Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Compliance Trends

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Presentation Outline

- MHRA New Look Data Trend
- Deficiency Data Trending 2015
- Comparison with PIC/S findings
- Learning and Reflection
- Notes to remember

Changes on Deficiency Trending

Data changes:

- High impact vs high frequency issues
- All classifications (C, M, O)
- ‘Big data’ opportunities

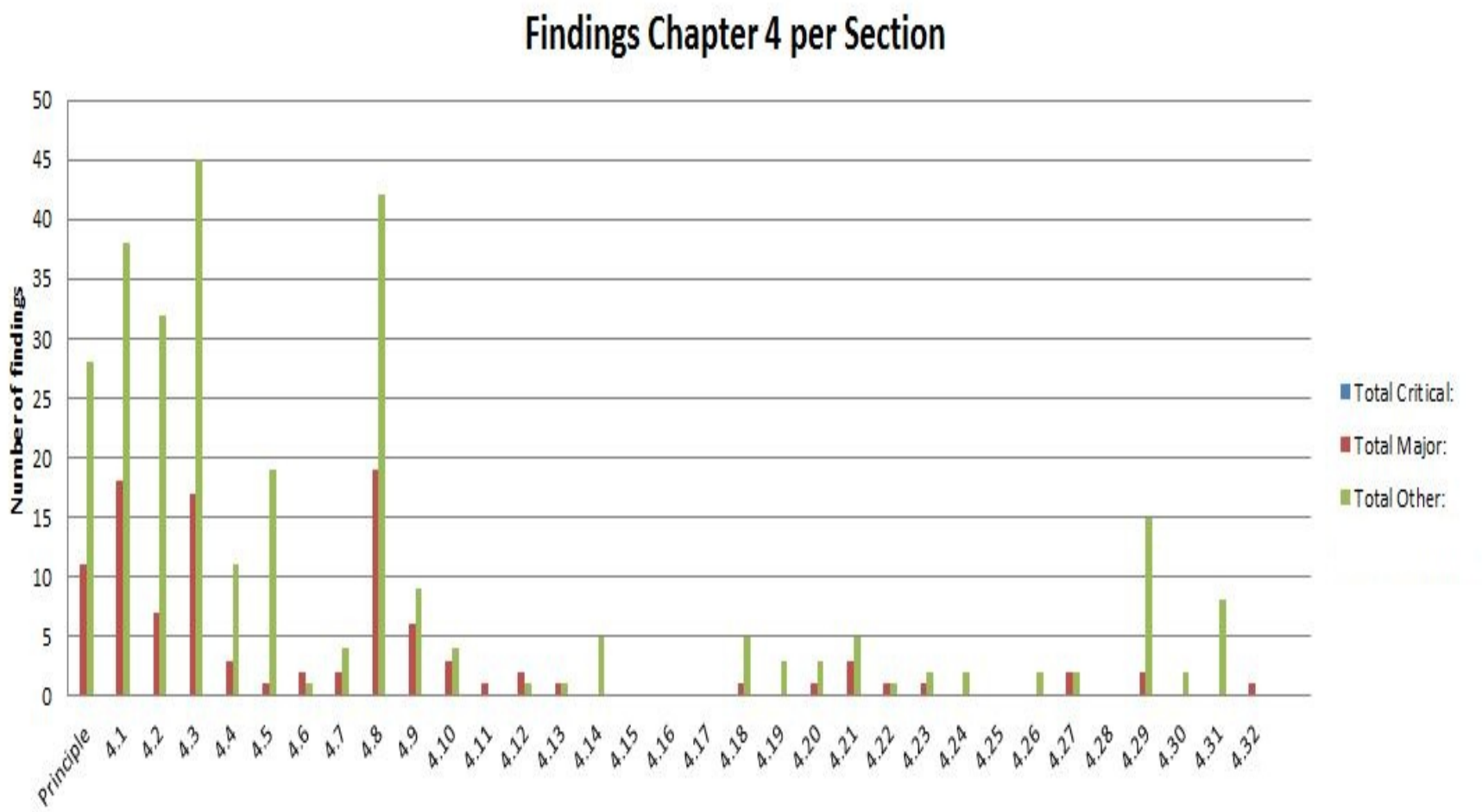
Reporting and analysis:

- Sub-chapters of EU GMP Guide
- Low frequency-high impact and high frequency low impact issues
- CMT/ IAG/ Regulatory action
- Sector, geography, size

Example – By site demographics

Country	IAG	CMT	SNC	GMPC restrictions	CMT/IAG follow up	GMP Category
Korea	N	N	N	N	N	2o
UK	N	N	N	N	N	2u
India	N	N	N	N	N	2o
Korea	N	N	N	Y	N	2o
India	N	N	N	Y	N	2o
India	N	N	N	N	N	2.1o
Indonesia	N	N	N	N	N	2o
UK	N	N	N	N	N	4U
UK	N	Y	N	N	N	1u
UK	N	N	N	N	N	1u
India	N	N	N	N	N	2o
UK	N	N	N	N	N	1u
UK	N	N	N	N	N	8u
UK	N	N	N	N	N	2u
UK	N	N	N	N	N	3u
UK	Y	N	N	N	Y	2u
UK	Y	N	N	Y	Y	2u
USA	N	N	N	N	N	2.1o
USA	N	N	N	N	N	2o
UK	N	N	N	N	N	9u
UK	N	N	N	N	N	1u
UK	N	N	N	N	N	2U
UK	N	N	N	N	N	2.1u
UK	N	N	N	N	N	2u
UK	N	N	N	N	N	2u
India	N	N	N	Y	N	2.1o
UK	N	N	N	N	N	3u
UK	N	N	N	N	N	3u
UK	N	N	N	N	N	6u
UK	N	N	N	N	N	2u
UK	N	N	N	N	N	4u

Example – by Chapters and references



Deficiency Data Trending 2015

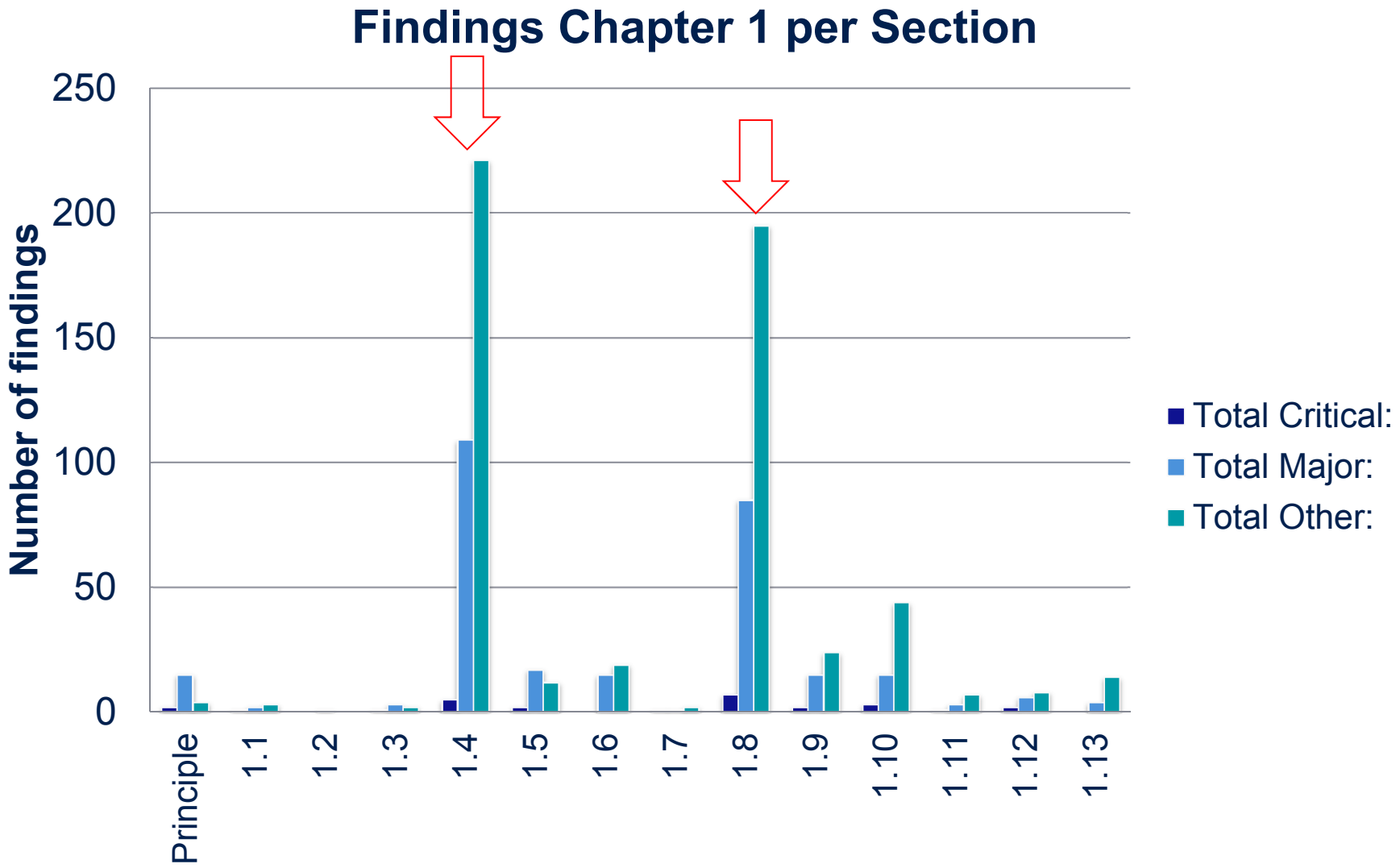
GMP Inspections 2015 & 2016

	2015	2016 (Jan – Aug)
Total number of inspection	303	195
UK inspections	224	173
Overseas inspections	79	22

Most cited deficiency groups (Top 10)

Ranking	Groups	Critical	Major	Others
1	Quality System	27	293	555
2	Complaints and Recall	10	25	94
3	Documentation	9	138	372
4	Quality Control	4	26	136
5	Computerised Systems	1	21	19
6	Production	0	161	357
7	Premises & Equipment	0	107	311
8	Validation	0	93	128
9	Personnel	0	41	95
10	Materials Management	0	19	134

Deficiencies in Quality System



Chapter 1.4

1.4 viii	A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality
1.4 xii	Prospective evaluation of planned changes and their approval prior to implementation
1.4 xiii	Post change evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality
1.4 xiv	Investigations - appropriate level of root cause analysis using Quality Risk Management principles Appropriate CAPA – effective implementation

Chapter 1.8

1.8 vii	Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented
1.8 x	A system is available to recall any batch of product, from sale or supply
1.8 xi	Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence

Deficiencies on Effective Monitoring

A state of control was not established or maintained by using effective monitoring and control systems for process performance and product quality, as evidenced by:

- The training of aseptic area operators was significantly out of date for aseptic area validation activities
- Annual competency checks for all relevant staff were also significantly out of date
- Training record showed no GMP refresher training evidence
- New technician started unsupervised manufacture but was not formally authorised to perform manufacture, indicative of a lack of control and invisible to product release staff

Deficiencies on Effective Monitoring

- There was no formal process on-site to ensure the updates to regulatory requirements were considered for impact on to the site quality system; for example Chapter 3, 5 and Annex 15

- There was no formal procedure to ensure that all updates to EU GMP were captured, reviewed and implemented

Deficiencies on Change Control

Change Control processes were deficient in that:

- The change control procedure did not include an appropriate process for effectiveness checks
- The change control form included a pre-populated statement of “approved changes have been implemented satisfactorily” and did not easily support any other comment
- Change controls were raised after projects were initiated
- There was no evidence for completion of actions within the change control reports prior to closure

Deficiencies on Investigations and CAPAs

Deviations were not fully recorded and investigated as a result appropriate CAPAs were not implemented as evidenced by :

- The nature of deviation was described incorrectly, as a result the quality impact of the deviation and CAPAs implemented were not appropriately assessed

- Complaints were not fully investigated as a result appropriate measures may not have been taken to prevent reoccurrence

Deficiencies on Investigations and CAPAs

Deviation investigations did not include an appropriate level of investigation and did not capture all relevant information

Root cause was not always adequately considered adequately. Example concluded a human error but did not consider that the error was influenced by the lack of a procedure to control the activity in question

No process for assessing the effectiveness of the corrective / preventative actions to ensure that these are monitored and assessed, in line with Quality Risk Management principles

Data Integrity (basic ALCOA)

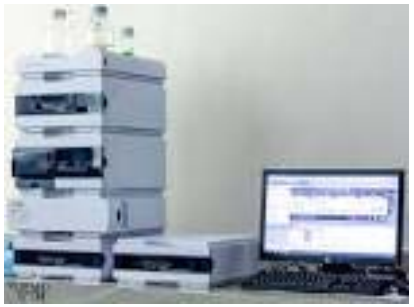
A - Attribute

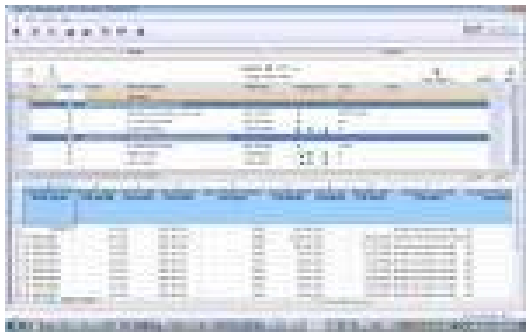
L - Legible

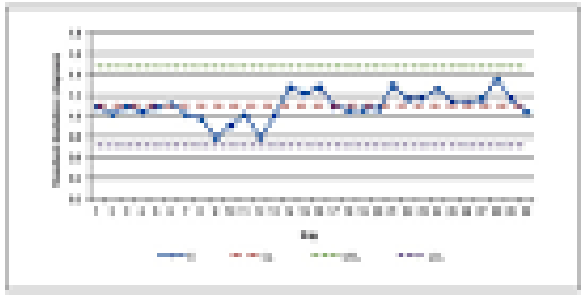
C - Contemporaneous

O - Original

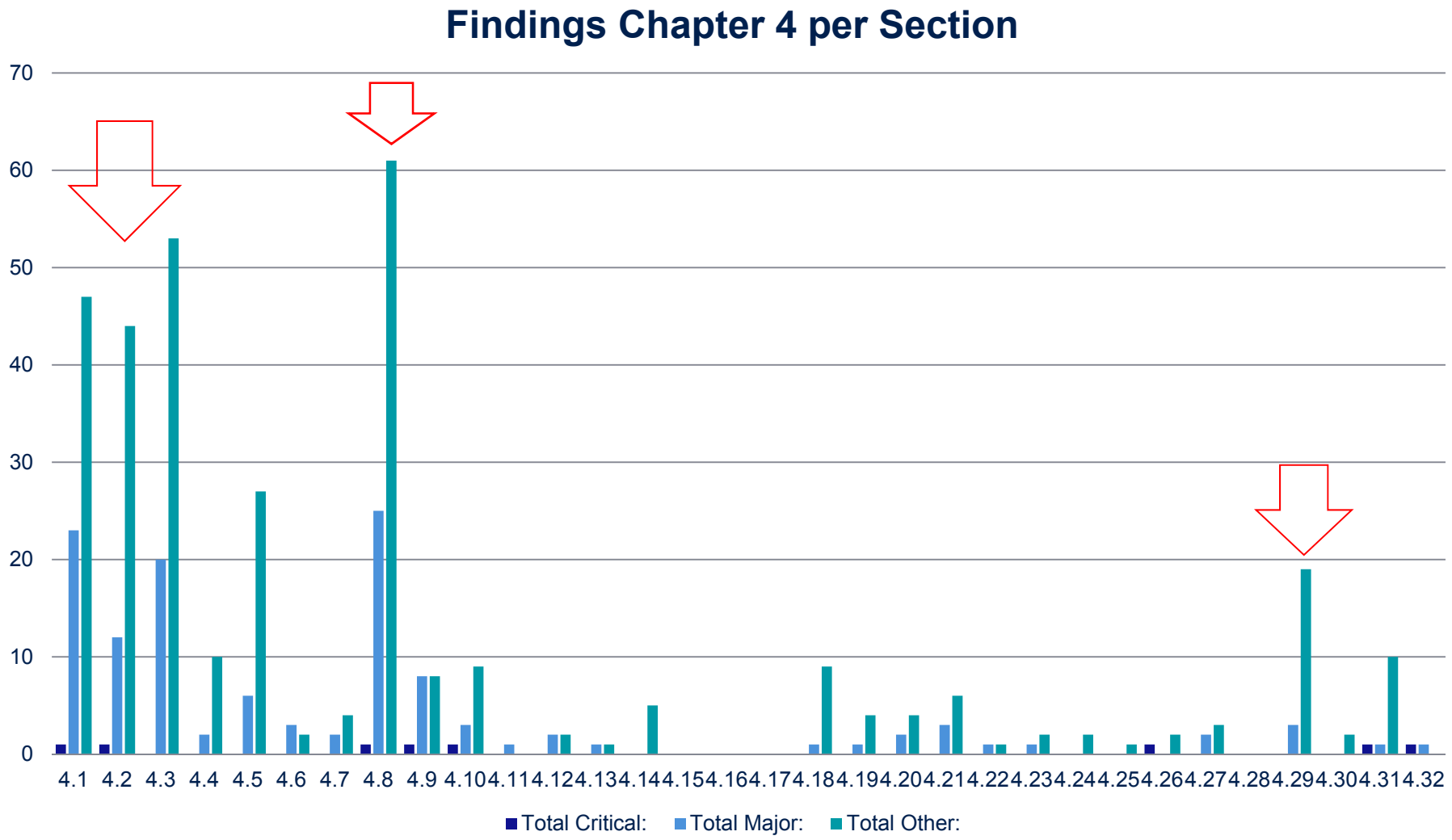
A - Accurate







Deficiencies in Documentation



Chapter 4

4.1	All types of document should be defined and adhered to. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.
4.2	Documents should be designed, prepared, reviewed, and distributed with care.
4.3	Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.
4.8	Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
4.29	There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached.

Deficiencies on Documentation

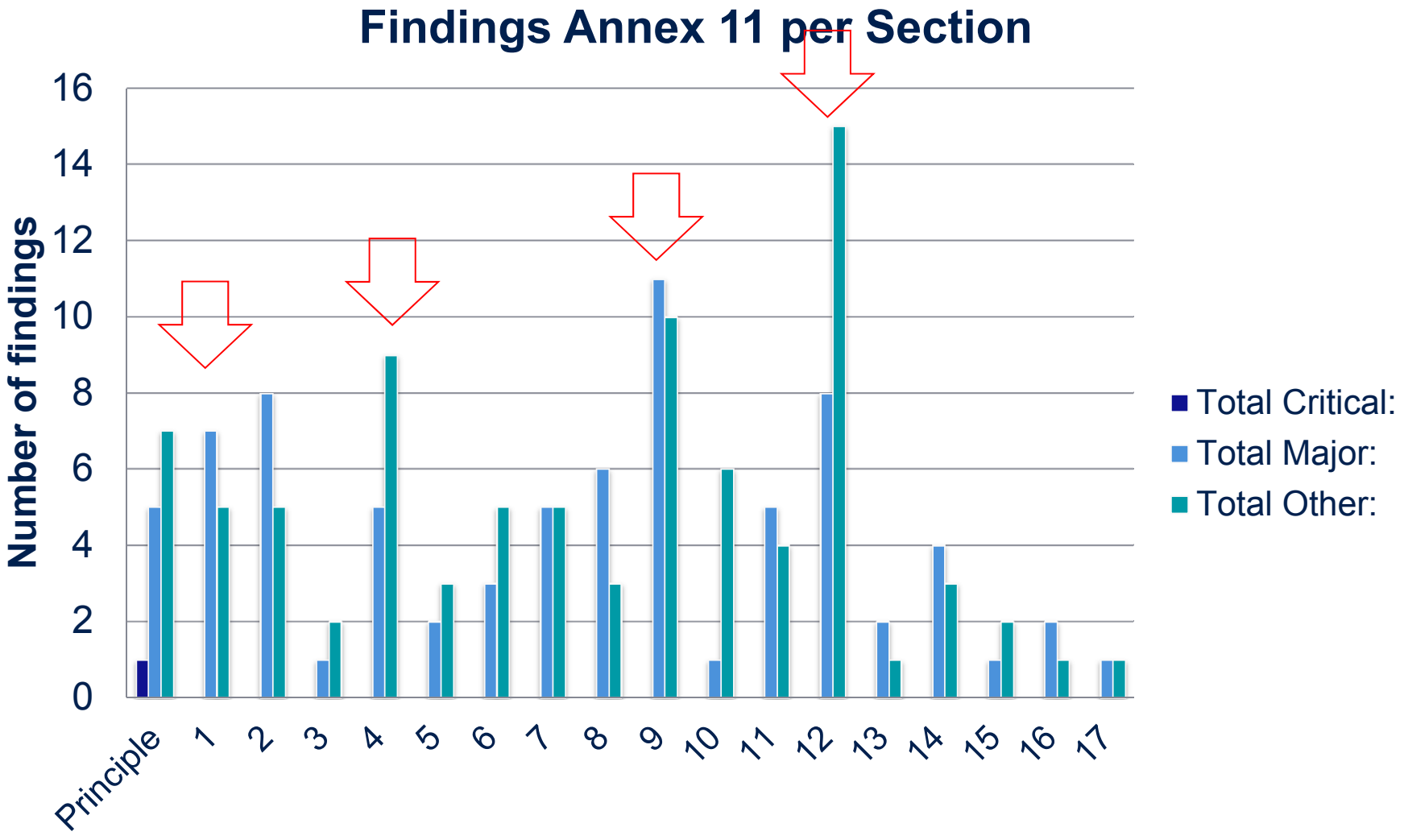
- Pencil and tippex were present in the facility
- Overwriting hand recorded data and lack of adequate explanation for changes
- ‘Post-it’ notes, loose note paper and hand-written notes on labels seen throughout the facility
- Inappropriate changes made by obscuring data via fixing stickers over entries to amend the data recorded
- An uncontrolled, hand-written SOP for label printing was present in the printing area. This also included the system password

Deficiencies on Documentation

There was evidence of destruction of multiple parts of records of prime data

- Records were partially burnt or in waste bags awaiting destruction at the rear of the site
- Included signed batch documentation, signed balance print outs, Certificates of Analysis and formally issued engineering record sheets
- Some of the documents had been re-issued and completed retrospectively with the sanction of QA
- No explanation or record of the replication of data

Deficiencies in Computerised Systems



Annex 11

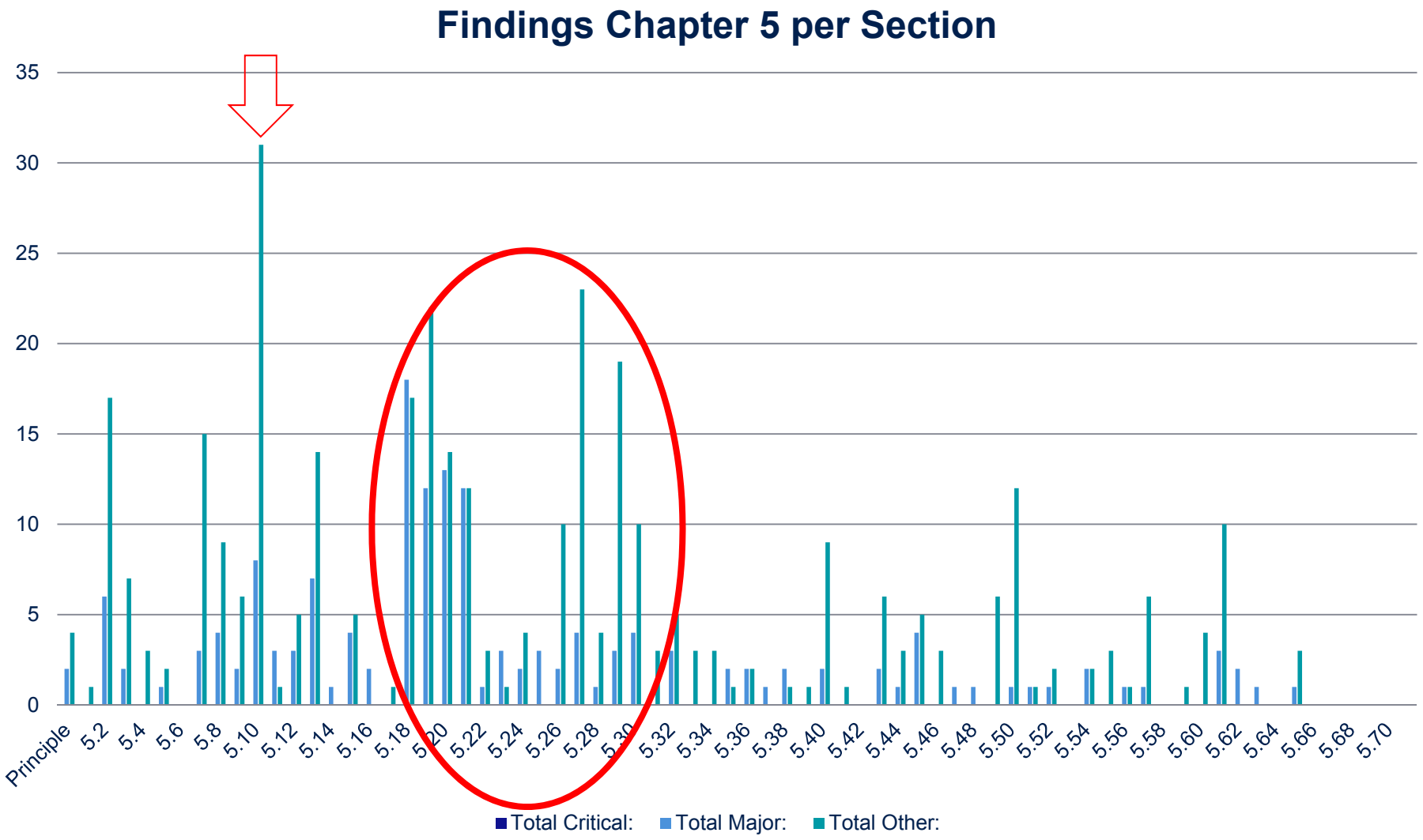
1	Risk Management
2	Personnel
4	Validation
9	Audit Trails
12	Security

Deficiencies on Computerised Systems

Systems and procedures to ensure data integrity was maintained within the laboratories were deficient in that:

- Risk management principles not applied throughout the lifecycle of computerised systems to determine the extent the validation and data integrity controls required
- Electronic data not used to check analytical results
- No control of user permissions on HPLC systems, e.g. no individual log-on and no separation of access levels
- Setting within HPLC software not fully enabled e.g. audit trail
- Analyst had access to delete data

Deficiencies in Production

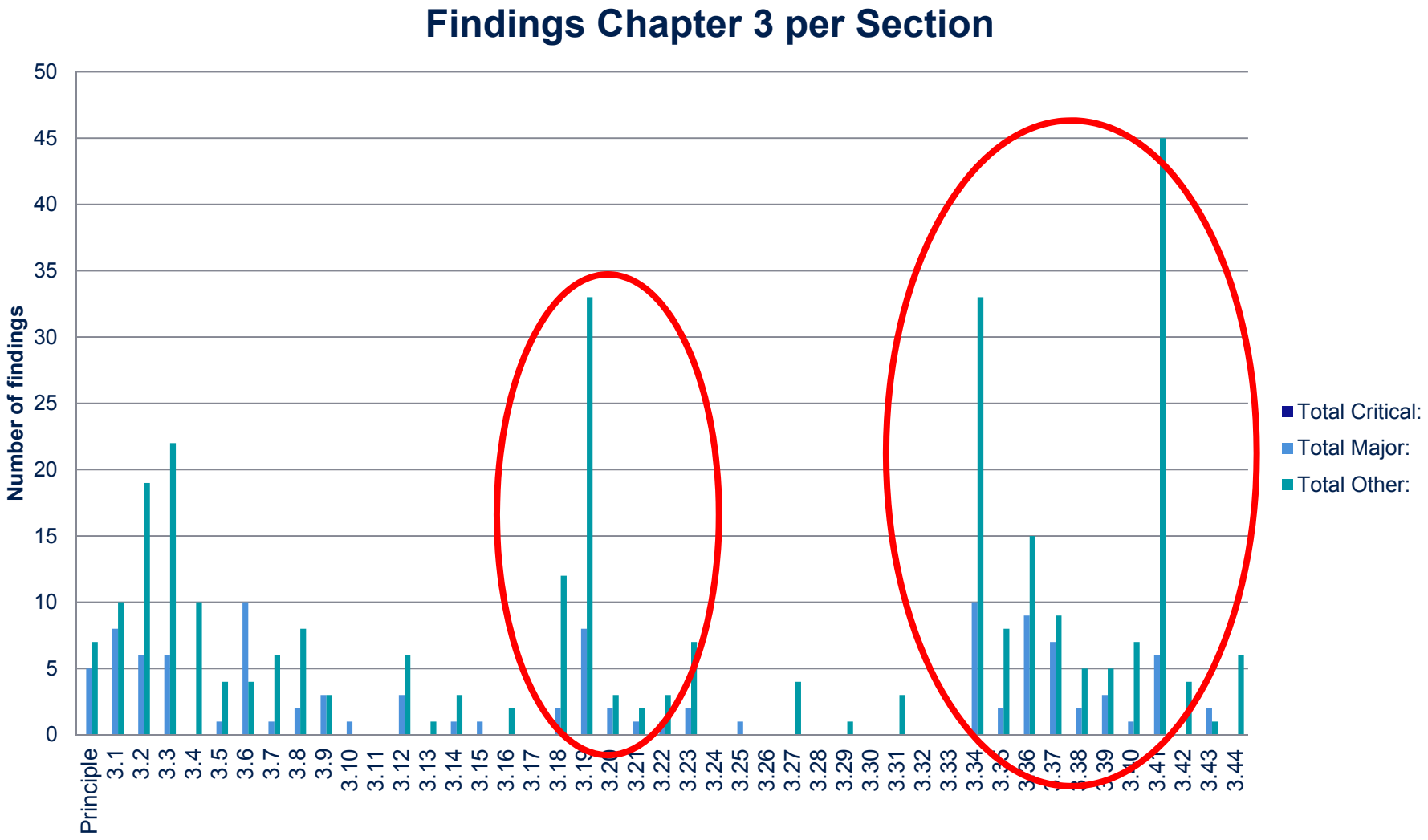


Deficiencies in Production

General measures to prevent contamination of, and cross contamination between, products was not adequate in that:

- New product introduction process did not consider the toxicity and potency risks to determine the need for any degree of dedicated facility
- No formal process to define how organisational and technical measures should be developed and implemented to prevent cross contamination between products
- No planned schedule for cleaning of the local extract and dust collection system in the compression room

Deficiencies in Premises & Equipment



Deficiencies in Premises & Equipment

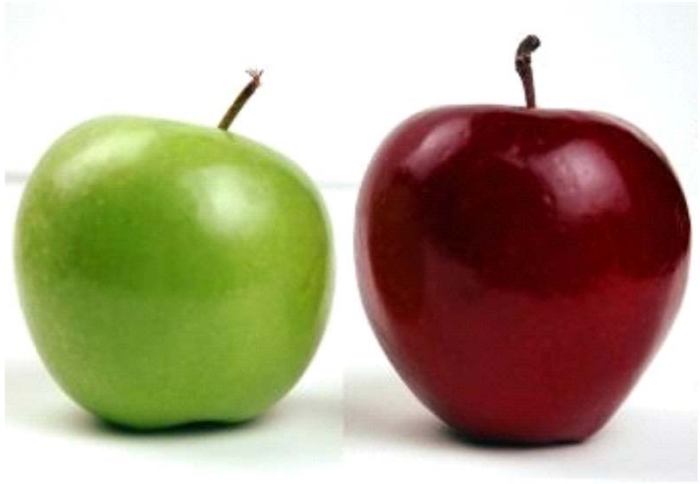
The temperature mapping of the facility and storage areas was deficient in that:

- Retention sample storage area did not have a temperature logger in the vicinity
- The mapping of the production and warehousing areas performed by the contractor had not been approved by the company
- The configuration of the drug storage room had changed with no assessment of the potential impact on the validity of the temperature mapping of the area

Deficiencies in Premises & Equipment

- QC sampling of chemicals were performed in the material airlock in the pilot rooms. Room usage not recorded and no record room was clean and clear prior to use
- QC sampling of packaging materials were not performed in a dedicated area in the Goods-in area
- Areas of the facility and equipment were in a poor state of repair, e.g. damaged filter panel covers in the drying tunnel and damaged vents
- The rubber seal within the dispensing equipment showed evidence of deterioration and shedding

Comparison with PIC/S findings



Most cited deficiency groups

Ranking	MHRA	PIC/S
1	Quality System	Quality System
2	Complaints and Recall	Production
3	Documentation	Validation
4	Quality Control	Premises & Equipment
5	Computerised Systems	Quality Control
6	Production	Data Integrity
7	Premises & Equipment	Personnel
8	Validation	Regulatory Issues
9	Personnel	Materials Management
10	Materials Management	Miscellaneous

PIC/S Guidance on Classification of Deficiencies

- Provides a tool to support the risk based classification of deficiencies from GMP inspections
- Provides a framework to support consistency amongst Inspectorates
- Informs industry on the principles used to classify deficiencies
- Details examples of the classification of different types of deficiencies
- Provides additional support to help understand how to write observations and what may be considered poor practice in writing observations

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Inspection Action Group (IAG) and Compliance Management Team (CMT)

Statistics - GMP

IAG & CMT Processes

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Year	IAG cases	CMT cases
2012	23	-
2013	21	-
2014	12	15
2015	12	18
2016	7	16