MHRA
Regulating Medicines and Medical Devices

GMP Inspection Deficiencies 2013

Review of Deficiencies Observed in 2013

Medicines and Healthcare Products Regulatory Agency

Executive Summary

- The most frequently encountered defect categories raised over the previous five years have remained relatively consistent with the exception of ‘Contamination, chemical/physical (or potential for)’ which has significantly increased.
- Deficiencies relating to ‘Quality Systems’ are by far the most prevalent observed during inspections.
- Over the last five years, where inspections identified Major or Critical deficiencies;
  - the ratio of Majors raised per inspection has remained relatively constant
  - the ratio of Criticals raised per inspection had remained relatively constant until 2013 where there was an increase observed. This is due to a cluster of data integrity issues with potential impact to public health.
  - the relative number of Critical deficiencies raised per inspection in a given continent is higher in Asia than other the other continents where inspections were carried out.
- A number of areas for focus by the inspectorate have been identified based on review of the attached data, changes in the regulatory environment and due to intelligence gained from other agencies.

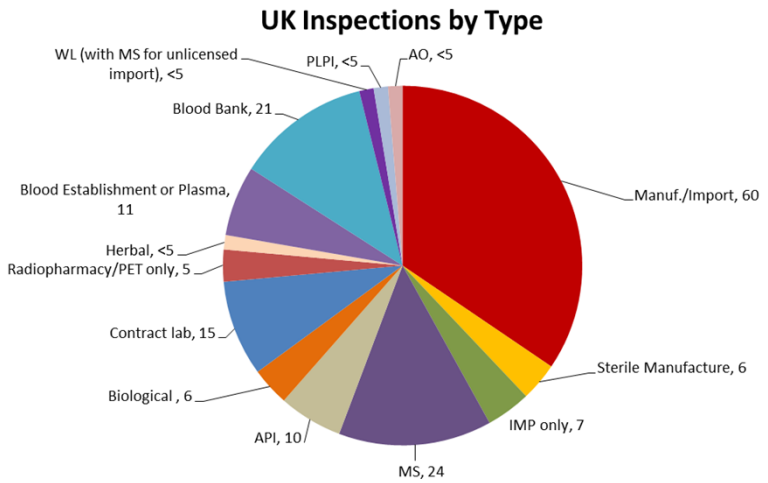
Overview of GMP Inspections Carried Out

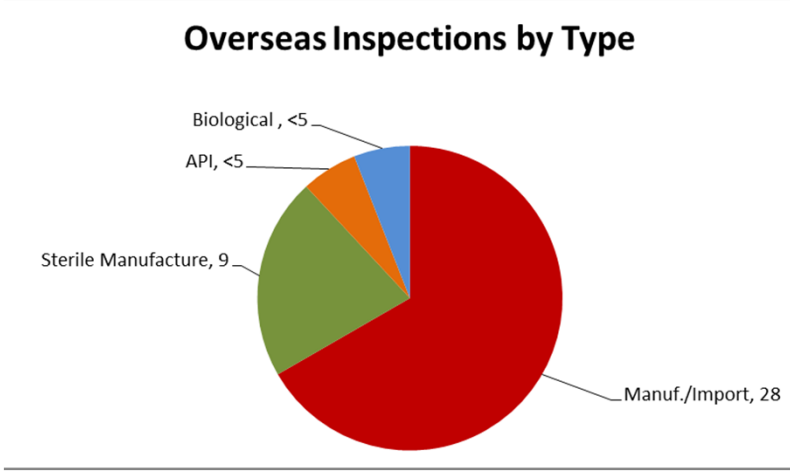
- Of 630 GMP inspections carried out in 2013, 216 resulted in Major or Critical Deficiencies.
  - Of the inspections with Major/Critical deficiencies
    - 174 were in the UK
    - 42 were overseas
  - The sites with Major/Critical deficiencies comprised of
    - 170 Facilities with MIA, MS & IMP licences, or overseas manufacturers
    - 32 Blood Sites
    - 14 API Manufacturing Facilities

Detail of Site Types with Major/Critical Deficiencies

INSPECTIONS WITH MAJOR/CRITICAL FINDINGS		
Inspection Category	**UK** Inspections with Critical/Major Findings	**Overseas** Inspections with Critical/Major Findings
Manuf./Import	60 (28%)	28 (13%)
Sterile Manufacture	6 (3%)	9 (4%)
IMP only	7 (3%)	
MS	24 (11%)	
API	10 (5%)	<5 (<2%)
Biological	6 (3%)	<5 (<2%)
Contract lab	15 (7%)	
Radiopharmacy/PET only	5 (2%)	
Herbal	<5 (<2%)	
Blood Establishment or Plasma	11 (5%)	
Blood Bank	21 (10%)	
WL (with MS for unlicensed import)	<5 (<2%)	
PLPI	<5 (<2%)	
AO	<5 (<2%)	
	174	**42**
		216

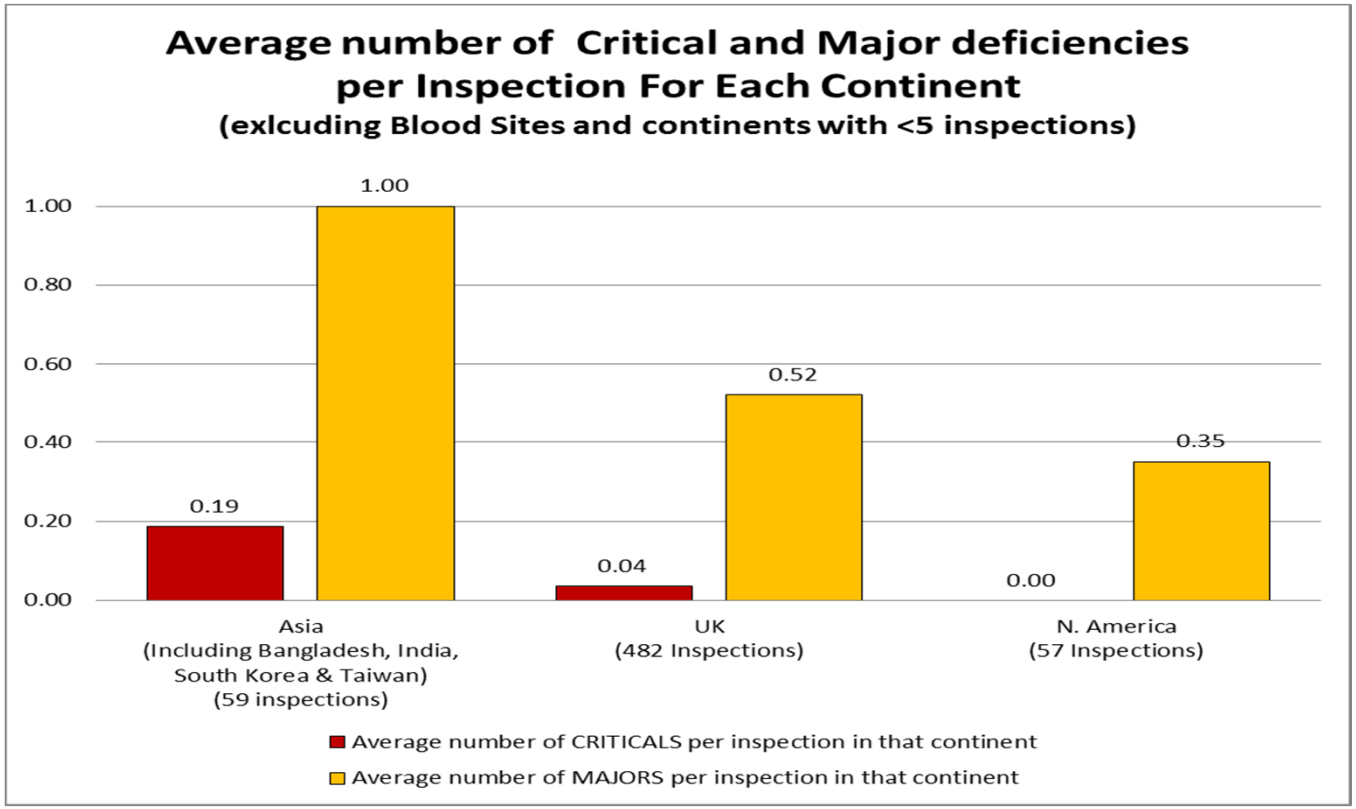
Note: Values in brackets give % relative to the 216 inspections with Critical /Major findings





Overseas Deficiencies Review Split by Continent

- The average number of Critical and Major deficiencies raised per inspection for each continent (where ≥5 inspections were carried out), is presented below;



Total Number of Critical / Major Findings in 2013

- **Criticals**
  - 29 Critical deficiencies raised
  - 3.0% of all 630 inspections raised Critical deficiencies
  - A maximum of 3 Critical deficiencies were raised on a site.
- **Majors**
  - 403 Major deficiencies raised
  - 31.6% of all 630 inspections raised Major deficiencies
  - A maximum of 7 Major deficiencies were raised on a site.

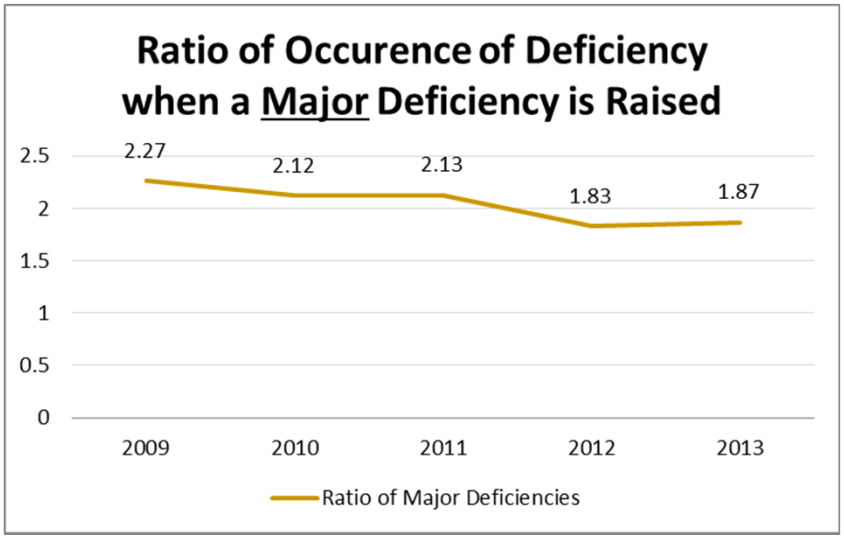
Critical/Major findings by Site Type for relevant inspections

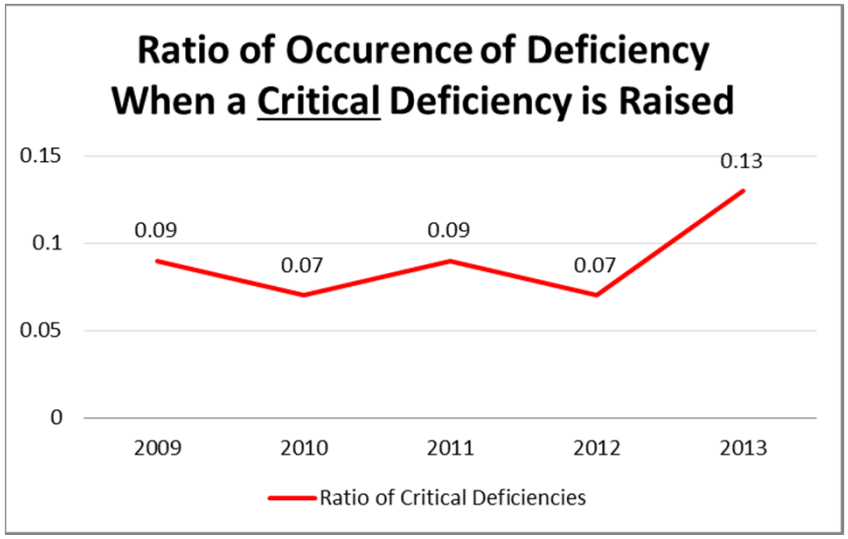
FINDINGS BY INSPECTION CATEGORY												
Inspection Category	UK						Overseas (OS)					
	Number of Inspections with Critical/ Major Findings	% of UK Inspections with Critical/ Major Findings	Total number of 'Criticals'	Max Number of Criticals on a Single Site	Total Number of 'Majors'	Max Number of Majors on a Single Site	Number of Inspections with Critical/ Major Findings	% of OS Inspections with Critical/ Major Findings	Total number of 'Criticals'	Max Number of Criticals on a Single Site	Total Number of 'Majors	Max Number of Majors on a Single Site
Manuf./Import	60	28%	6	3	117	6	28	13%	2	1	50	4
Sterile Manufacture	6	3%	0	0	10	2	9	4%	4	2	19	4
IMP only	7	3%	0	0	8	2						
MS only	24	11%	2	1	40	4						
API	10	5%	0	0	15	3	<5	<2%	5	3	13	7
Biological	6	3%	3	3	12	4	<5	<2%	0	0	1	1
Contract lab	15	7%	5	3	20	6						
Radiopharmacy/PET only	5	2%	0	0	9	5						
Herbal	<5	<2%	1	1	9	4						
Blood Establishment or Plasma	11	5%	0	0	20	4						
Blood Bank	21	10%	1	1	48	6						
WL (with MS for unlicensed import)	<5	<2%	0	0	3	2						
PLPI	<5	<2%	0	0	7	3						
AO	<5	<2%	0	0	2	2						
TOTALS	**174**		**18**		**320**		**42**		**11**		**83**	

Total number of 'Critical' & 'Major' deficiencies in UK and Overseas	**432**

Comparison of Deficiency Ratios in the last five years

- For inspections with Critical / Major deficiencies, the relative number of Criticals and Majors per inspection over the last 5 years was tabulated.

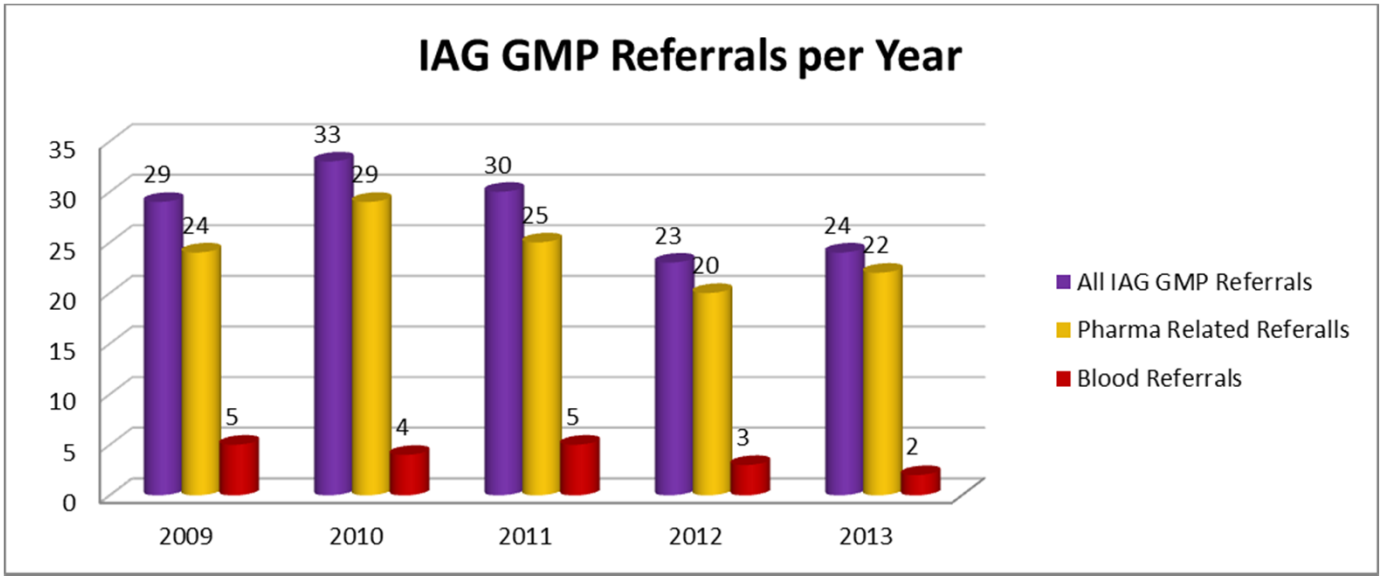




- It can be observed that for an inspection where a Critical/Major was raised;
  - the ratio of Major deficiencies per inspection has decreased since 2009
  - the ratio of Critical deficiencies per inspection increased in 2013 after being relatively consistent over the previous four years. This increase relates to data integrity findings.

GMP Referrals to IAG in the last 5 years

- A reduction in the number of overall regulatory action (IAG) referrals in 2012 and 2013 is apparent when compared to 2009 to 2011 inclusive, however, at present it is too early to conclude that a downward trend is developing.
- The implementation of MHRA's early intervention 'Compliance Management' process in April 2013 avoided the need for regulatory action referrals in 9 inspection cases.



Most Common Findings for Sites

(*Excluding Blood Sites*)

All Critical/Major Defect Areas

1. Quality Management	262
Batch release procedures	
Complaints and Product recall	
Quality management	
Quality management – change control	
Quality management – product quality review	
Quality management – risk management	
Self inspection	
Investigation of anomalies	
Investigation of anomalies – CAPA	
Investigation of anomalies – OOS	
Documentation - procedures/PSF/TAs	

2. Production	127
Sterility Assurance - Aseptic Practices	
Sterility Assurance - Sterilisation	
Sterility Assurance - Process Design	
Sterility Assurance - Media Fill	
Sterility Assurance - Sterility Investigations	
Contamination, chemical/physical – potential for	
Documentation – manufacturing	
Line clearance, segregation and potential for mix-up	
Housekeeping – cleanliness and tidiness	
Contamination, microbial – potential for	
Status labelling – work in progress, facilities, equipment	
Environmental monitoring	
In-process control and monitoring of production operations	
Handling and control of packaging components	
Production planning and scheduling	

3. Materials Management	102
Supplier and contractor audit	
Compliance with TSE guidelines	
Warehousing and distribution activities – General Issues	
Warehousing and distribution activities - Transportation Temp Control and Monitoring	
Warehousing and distribution activities - General Storage Temp Control and Monitoring	
Warehousing and distribution activities - Lack of inventory control and segregation	
Warehousing and distribution activities - Records – receipt and distribution	
Warehousing and distribution activities - Returns Management	
Starting material – API compliance with GMP	
Supplier and contractor technical agreements	

4. Premises and Equipment	86
Design and maintenance of equipment	
Design and maintenance of premises	
Environmental control	
Calibration of measuring and test equipment	

5. Quality Control	68
Sampling procedures and facilities	
Sampling procedures &facilities – retention & retain samples	
Documentation – specifications and testing	
Starting material and packaging component testing	
Computerised systems – data manipulation	
Finished product testing - chemical	
Finished product testing - microbiological	
Finished product testing – on-going stability monitoring	
Intermediate and bulk product testing	
Calibration of reference materials and reagents	

7. Validation	65
Validation master plan and documentation	
Analytical Validation	
Cleaning validation	
Equipment validation	
Computerised systems – validation	
Computerised systems – documentation and control	
Process validation	
Process validation - rework/reprocessing	

8. Regulatory Compliance	41
Regulatory issues – non compliance with MIA	
Regulatory issues – non-compliance with MA/CTA	
Regulatory issues – unauthorized activity	
Regulatory issues – non compliance with DMF	
Failure to respond to previous inspection findings	

10. Personnel	38
Personnel issues – training	
Personnel issues – duties of key personnel	
Personnel issues – hygiene and clothing	

- The total number of Critical/Major Deficiencies observed in each category is shown in the table above.
- It can be seen that '*Quality Management*' related deficiencies are by far the most frequent.

Top Critical/Major Defect Areas

Most Frequent Defect Categories Observed		
Rank	**Defect Category**	**Percentage of Critical / Major Deficiencies with this Defect Category**
1	Investigation of anomalies	6.5%
2	Quality management	5.5%
3	Investigation of anomalies – CAPA	4.7%
=4	Contamination, chemical/physical (or potential for)	3.7%
=4	Supplier and contractor audit	3.7%
6	Quality management – change control	3.6%
7	Documentation - procedures/PSF/TAs	2.7%
7	Personnel issues – training	2.7%
=9	Design and maintenance of equipment	2.6%
=9	Documentation – manufacturing	2.6%
=9	Finished product testing - chemical	2.6%

The Defect Categories presented above account for 40.9% of all Critical / Major Deficiencies raised in 2013.

Deficiency Category Trends Over Previous Five Years

- A review of the top 10 Deficiency Categories over the previous five years highlights the following;
  - '*Investigation of Anomalies*' remains the most common category
  - '*Quality Management*'; '*Investigation of Anomalies – CAPA*'; '*Supplier and Contractor Audit*'; '*Quality Management – Change Control*'; & '*Documentation Procedures/PSF/TAs*' were consistently found in the most common deficiencies.
  - The identification of deficiencies relating to '*Contamination, chemical/physical (or potential for)*' has increased significantly in 2012 and 2013

	Year and Ranking in that Year				
Deficiency Category	2009	2010	2011	2012	**2013**
Investigation of anomalies	1	1	1	1	1
Quality management	-	2	5	9	2
Investigation of anomalies – CAPA	3	5	3	4	3
Contamination, chemical/physical (or potential for)	-	-	-	10	4
Supplier and contractor audit	7	8	6	2	4
Quality management – change control	2	3	2	8	6
Documentation - procedures/PSF/TAs	5	4	8	-	=7
Personnel issues – training	-	-	-	-	=7
Design and maintenance of equipment	-	-	-	7	=9
Documentation – manufacturing	-	9	9	-	=9
Finished product testing - chemical	-	-	-	-	=9

  - There were no significant collective issues apparent in the data i.e. where a number of deficiencies in related categories indicate a bigger issue.

Examples of Top 5 Defect Area Findings

1. Investigation of Anomalies
   - There was no scope to define when or how planned deviations may be used. This allowed such deviations to be used indefinitely.
   - A planned event was raised for a damaged/worn item of equipment, when a deviation was appropriate. There was no investigation as to the cause of the damage and although a critical item, no spare was available for replacement, production was therefore allowed to continue potentially compromising the product.
   - Following identification of failings in the returns process resulting in an update to the procedure, there had been no consideration of the impact of the failings in the process on previously returned materials.
   - A significant number of investigations were not being completed in a timely manner with a large number still open over a year after initially being raised and one example had been open for 15 months.
   - The complaint for a missing label on a product bottle was not rigorously investigated to identify root cause. Instead the investigation was used to predominantly justify the current controls.

Examples of Top 5 Defect Area Findings

1. Investigation of Anomalies [contd.]
   - An appropriate level of root cause analysis was not applied during investigation of deviations. The true root cause(s) of deviations associated with numerous reconciliation issues were not adequately determined.
   - The product impact assessment and associated rationale for determining whether any issue encountered was a significant deviation or a lower level incident, was not formally documented.
   - Complaint Investigations for unfit tablets were lacking in that the complaint investigations did not document all the decisions and measures taken as a result of the complaints. There were no root cause or corrective and preventative measures identified. The implication for other batches was not documented despite being noted as a repeat issue and it was not apparent that the Qualified Person had been involved in the investigation process.

Examples of Top 5 Defect Area Findings

2. Quality Management

- There were no Self inspections carried out in the previous year, nor was there a programme established for the current year.
- The laboratory pharmaceutical quality system was silent with respect to stability sample management. The company stated that R&D procedures were in place to manage the latter however it was noted that a significant number of R&D procedures were overdue and that there was no oversight of the R & D function via self-inspection.
- There was no Quality Risk Management procedure.
- All significant Quality incidents were not included in the PQRs.
- The Complaints, Errors and Exceptions Procedure was weak in that:
  - The implications of complaints on other batches/analyses potentially affected and the trending of complaints was not formalised. In addition the procedure did not reflect the current complaint handling process.
  - The exceptions procedure was ambiguous as to how to perform an impact assessment or root cause analysis for the investigation levels detailed.

Examples of Top 5 Defect Area Findings

2. Quality Management [contd.]

- Quality risk management procedure, although based upon on GMP Part III (ICH Q9), was lacking in suitable detail as to how risk management would be applied on-site both proactively and retrospectively.
- The quality system was not being maintained in that:
  - Product Quality Reviews (PQRs) had not been completed during the required period.
  - A significant number of SOPs were past their review date, multiple change controls had been open for longer than 6 months and a number of complaints had not been closed.
  - Quality management reviews were not carried out at as per procedure.
  - API audits for two APIs had not been performed as per the formal plan. There was no process to justify why these suppliers could continue to be used.
  - One third of the planned self inspections had been completed in the defined period.

Examples of Top 5 Defect Area Findings

3. Investigation of Anomalies – CAPA

- During the review of CAPAs, the following issues were identified:
  - It was not clear how CAPA actions were linked to the root cause
  - There was no expected time given for implementation.
  - There was no mechanism as to how CAPA could be measured and shown to be effective.
- The manufacturing investigation into extraneous matter found in an API manufactured by a contract company failed to detail the final disposition of the material or the actions that needed to be performed i.e. that multiple batches of the API were to be returned to the supplier to be reprocessed.
- There was no process to ensure CAPA actions from any system including regulatory inspections were completed on time and in full.
- CAPA systems did not ensure that commitments made to the Licensing Authority following the last inspection were completed in line with the commitments provided.
- The CAPA raised regarding an API supplier that had been determined as unacceptable had not included an action to remove the manufacturer from relevant Marketing Authorisations.

Examples of Top 5 Defect Area Findings

4. Contamination, chemical/physical (or potential for)
   - There was no documented process for assessing suitability of new molecules to be introduced to site to ensure that they were not manufactured in a facility that was non compatible with the toxicity profile of the molecule and that cleaning procedures were appropriate for the risks posed.
   - A roller compactor in the engineering workshop was covered in white powder. The unit had been there for ~6 months and the powder identity was unknown.
   - Unidentified white powder was noted on the floor of the production corridor and on a hand pallet truck in the area.
   - Cleaning validation did not include an assessment or criteria for individual swab results. Consequently, individual swabs could fail acceptance criteria with average results still being within limits. The approach limited the capability to identify hard to clean locations and evaluate the overall effectiveness of cleaning processes.

Examples of Top 5 Defect Area Findings

4. Contamination, chemical/physical (or potential for) [contd.]
   - Maximum allowable dirty equipment hold times had not been established to support the effectiveness of cleaning processes subject to cleaning validation.
   - There had been no attempts to operate on a campaign basis and no specific containment measures had been used. In addition, the cleaning systems applied were not considered to be acceptable for products of this nature [*potent*] handled in shared facilities.
   - There was no justification or risk analysis performed for the manufacturing of multiple batches [*of different products*] within the same granulation suite.

Examples of Top 5 Defect Area Findings

5. Supplier and contractor audit

- The audit report for a supplier was not available when the site was added to the approved supplier list. As such there was no contemporaneous evidence upon which to base the approved manufacturer decision.
- The address of a supplier site on the approved supplier file for an API differed from the address as listed on the most recent audit report.
- Audit Reports for an API were high level and it was not apparent what had actually been audited, this contravened the site procedural requirements.
- The maintenance and control of the approved supplier list was not robust as evidenced by an API supplier being listed as an approved supplier on the approved supplier list despite an audit four months previously specifying that the supplier was no longer to be approved. In addition, API had been received on site since the audit date.
- Audit frequency was specified as required by Risk Assessment however there was no maximum time frequency specified in a number of instances.

Examples of Top 5 Defect Area Findings

5. Supplier and contractor audit [contd.]
   - In a Quality Assurance Agreement it was observed that the contact name for the contract giver was a person located at a site which has been closed for some time. The agreement failed to adequately describe the transportation conditions for APIs i.e. that an API should be transported at 3-8°C.
   - The approved supplier listing contained a number of errors, e.g. missing suppliers, and some suppliers were on the list that should not have been.
   - Supplier audit SOP was silent with respect to API suppliers and was ambiguous with respect to services.
   - An audit report for a supplier was held concluding that the site was not suitable for supply of an API due to GMP issues. However, the action taken was not sufficient as the active substance stock held that had been manufactured on the aforementioned site was not all quarantined and rejected.

Areas for Attention

- Based on review of the observed deficiencies, upcoming changes to GMP legislation and information received from other authorities; the following areas have been targeted as priority areas;
  - Data Integrity (DI)
    - DI issues, both as a result of bad practise and to a significantly lesser extent intentional fraud, have been observed across all geographical locations and sectors of the industry with some very high profile cases being observed recently. There will therefore be a focus on this area during inspections in the near future. In addition;
      - the MHRA has communicated an expectation that companies will carry out a routine effectiveness review of their governance systems to ensure data integrity and traceability are maintained (see MHRA communication issued on the 16th Dec 2013)

        http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/News/CON355490

Areas for Attention (cont.)

- Falsified Medicines Directive (FMD)
  - When the FMD legislation (European Directive 2011/62/EU) came into force in the UK on 20 August 2013, a number of requirements were introduced, including;
    - manufacturers, importers and distributors of APIs are required to register with the MHRA. MIA holders are required to confirm the registered status of their API suppliers.
    - API imported from a third country is required to be accompanied by a third country authority written confirmation of EU GMP equivalence, or a waiver described in Art 46(b) of the Directive.
    - Brokers of finished medicinal products in the UK have to register with the MHRA
  - Compliance with the requirements of the FMD legislation along with the knowledge and maintenance of the supply chain will be a focus during inspections.
- '*Investigation of anomalies*' remains the most cited inspection deficiency over the last five years
  - This will therefore remain an area of focus during inspections
- Potential for Contamination
  - This area will be a focus during inspections for the following reasons;
    - Deficiencies categorised as '*Contamination, chemical/physical (or potential for)*' have significantly increased in occurrence in the last two years (fourth most frequently sited category in 2013).
    - There has been a general trend towards higher potency active substances, therefore increasing the potential for a contamination event to have a greater impact.
    - Changes in EU GMP Chapters 3 and 5 regarding 'dedicated facilities'

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Regulating Medicines and Medical Devices

Thank you

Medicines and Healthcare Products Regulatory Agency