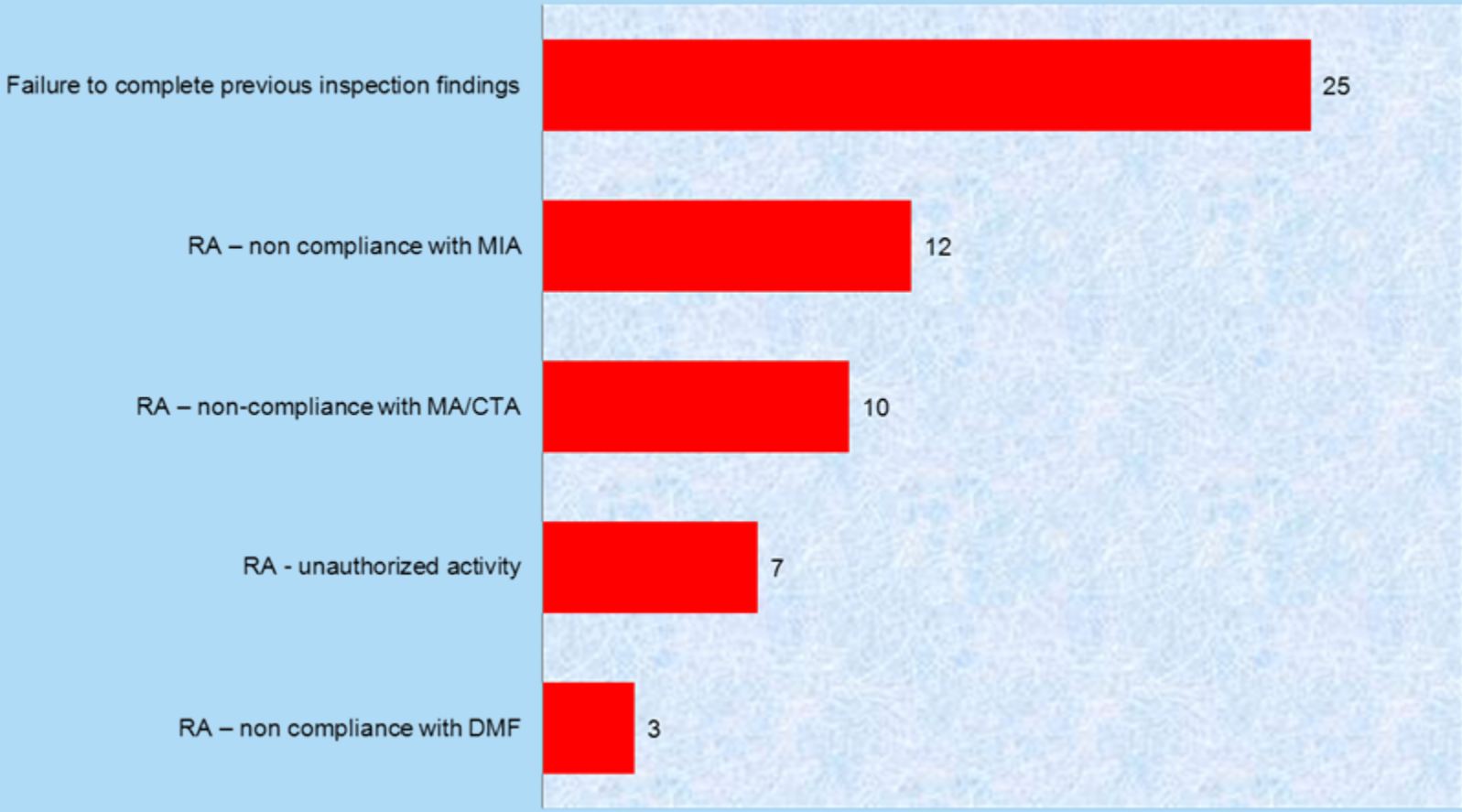


Materials Management




Validation
Process Validation
34
Validation Master Plan & Documentation
31
Equipment validation
24
Cleaning Validation
15
Computerised Systems – Validation
13
Computerised Systems – Documentation
11
Analytical Validation
10
Process validation - rework/reprocessing
5

Regulatory Compliance



INSPECTION FINDINGS – Top 10 Categories

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1. Investigation of anomalies
2. Quality management (Change Control)
3. Corrective action/preventive action (CAPA)
4. Complaints and Product Recall
5. Quality management

INSPECTION FINDINGS – Top 10 Categories

6. Supplier and Contractor Audit
7. Contamination, Chemical/Physical – Potential For
8. Documentation – PSF/Procedures/Technical Agreements
9. Documentation – Manufacturing
10. Process Validation

INSPECTION FINDINGS – Top 10 Categories 1 - Investigation of Anomalies

Continuing to be the number 1 deficiency

The management of 'high' risk deviations was deficient:

- The investigation into 2 positive sterility tests recovered in November 2011 was not complete at the time of the inspection; only a one page interim report was available on day 1 of the inspection.

- The November 2011 Sterility test failure investigation appeared prejudiced to implicating sterility testing; for example sterility testing had been immediately suspended but manufacturing operations had not been suspended.

- There was no overall assessment of the 4 sterility test failures that had occurred in 2011.

INSPECTION FINDINGS – Top 10 Categories 1 - Investigation of Anomalies

Control of Investigations was deficient:

- The procedure allowed up to 60 days for the completion of the investigations categorised as critical. This was considered too long to ensure a timely review and impact assessment to be performed.
- The procedure did not detail a system for reviewing of overdue investigation and an appropriate extension process.
- A large number of investigations were seen that were not closed in a timely manner or were still open a number of months beyond the stipulated expected closure time. There was no assessment of the impact of these overdue investigations and no assessment as to the root cause of the failure to follow the procedure.
- A number of investigations were seen that did not include detailed robust root cause investigation. Therefore potential impacts were not fully assessed and the root cause and subsequent CAPA were not robust.

INSPECTION FINDINGS – Top 10 Categories 1 - Investigation of Anomalies

There were multiple examples from the inspection where deviations had not been raised in circumstances where the procedures in place indicated that such documentation was required.

On-going serious deviation (related to human operational failures) had not been resolved in a robust and timely manner.

Deviations were routinely incorrectly classified in a lower classification than required by the SOP.

The Deviations procedure was lacking in that:

- There was no detail provided with respect to how investigate and assess the impact of an incident.
- There was no requirement to consider the implications for other batches.
- There were no defined timelines associated with investigations ie raising, approval by QA and closure.
- Stability OOS/OOT incidents were not managed by the Non-conformance /Deviations procedure.

INSPECTION FINDINGS – Top 10 Categories 1 - Investigation of Anomalies

The quality of investigations performed was not of the required standard to consistently identify the root cause of the issue and hence suitable corrective and preventative actions, including a robust assessment of the impact of the findings on other batches or systems. A number of specific examples are documented below; these are examples of issues found rather than a comprehensive listing of all issues noted.

The investigation into the recall arising from the …..l complaint batch no. …. concerning a carton of 8 mg …. containing 2 mg blister was deficient in that:-

- There was no documented consideration of other components received from the supplier. At the time of the inspection items from this supplier were still on stock, although in quarantine triggered by retest date.
- There was no documented consideration as to whether similar issues could exist at alternate suppliers given a common approval process.
- The investigation did not consider other ways that electronic identification systems could be bypassed – for example during line set up.
- There was no justification from the findings for the retraining of manufacturing staff for example. A number of the investigations appeared to place an over reliance on retraining in the absence of a critical review of systems and supporting documentation in place at the time of the incident.

INSPECTION FINDINGS – Top 10 Categories 1 - Investigation of Anomalies

- There appeared to be a discrepancy between supplier status on SAP and the approved vendor list as … was listed as an approved supplier on the list dated 1 July 2011.
- There appeared to be an excessive time delay between the decision to block … following the audit on the 25 January 2011, email request on 25 March 2011 and confirmation of status change on 26 April 2011.
- The current mechanism for transferring actions between complaint form and CAPA and subsequent tracking does not adequately distinguish between actions of different priority. The CAPA for the above complaint was not signed off until 10 June 2011.
- There was a noted discrepancy for investigation status between SAP print (open) for … (foil) and investigation report (closed).
- There were a number of examples observed where SAP data errors were being corrected using the change control processes without the supporting notification to understand how and why the error arose.
- The reviewed investigation into the supply of product using the incorrect grade of … had not adequately documented the root cause; hence it was difficult to assess the quality of the actions taken.

INSPECTION FINDINGS – Top 10 Categories 2 – Quality Management – Change Control

2010 – 2011 was number 4

Change Control was deficient in that:

- There was no comprehensive change control checklist.
- The management of artwork changes was lacking as there was no mechanism to ensure that variations were implemented in a timely fashion or in line with competent authority notifications, neither the change control procedure nor changes reviewed detailed time in pack requirements.
- There was no change control for the new Braille label print machine.

INSPECTION FINDINGS – Top 10 Categories 2 – Quality Management – Change Control

Procedures for Management of Change as defined in SOP were not being satisfactorily applied as exampled by:

- The acceptance of post of major changes by customer is not permissible as some major changes include registered details.
- No Change Control was raised for the change in supplier of …. from …. to …..
- The change of primary packaging from PE bag to PE lined aluminium bag was seriously mismanaged in that:
- The change control … was raised on 24/12/10 after changes to specifications to permit the aluminium bag had been made on 24/8/10.
- The change was classified as minor resulting in no detailed impact assessment.
- The customer and assessor have not been notified of nor authorised the change although batches of material are already being packed in the new format.
- The Change Control log is not an authorised, version controlled document.

INSPECTION FINDINGS – Top 10 Categories 2 – Quality Management – Change Control

Change management was deficient in that:

- No change controls had been raised for several engineering changes for example, fan and filter changes on the HVAC system and the introduction of the … detection system or the … sampling system.
- Change controls started in 2010 had not been signed had not been completed by QA.
- Change control was not used for the introduction of new products and there was no new product introduction procedure.

INSPECTION FINDINGS – Top 10 Categories 3 - Corrective action/preventive action (CAPA)

2010 – 2011 was also number 3

There was a lack of a robust investigation for the reviewed compounding complaints and non conformances designed to identify root cause and hence appropriate actions to minimise the potential for reoccurrence. It was noted that the frequent use of terms such as ‘human error’, ‘isolated occurrence’ and ‘no trend’ appeared to limit the investigation conducted.

The CAPA raised for the leaking of terminally sterilised product did not include a review of the completeness of the validation process for the introduction of automated handling equipment to ensure that future exercises cover the lessons learnt.

Non conformance Report …. was lacking in that the batch disposition by the QP was not clearly stated and the corrective and preventative actions (CAPA) were weak in that there was no clear action to prevent reoccurrence within the commercial department and there was no conclusions drawn with respect to the review of the appropriate technical agreements.

INSPECTION FINDINGS – Top 10 Categories 3 - Corrective action/preventive action (CAPA)

Several investigations were reviewed and were found deficient in the following areas:

- It was not possible to piece together the events or any accompanying risk evaluation which may have taken place.
- Root cause, implications for other batches, CAPA and batch disposition were not clearly defined.
- Investigations were not raised in a timely fashion as evidenced by ….. In addition it was not clear if … had been contacted and / or if a variation had been raised.
- Lack of investigation as evidenced by …. temperature excursions.

The site had failed to instigate effective remedial actions in a number of areas as evidenced by deficiencies raised at this inspection being of a similar nature to those raised at previous MHRA inspections. This indicated that the quality management system was focussed on dealing with the specifics of the deficiency rather than taking a holistic view to enable the quality management system and site practices to be strengthened.

INSPECTION FINDINGS – Top 10 Categories 3 - Corrective action/preventive action (CAPA)

Deviations:

- Procedural NCRs were only logged on a spreadsheet and were not formally approved by the Operations Executive or QP.
- Investigations were not fully documented.
- There was no evidence of corrective and/or preventative actions being performed.
- There was no batch disposition decision recorded for batches subject to a NCR.

Non conformance procedure & corrective action procedure did not consider the implication for other batches to be affected.
Non-conformances reviewed failed to identify the implications for other bathes to be affected and the preventative action stated by the company for repeat issues with label reconciliation were not documented in the investigations.

INSPECTION FINDINGS – Top 10 Categories 3 - Corrective action/preventive action (CAPA)

CAPA was deficient as evidenced by:

- CAPA was not being applied to the full scope as defined in SOP … as the only evidence of use presented encompassed actions following internal or external site audit.
- There was no chronological log of CAPAs whereby actions may be tracked to completion.
- It is unclear how Quality Assurance can fulfil their requirement to review the effectiveness of CAPAs as there was no forward tracking procedure.
- There was no evidence that the CAPA procedure had been applied to ensure the increased observation of batches of …. and … was being documented following the identification of significant trends during Product Quality Review.

INSPECTION FINDINGS – Top 10 Categories 4 – Complaints and Product Recall

2010 – 2011 was number 7

There was no mock recall exercise performed in 2009. This is a repeat deficiency, failure in post inspection commitment and non compliance with the company's recall procedure.

Complaints Process was deficient in that:

- There was no trending upon receipt.
- Timelines associated with complaints management were not being adhered to as define in the procedure.
- Complaints were not reviewed by the QP as defined in the procedure.

INSPECTION FINDINGS – Top 10 Categories 5 - Complaints and Product Recall

Complaints Procedure was deficient in that:

- The Complaints Handling procedure makes no reference to the requirement to verify complaint for counterfeit product.
- There is no historical review of the complaint on receipt.
- There is no assessment of possible impact on other related batches or products.
- The complaints log is being completed as 'closed' when CAPA actions remain outstanding eg three complaints were received from the same customer for out of specification related substances of ….. The recommendation to discuss possible causes with the customer has not been fulfilled although documented to do so on 1 April and again 11 August 2011.
- No documentation could be found for Complaint ….. although the log indicated closure on 11 February 2011.
- The root cause of the complaint of out of specification water content of …. has not been adequately investigated and documented.

INSPECTION FINDINGS – Top 10 Categories 4 – Complaints and Product Recall

Recall Procedure …:

- The Recall procedure does not require periodic challenge of the system when no actual recalls have been required.
- There was no required assessment of the possible impact of the recall on other batches or products.

There was no procedure for the management of complaints against suppliers to ensure a timely and comprehensive investigation designed to minimise the potential for recurrence. Such a process should also include a review of the supplier status and the impact on materials already in the supply chain.

INSPECTION FINDINGS – Top 10 Categories 5 - Quality Management (systemic issues across all systems)

2010 – 2011 was number 2

The site had failed to instigate effective remedial actions in a number of areas as evidenced by deficiencies raised at this inspection being of a similar nature to those raised at previous MHRA inspections. This indicated that the quality management system was focussed on dealing with the specifics of the deficiency rather than taking a holistic view to enable the quality management system and site practices to be strengthened.

The trending of deviations was only performed at a 6 monthly frequency and failed to address the root causes. The site would thus not become aware of emerging issues to enable appropriate remedial actions to be taken.

The recalls process was restricted to use with the complaints process. No reference to the possibility of a deviation or OOS result triggering a recall was considered.

INSPECTION FINDINGS – Top 10 Categories 5 - Quality Management (systemic issues across all systems)

Remediation proposals submitted by the company in response to the 2010 inspection had not been implemented or maintained in accordance with the commitments given, as evidenced by:

- A number of the actions were not completed in line with the committed timeframe. No communication of the departure from the agreed plan was made to the Agency – for example via an interim update.

- The remedial actions had not always delivered the desired outcome. Examples include:
- The records relating to the previous (inspection of 2010) finding … indicated that … was a potential contaminant of the …. from the …. company but there was no documented explanation as to why QC testing did not look for this contaminant.

- There remains no record of the retrieval / destruction of superseded copies of procedures.

- Despite uniquely identifying dispensary buckets, there remains inconsistency in the approach to the dedication of all product contact materials in the dispensary. There was no documented risk assessment / justification for the approach taken with respect to controlling risks of cross contamination.

INSPECTION FINDINGS – Top 10 Categories 5 - Quality Management (systemic issues across all systems)

- The cleaning process and associated records remain unclear. The process for cleaning between different materials (e.g. API and excipient) remains poorly defined.

- The installation of hooks to enable drainage of water hoses was observed to be ineffective. In Room … the water hose was hanging on the hooks system but standing water remained trapped within the hose loops.

- A remedial action appeared to have subsequently reverted back to the identified deficient process. The 2010 response to previous finding detailed the planned approach to weighing … charge; the site has since reverted to accepting the weight as received from the vendor. No communication to this effect been made to the Inspectorate.

Site quality systems, facilities and controls were considered inadequate to provide sufficient assurance of the quality, integrity and security of supply of …….

INSPECTION FINDINGS – Top 10 Categories 5 - Quality Management (systemic issues across all systems)

The Company failed to demonstrate satisfactory application of the Quality System as exampled by the following incidents:

- Batch Manufacturing Record number for the …, permitted a batch size of 40kg +/- 10kg with no validation to justify this range.
- The subsequent increase in the routine batch size from 40kg to 48kg was not documented through the established quality system.
- Attempts to establish a method for the re-processing of … back to …, step …had been made outside of a formal validation exercise.
- Approval for the use of …. beyond its approved shelf-life was granted although the purity result at 98.33% failed the specification of >/= 98.5%. No deviation was raised or justification documented.
- Sodium Bicarbonate … was manufactured and released on 9 April 2009 before validation of the process which was not completed until 30 December 2010.
- The change control for the introduction of a new bag sealer was raised on 2 May 2011 but validation of the equipment commenced on 29 April 2011.
- The procedure for the Handling and Re-use of Recovered Solvent, … required that testing must include reference to the number of recovered cycles. In the example reviewed this had not been included.

INSPECTION FINDINGS – Top 10 Categories 5 - Quality Management (systemic issues across all systems)

- The procedure for Rework and Reprocessing, … required reprocessing to be validated over three batches and included in the stability programme. It was identified that reprocessed batches had been released although there was no validation data to support this. The Inspector acknowledges that the reprocessed batches will not be supplied to the EU markets.
- The above procedure still did not provide clear instruction that rework was not permitted for EU markets or that reprocessing was not permitted to certain customers as defined in the Technical Agreements.
- The procedure for handling Critical Process Parameters … required period review of the CPPs by Production and Quality Management. Outside of the Annual Product Review this was not defined.
- No Risk Assessment had been performed to evaluate the wider impact of the new factory.
- There had been no consideration of the requirement to increase environmental monitoring during the build period.
- Change Control procedures were deficient in that there was no established system within the Change Control process for documenting required completion dates and tracking on-time closure.
- The Change Control procedure did not identify the additional application forms required to be raised for individual changes.
- There was ambiguity as to the status of completed actions eg validation and calibration log revision for the thermal sealer.

INSPECTION FINDINGS – Top 10 Categories 6 – Supplier and Supplier Audit

2010 – 2011 was number 11

Supplier Audits was deficient in that:

- Not all suppliers had been audited in line with the stated annual frequency.
- The Contract laboratory, had not been audited, nor was it detailed on the audit schedule.
- The audit report for ……. was reviewed. The inspectors commented that on review significant issues were identified, all of which were classified as minor. Issues identified related to the control and management of artwork. The company had experienced incorrect artwork being supplied by the vendor.

The Audit procedure was not approved. The draft document was reviewed and found lacking in a number of areas, for example (but not limited to):

- Audit frequency for suppliers.
- Definitions for critical, major and minor deficiency classification.
- The actions to be taken if critical observations are identified during a supplier audit.
- There was no checklist for auditing.
- Auditor competency, skills or knowledge was not defined.

INSPECTION FINDINGS – Top 10 Categories 6 – Supplier and Contractor Audit

Supplier Assurance was deficient in that:

- There was no process for periodic on-going evaluation of suppliers. Supplier de-qualification was defined in …. however the latter in essence was based on rejections and out of specification (OOS) results and was purely reactive.

- The applicable procedure … was deficient in that:
  - Primary, Printed Packing materials and brokers were not defined and as such the suppliers were not assessed or audited.
  - Audit of materials including Active Pharmaceutical Ingredients (API) was not required if the manufacturer was not local i.e. within India.
  - There was no audit period defined for critical Excipients.
  - The evaluation and approval procedure did not define the actions to be taken if critical observations were obtained at a supplier audit.
  - The de-qualification procedure was not linked to the deviation quality system as such it was not clear if the implications for batches in the manufacturing stream and supply chain would be assessed. In addition this was purely focussed on API and not all materials.

INSPECTION FINDINGS – Top 10 Categories 6 – Supplier and Contractor Audit

- Audit reports performed were to a predefined general generic checklist, there was no data to support the audit except ticks on the checklist. There was no information relating to date of audit, auditor knowledge and experience, the standard against which the supplier was assessed, what areas were audited, observations made and hence how the impact assessment on the material in question was derived. All audits performed had been done in this manner and as such no audits were available for inspection.

- The audit plan was not generated in line with QA. Note in the inspectors opinion the plan is unrealistic and unachievable as 706 were required in the year.

INSPECTION FINDINGS – Top 10 Categories 6 – Supplier and Contractor Audit

Control of Starting Materials with specific respect to … was deficient in that:

- Neither the supplier, … nor the manufacturer, … had been subject to site audit contrary to GMP expectation and the Company's own internal procedure for Vendor Qualification and Audit.
- The above procedure permits qualification of a critical raw material supplier up to 3 months before the manufacturer is audited.
- The evaluation questionnaire has been completed by the supplier who is not qualified to complete on behalf of the manufacturer.
- The Certificate of Analysis supplied by … specifically states that the company " makes no warranty as to the suitability of the goods for any purpose whatsoever." This was not acceptable for as material destined for subsequent intravenous use.
- There was no Technical Agreement in place between … and …

INSPECTION FINDINGS – Top 10 Categories 6 – Supplier and Contractor Audit

Vendor Assurance activities were deficient in that:

- A QP API declaration had been approved without an acceptable audit having occurred. The QP had approved the API declaration pending the performance of an acceptable audit occurring.

The control of API site audits was deficient in that:

- There was no mechanism to ensure that API site audits performed by 3rd party companies (e.g. Indian manufacturing sites) occurred in a timely manner.
- The audits of the manufacturing sites did not consider the API site audit process.
- Two API site audits had not had the deficiencies classified. It was not clear if these were deficiencies or recommendations.

INSPECTION FINDINGS – Top 10 Categories 7 – Contamination, Chemical/Physical – Potential For

2010 – 2011 was number 13

Cleaning Validation was deficient in that:

- Whilst the site had proposed a matrix approach to cleaning validation, the identified API candidate in respect to toxicity and solubility, …., had not been subjected to cleaning validation. It was noted that two more potent candidates were available but assay methods on site were inadequate to detect the required levels of these compounds.

- Whilst line one was used for the filling of all regulated products, it was also available for all other products made on site. As a consequence of the lack of adequate cleaning validation, no assurance was available to demonstrate that residual material from one product did not cross contaminate the following products, which may have potential for causing patient harm.

INSPECTION FINDINGS – Top 10 Categories 7 – Contamination, Chemical/Physical – Potential For

Provisions to prevent Cross Contamination of product, equipment and personnel are deficient in that:

- With the exception of …. which was manufactured in dedicated rooms a range of prostaglandins and non-prostaglandins were being manufactured and packed in common areas. (NB Prostaglandins are classified as Class 1B products with the requirement to be manufactured in either dedicated facilities or in infrequent campaign runs in an appropriate area.)

- The common air handling system utilising recirculation and make-up air drawn from the open roof space was insufficiently secure for a facility where there was no dedicated area for the segregation of Class 1 product.

- There was no differential pressure between area … used for prostaglandins and adjoining room … used for non-prostaglandins with increased risk of cross contamination.

- No local extract is used when adding solids to the re-crystallisation vessel in room….

- Dirty equipment and gowns were put in a sealed bag for transfer to the wash bay but there was no process of cleaning the outside of the bag with possibility of contaminating other areas and equipment.

- There was no differentiation of gowns worn by operators for processing of prostaglandins and it was unknown if the cleaning process followed by an external company was adequate to remove traces of prostaglandin contamination.

INSPECTION FINDINGS – Top 10 Categories 7 – Contamination, Chemical/Physical – Potential For

The current cleaning validation exercise was carried out in 2005 and there had been no subsequent review.

- There was no documented rationale or comparison with new products to confirm the products chosen for the cleaning validation exercise were still relevant with respect to potency and solubility.
- There was no documented risk assessment for the need for microbiological monitoring and none had been carried out apart from on the final rinse water used for cleaning.
- No deviation had been raised for a failure in purified water monitoring results.
- The …. filling machine was not subject to any routine strip down or clean. Large amounts of residue were seen in the product transfer pipe work.
- There was no Validation Master Plan for cleaning or process validation.

INSPECTION FINDINGS – Top 10 Categories 7 – Contamination, Chemical/Physical – Potential For

Controls surrounding the prevention of cross contamination were lacking in that:

- Air was recirculated from different processing rooms, which could manufacture different products, by one air handling unit. The grade of filters used was less than those expected for such a situation to prevent cross contamination.

- The documented rationale for selecting worst case products for cleaning validation studies was not an approved, controlled document.

- …, as a coated tablet, was not deemed to be the worst case choice to be used to perform packing cleaning validation.

- There was no cleaning validation performed of multi-product fluid bed drier filter socks.

- The validation of …. batch campaign length found the Fluid Bed Drier was not visually clean after one Clean In Place cycle, however the cleaning procedure was accepted and had not been updated to reflect that a second cycle was required.

- Differential pressures across solids manufacturing areas were only being read once per month.

INSPECTION FINDINGS – Top 10 Categories 7 – Contamination, Chemical/Physical – Potential For

- Several instances of out of limit pressure differentials in solids manufacturing were seen, with no documented investigation or assessment performed.

- Operators may dispense different active agents while wearing garments that have previously been exposed to different products.

- …..forming head was labelled as clean but had white residue seen on it.

The company had failed to meet the commitment from the previous inspection to improve the compression area HVAC to reduce the risk of cross contamination. The action had been due for completion by April 2010.

Cleaning of production drums had occurred in the Liquids area processing vessel without a completed change control in place. There was no SOP, training records or validation to support this revised cleaning practice. It was noted that the process vessel appeared to have been contaminated by this cleaning activity despite the room documentation indicating that the vessel was clean and QA approved as such.

INSPECTION FINDINGS – Top 10 Categories 8 – Documentation – PSF/Procedures/Technical Agreements

2010 – 2011 was number 5

There were no technical agreements with the manufacturers / suppliers of unlicensed medicinal products.

Documentation – generation, control and completion.
• There were uncontrolled, incorrect and out of date documents throughout the operation.
Examples include:

- uncontrolled “Accepted” status labels on the QA table in secondary packaging
- detailed instructions for change parts
- on line identifiers of hot spots.
- a sign relating to the tin line head in the Balm production room.
- out of date cleaning logs in a cleaners cupboard.

INSPECTION FINDINGS – Top 10 Categories 8 – Documentation – PSF/Procedures/Technical Agreements

Technical Agreements (TA) was deficient in that:

- TA were not in place with all supplier's as per detailed in the procedure (GN003) as evidenced by:
  - Contract laboratories.
- The TA with…, Authorisation …. was lacking in the following areas:
  - Documentation retention periods specified were not compliant as they failed to meet the requirement of expiry + 1 year, or 5 years from certification, whichever is the longer.
  - The responsibility for transportation and assurance with product label claim was not defined.
  - Other records such as the documentation made available to the QP for certification were not defined.
  - There was no review / expiry date.

- The TA with …..was very high level and was found significantly lacking in a number of areas for example (but not limited to), investigations (Out of Specification & Deviations), Change Control, Starting Materials, TSE etc

- The TA procedure was lacking as no review period for TA's was defined and the procedure stated that a TA must be in place prior to first batch being released, this is deemed to be inappropriate.

INSPECTION FINDINGS – Top 10 Categories 8 – Documentation – PSF/Procedures/Technical Agreements

- Warehouse SOPs were observed stored in a locked cupboard restricting access to all relevant staff.

- Reviewed SOPs lacked detail or were not available for a number of operations including:-
  - There was no procedural requirement for the PQR to be sent to the MAH/QP
  - No requirement for line clearance for dispensing of printed packaging items
  - The Warehouse returns procedure was not clear as to what printed packaging items can be received back from production e.g. intact bundles or loose leaflets (inserts)
  - There were apparent anomalies regarding the use of the balance for label dispensing and the requirement for a manufacturing licence on incoming goods check
  - The use of the received CoA as part of goods receipt was not adequately described in the procedure
  - Scheduling of stability studies
  - Item code translation for leaflets
  - Soft copy control and Corporate responsibilities for artwork generation and control.

INSPECTION FINDINGS – Top 10 Categories 9 – Documentation – Manufacturing

2010 – 2011 was number 6

There were a number of deficiencies in the batch manufacturing documents and related standard operating procedures. In general they were lacking in detail.

Batch Documentation practices were unsatisfactory in the following:

- Expected criteria was not always included at all IPC steps where actual data eg temperature or humidity was being recorded. There was therefore no opportunity for the operator to be alerted to a possible processing issue.

- Print had faded to the point of being illegible in the raw data included in ….Batch record for Lot ….. Additionally, photocopies taken to preserve raw data print outs were almost totally blank. Of concern was the fact that the batch record had been reviewed by both Production and Quality personnel with no comment made.

- No sample labels were included in the batch document sets for finished API.

- There was no documented reconciliation of labels.

- The above batch failed specification for residual solvent and subsequently rejected. However there was no clear indication of batch status on the document.

INSPECTION FINDINGS – Top 10 Categories 9 – Documentation – Manufacturing

The documentation in place was inadequate in that:-

• There were numerous examples of a poor integration and conflicts between the electronic ERP system (SAP) and local document systems.

• Batch documentation was lacking as evidenced by:-

- The Batch Manufacturing Record (BMR) reviewed did not provide detailed stepwise processing instructions following the sequence of required activities.
- There was evidence of unofficial calculations on the SAP screen shot included as part of the reviewed batch documentation. There were no instructions available to describe this action.
- The risks associated with transcription for BMR had not been adequately assessed nor was there a robust process to ensure independent checks on calculations including details of source data e.g. potency.
- Sample of IPC labels were not included as part of batch documentation. In addition there was not a consistently identified step to ensure the clearance of the print station before printing such labels.
- The document summary sheet did not provide an accurate listing of documents. In addition the SOP listing was manual without any clear instruction as to how to complete.

INSPECTION FINDINGS – Top 10 Categories 9 – Documentation – Manufacturing

- Raw data used to derive IPC results was not included as part of BMR.
- There was no code number for polyethylene bags used for storage (product contact).

Documentation:

- The requirement to sign the register for entering production areas was not specified in the SOP.
- There was insufficient instruction available at the point of use to enable production processes to be completed in a consistent manner
- The bulk solution sterilisation time was critical to ensure correct viscosity but there was no procedure which described how it was calculated.
- Checks on vacuum distillation temperature only reported a single value and did not confirm the temperature was in specification for the whole process.
- There were no instructions available with respect to the preparation and use of the filtration area heat exchanger, used to heat or cool WFI. In addition, no reference was made by site staff to ensuring that the device was suitably sanitised prior to use.
- There was a lack of evidence within the batch record reviewed with respect to the required filling line recovery time following a power failure.

INSPECTION FINDINGS – Top 10 Categories 9 – Documentation – Manufacturing

The batch records and procedural documentation reviewed did not contain sufficient detail, laid out in an orderly fashion to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products supplied by the site in that:-

- There was no procedure to describe the switching off and restarting of HVAC units, including muting of alarms, or to confirm the satisfactory operation of the required HVAC overnight before commencing operations.
- The observed practice of back calculating the reconciliation of packaging items negates the value of this exercise. The checks in place on document completion had not detected this practice. (This inspector accepted that there was no attempt to hide issues rather the detail of the process and subsequent instructions had not been adequately established.)
- The batch release SOP sequencing is not in line with the practice observed.
- Risks associated with transcription on the batch documentation had not been adequately identified and controlled, for example potency derivation and calculation and batch number / expiry date assignment.
- There was evidence of the use of uncontrolled documentation systems. An electronic document issued by QC detailing required sample quantities was found on the PC in the IPC area.
- The batch documentation did not provide limits for recorded variables such as rpm for IPC blender and blister machine speed (see previous inspection).

INSPECTION FINDINGS – Top 10 Categories 9 – Documentation – Manufacturing

…. tablets with known manufacturing issues were being inspected in an unofficial and undocumented way. Unofficial documentation in the in-process batch indicated that 8 out of 10 tablets weighed did not meet the applied specification. No deviation had been raised and the company had assumed that the packing operators, with no formal instruction, procedure or validated training, would inspect out all damaged and underweight tablets. All unofficial records were removed from the final batch records thereby reducing the visibility of this issue.

INSPECTION FINDINGS – Top 10 Categories 10 – Process Validation

2010 – 2011 was number 21

Validation was deficient as evidenced by:-

- Analytical laboratory risk assessments for both method and equipment did not contain a full list of methods and equipment was reviewed.
- A number of methods and equipment had the same score but were then not prioritised within the group.
- There was no review of how these plans were connected to the Production equipment remediation plan and process validation plans.
- None of the plans were linked to the Site Validation Master Plan.
- There were no details on how the plans would be tracked and monitored and how this would link to the Batch disposition process.
- The IQ/OQ for the Drum Hoop Mixer did not contain sufficient details with regard to the acceptance criteria or how the protocols were enacted. A discrepancy was identified but no explanation or impact was documented.
- There was no requirement within the IQ/OQ documentation that the calibration and or maintenance requirements had been identified and included within the pm system.
- The validation status of …. products was not clear in terms of batches produced changes made and conclusions drawn. The documentation for ….. did not describe the blender used nor did it explain why the 60minutes data was out of specification or reference what CAPA actions were to be taken.

INSPECTION FINDINGS – Top 10 Categories 10 – Process Validation

The arrangements for validation of equipment and processes were deficient in that:

- The blister packing machine range of temperatures mentioned on the batch documents for forming and sealing had not actually been validated. Instead the company had chosen an intermediate temperature to run the machine at and had not demonstrated that all temperatures in the ranges given were acceptable. Furthermore, the speed of the machine had not been specified.
- Validation of the pvc film was last performed in 2006 and the pvdc film had not been qualified.
- It was noted that there were at least two types of pvc film, white and clear, and that the company had not identified unique materials codes on either the validation or batch documents so it was unclear which product had been used in the qualification work.
- There was no list of equipment to aid in assessing the need for periodic evaluation of its validation status.
- The list of laboratory equipment requiring calibration was incomplete.
- There was no requirement in the product quality review procedure for an assessment of the validation status of the product.
- There was no pre-authorised validation protocol for the …. process.
- No report had been written for the validation of the product. There was no conclusion stating that the validation had been successful.

INSPECTION FINDINGS – Top 10 Categories 10 – Process Validation

The management systems required to ensure compliance (regulatory and GMP) with the Marketing Authorisation were still inadequate:-

- There was no cohesive plan that defined all activities that were required to be performed to ensure all GMP and regulatory compliance aspects were completed in a timely manner.
- Validation activities were only considered as part of a products technical transfer and were not considered if the manufacture stayed at the existing company resulting in a number of products that have incomplete process validation, analytical validation and artwork issues.
- The gap analysis template used to determine the scope of work did not include validation activities (process or Quality Control).
- Justification for delays in the programme was not formally documented as seen in the example ……. for …….. tablets.
- There was no risk assessment available for each product for which the validation/qualification activities had not been performed.
- There was no formal process to track due dates of activities that had been identified for some products and therefore no impact assessment was performed when overdue.

INSPECTION FINDINGS – Top 10 Categories 10 – Process Validation

The companies' validation system had consistently failed to identify and controls the risks associated with process and equipment changes. This issue had been raised in previous MHRA inspections and the company had yet to fully address it.