Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

MHRA GMP Inspection Deficiency Data Trend 2015

Introduction

The GMDP Inspectorate has improved the way of gathering the inspection deficiency data for 2015. The new data trending can allow stakeholders to identify:

- The severity and frequency by the EU GMP references
- The overall number of deficiencies by categories: Critical, Major, Other
- The high impact vs high frequency issues

The purpose of publishing the inspection deficiency data is to allow stakeholders to perform their own assessment against the deficiency findings as part of self-inspection and continuous improvement. Deficiency examples are included for each relevant chapter and annex for information.

Note: This is the data set for dosage form only.

Deficiency Data Trending 2015 (Dosage Forms)

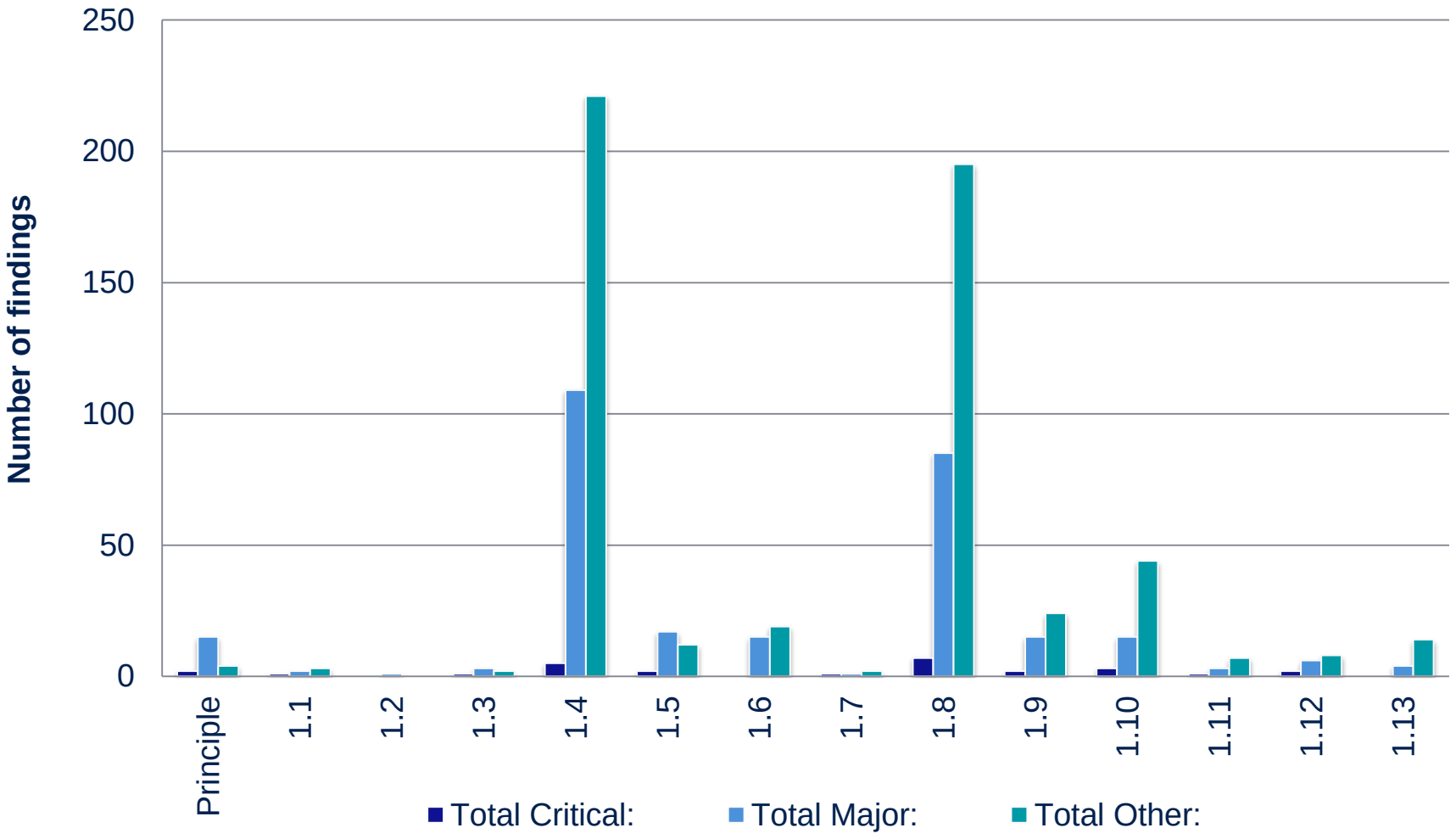
GMP Inspections conducted in 2015

Total number of inspection	303
UK inspections	224
Overseas inspections	79

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

Findings Chapter 1 per Section



Examples Deficiencies – Chapter 1

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- The training of aseptic area operators was significantly out of date for aseptic area validation activities
- Annual competency checks for all relevant staff were also significantly out of date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

Examples Deficiencies – Chapter 1

- 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

Examples Deficiencies – Chapter 1

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

Examples Deficiencies – Chapter 1

- The change control system had not been used in support of the change of use of production rooms/ workflow
- The Change Management SOP did not include formal post implementation review of changes
- The Change Control procedure did not include any requirement for appropriate effectiveness checks. The procedure did not refer or link to the Quality Risk Assessment SOP, and the requirement for risk assessments was unclear
- Change controls could be closed off before all implementation actions could be completed

Examples Deficiencies – Chapter 1

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

Examples Deficiencies – Chapter 1

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

Root cause was not always adequately considered. 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

Examples Deficiencies – Chapter 1

Deviations were not subjected to adequate root cause analysis or specific actions to prevent recurrence:

- Deviation XX had recorded that personnel had been made aware of the issue to prevent recurrence pending full CAPA, however there was no evidence this had been done and the incident log indicated that a similar issue had occurred 5 days later
- A lump seen in Product name batch XXX (reported in the batch releaser review) and passed to QC for investigation by Production was not recorded on batch documentation, in the incident log or as a deviation. As such there was no record of events at the time each action was taken. There had been no recorded measures to consider prevention

Examples Deficiencies – Chapter 1

Sterility Failure investigations were deficient in that there was a significant lack of detail in investigations conducted following a failure, for example;

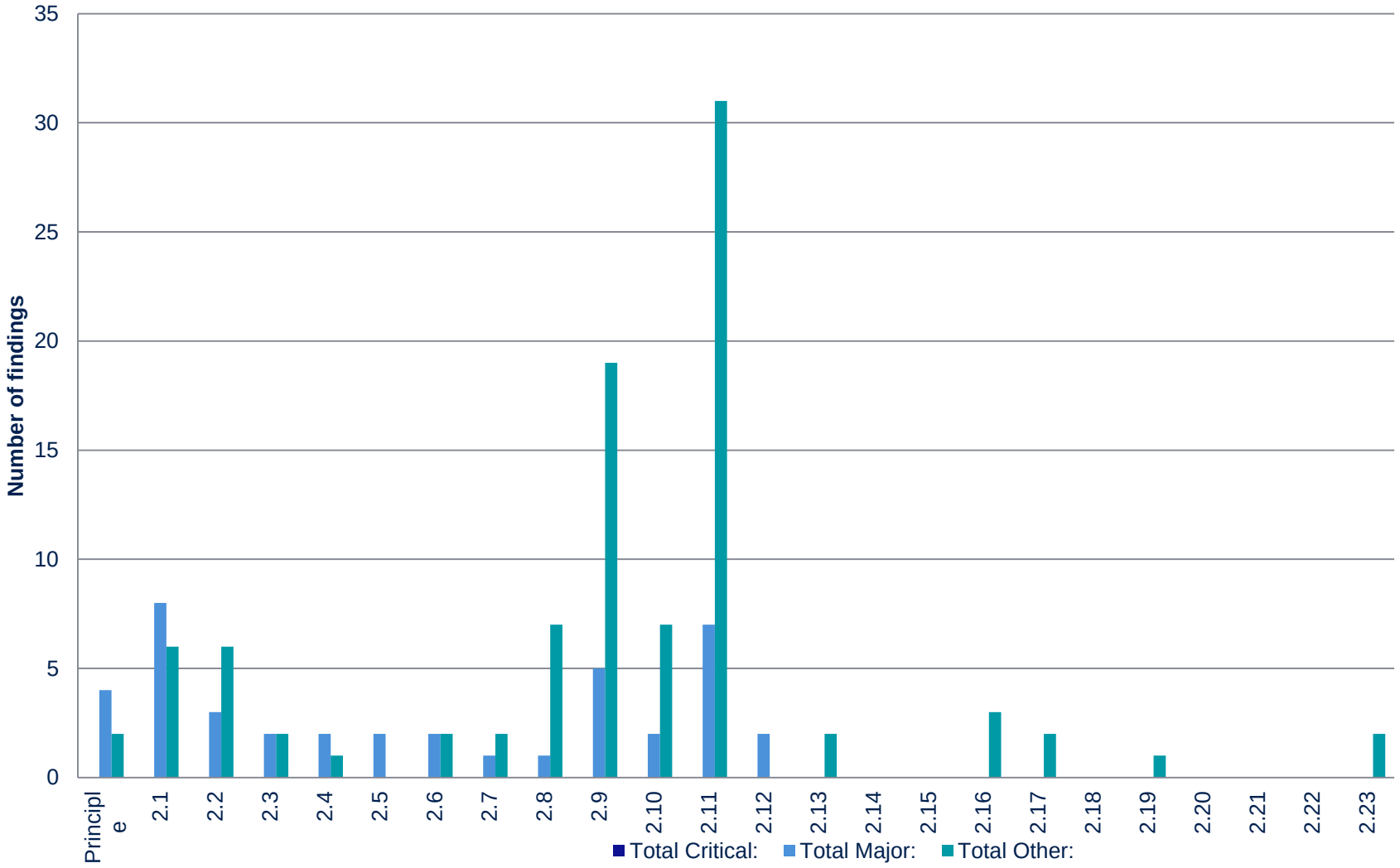
- There were no root causes identified and subsequently no actions taken to prevent any recurrence
- There has been nothing documented and no assessment performed to support continued manufacture and batch release of potentially affected product
- There was no justification for the batches made at the same time and documentation to identify where the sterility test failures took place

Examples Deficiencies – Chapter 1

NCR-XX was raised for the Marketing Authorisation (MA) number being incorrect on cartons. Although this was picked up at the point of QP certification, there was no investigation into why the incoming material checks had not picked this up and also no corrective actions

PDV–XX was raised as an incorrect MA number was printed on a packing specification. The investigation did not detail how the issue was identified. It also did not detail why it had occurred and what had been done to prevent reoccurrence

Findings Chapter 2 per Section



Examples Deficiencies – Chapter 2

There was no job description for the Data Analyst and no training records to demonstrate appropriate training had been provided for the duties assigned to him

There was no formal record of assessment of competence for GMP training

The record showed that the training on the Deviation procedure had not been performed since July 2011, this had been to version 2 when version 3 had already been issued. The company were currently at version 5 with no evidence of training against the new updates

Examples Deficiencies – Chapter 2

Management had not provided adequate and appropriate resources to effectively maintain the pharmaceutical quality system and production operations in that:

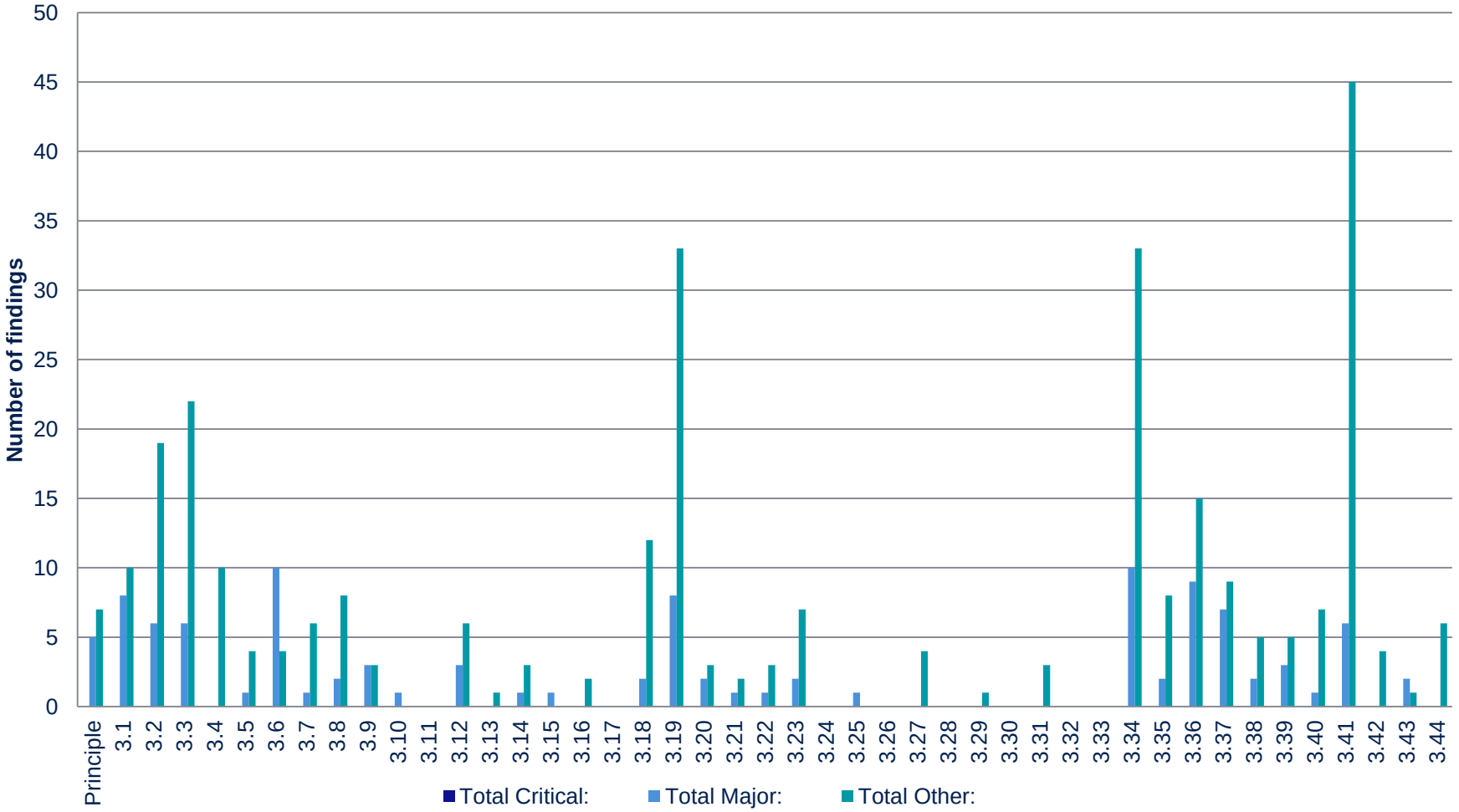
- Vacancies in key production and QC analytical personnel had not been filled for extended periods
- There were inadequate resources available to support the required improvements in the pharmaceutical quality system in parallel with introduction and qualification of the new facility as well as supporting routine production

There was no process for, or record of, training in all procedure updates

Examples Deficiencies – Chapter 2

- Personnel had no documented training in the procedures or systems
- The appropriate training for the QP and Managing Director was not clear as they were not identified within the training matrix
- Although comprehension questions were asked at the end of each module, there was no clearly defined pass mark therefore it could not be confirmed that the personnel understood the training
- There was no training and development plan in place for the staff member allocated to manage the non-conformance process to ensure adequately broad GDP awareness
- The person checking returns had not been trained in the current procedure requirements

Findings Chapter 3 per Section



Examples Deficiencies – Chapter 3

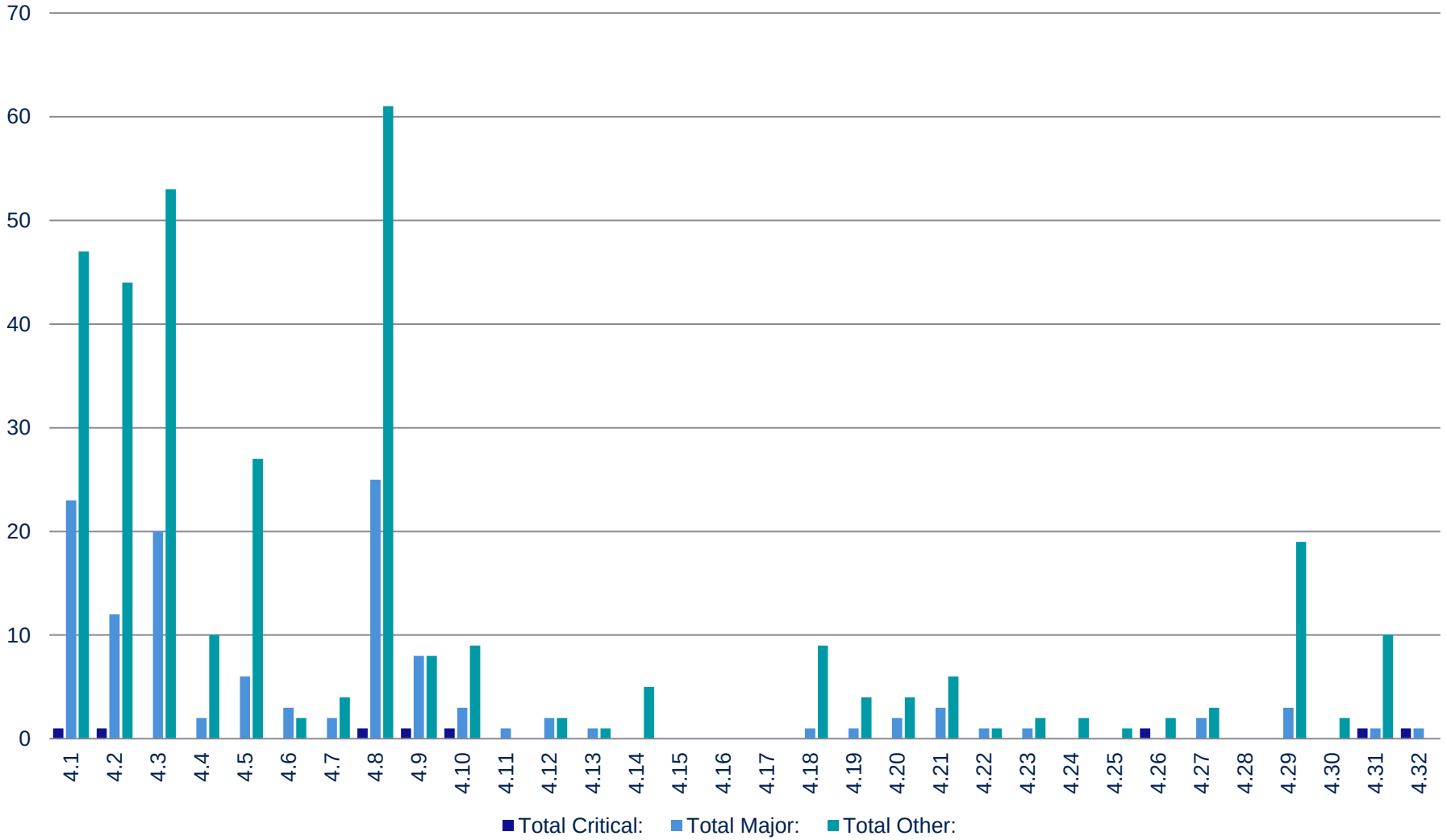
The temperature mapping of the facility and storage areas was deficient in that:

- 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

Examples Deficiencies – Chapter 3

- QC sampling of chemicals were performed in the material airlock in the pilot rooms. Room usage was not recorded and there was no record that the room was clean and clear prior to use
- QC sampling of packaging materials was 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

Findings Chapter 4 per Section



Examples Deficiencies – Chapter 4

- Pencil and tippex were present in the facility
- Overwriting of 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

Examples Deficiencies – Chapter 4

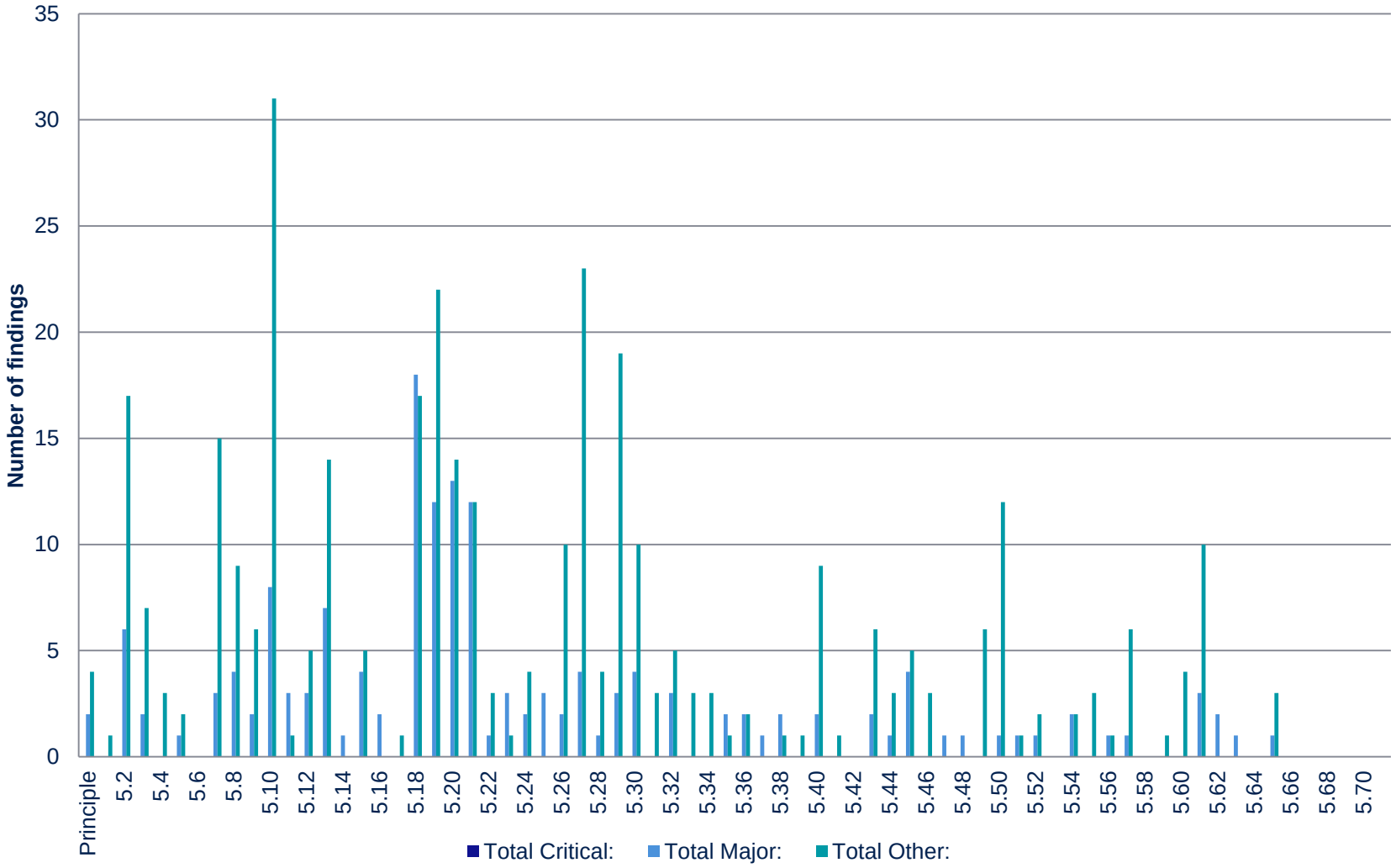
There was evidence of destruction of multiple parts of records of prime data

- 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

Examples Deficiencies – Chapter 4

- There was no procedure for sessional visual checks of gloves on the isolator
- Procedures and forms did not always reflect actual or required practice
- Procedures were not always available or implemented adequately
- There was no documented check for the incoming condition of materials received to the stores

Findings Chapter 5 per Section



Examples Deficiencies – Chapter 5

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

Examples Deficiencies – Chapter 5

- A jug of cleaning liquid with a used cloth was found sitting on the capsule polishing unit that had been signed off as clean. The solution was said to be IPA but emitted a mal odour associated with microbiological contamination. The solution should have been discarded within 24 hours of make-up according to site procedure

- A ‘bulk’ container of IPA solution in the housekeeping store had a similar odour to the quantity found in the encapsulation room

Examples Deficiencies – Chapter 5

There is no formal quality assessment (potency, sensitisation, clean ability), of any new IMP or API prior to receiving it on site and using it during manufacturing/packaging

There was no validation of the cleaning of items used for multiple products:

- The cleaning risk assessment did not consider the toxicity or potency of the materials being handled and was restricted to the difficulty of cleaning
- The automated tablet counter and tablet counting trays, which were used for multiple products, had not been considered as part of the cross contamination risk assessment
- There was no confirmation that the cleaning methods would remove detergent residues

Examples Deficiencies – Chapter 5

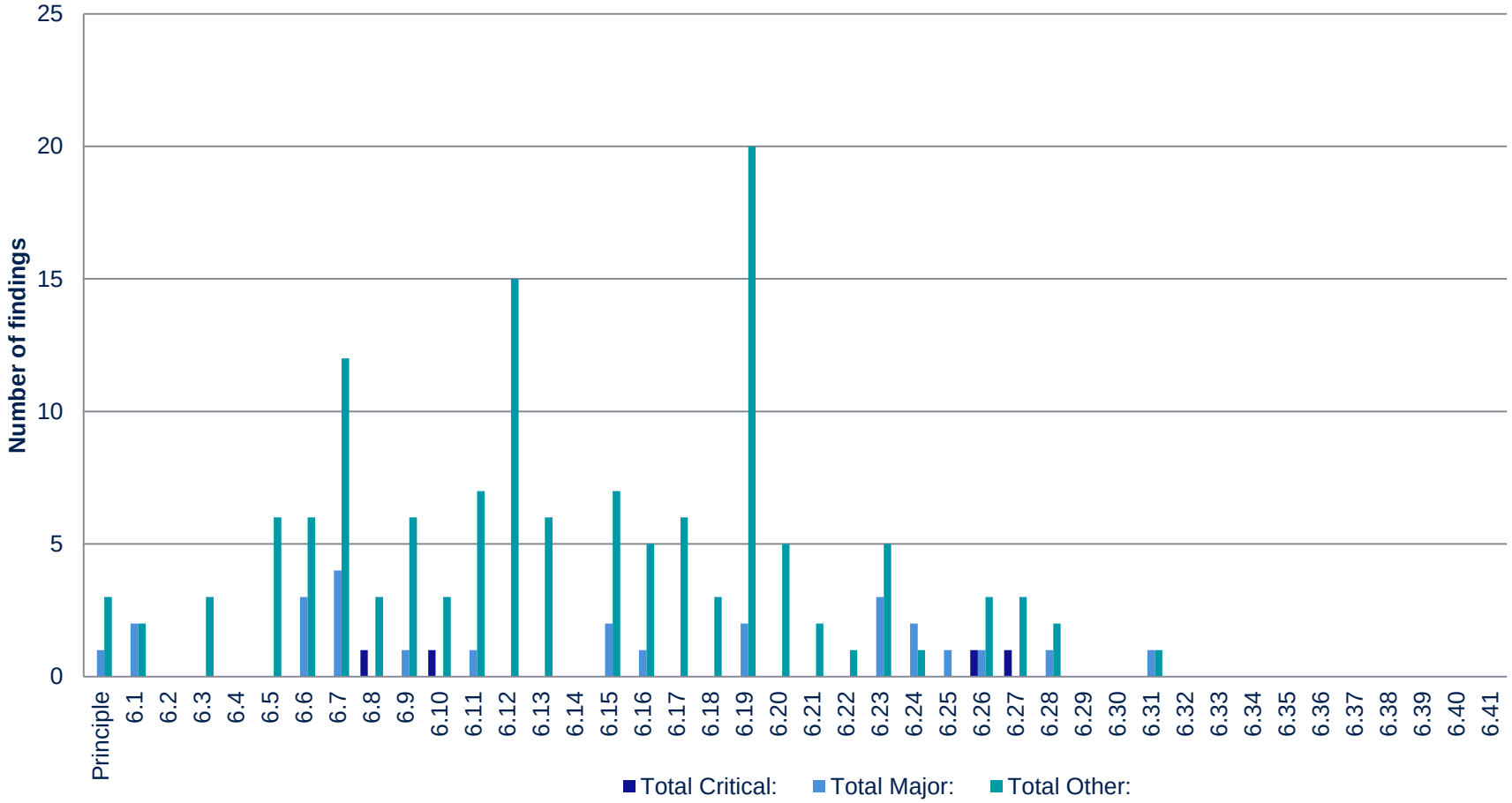
Supplier management was not adequately controlled in that:

- The Active 1 and Active 2 API supplier had been approved without any evidence of audit of the facility. An EDQM certificate of suitability was on file for Active 1 however no certificate was on file for Active 2. The technical agreement with the company only cited Active 2 and did not include Active 1

- An audit of the HDPE bottle supplier had been performed; however no response to the audit was available. The technical agreement with the company was very brief, and did not include details such as TSE certification or labelling requirements

- The approved vendor list observed in the secondary packaging warehouse did not include addresses for all suppliers

Findings Chapter 6 per Section



Examples Deficiencies – Chapter 6

The handling and review of stability study data were deficient in that:

- The review failed to identify the atypically high Equilibrium Relative Humidity (ERH) at 36 and 48 month time points. The out of trend event was not reported and investigated. A risk assessment had not been performed on the products that were available on the market

- An OOS result on appearance was reported at 30 month time point. No action was taken while there were products potentially available in the market

Examples Deficiencies – Chapter 6

QC analytical records for the testing of Product X were deficient in that the IR spectra were missing from the data package and it could not be proven that a check of electronic data had taken place; the only recorded check being a tick on the front page of the data pack with the section on the Certificate of Analysis relating to IR ID testing being entirely blank.

The test sheet for raw material X batch xxxxx was signed and checked as passed although it was still awaiting tests. The trend card associated with this material had also been completed ahead of results and checked.

Examples Deficiencies – Chapter 6

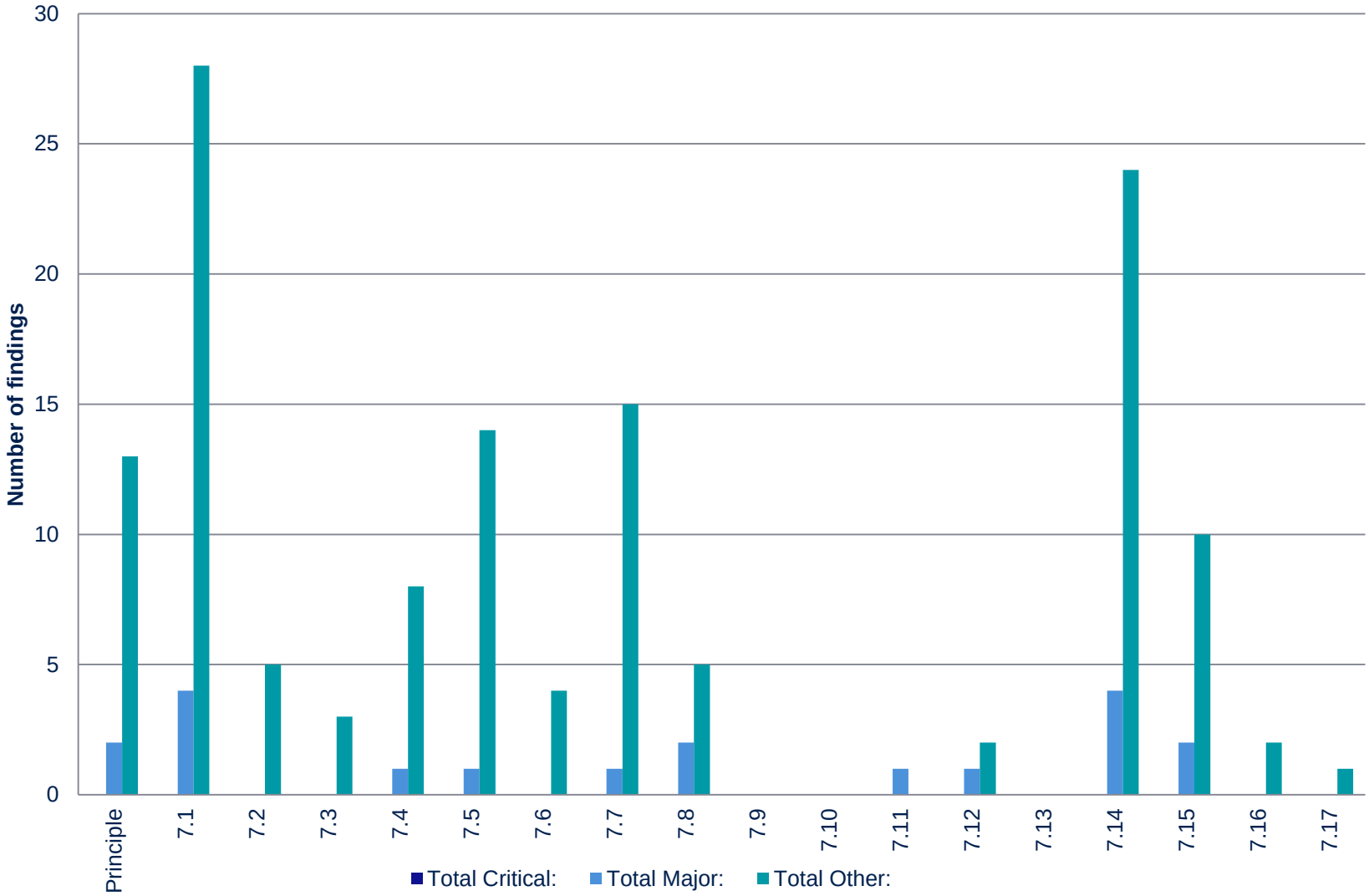
Glassware found within the main Chemistry laboratory was found to be stored wet

pH meter electrodes located in the new microbiology laboratory had not been topped up with buffer storage solution so the pH probes had dried out

Room temperature was not recorded or monitored in critical laboratory areas including the sample storage area and standard storage area

The tests to ensure media was able to support microbial growth were not robust, for example there was no growth promotion test on each batch of media and there was no pH testing of media

Findings Chapter 7 per Section



Examples Deficiencies – Chapter 7

The management of outsourced activities was deficient as evidenced by:

- There was no proceduralised assessment of the suitability of the Contract Acceptor to carry out the outsourced activities
- There had been no documented assessment of the suitability of Contract Acceptor A to carry out the relabeling activities for the parallel distributed products
- The company had not reviewed or assessed the records and the results related to the outsourced activities to Contract Acceptor A

Examples Deficiencies – Chapter 7

Technical Agreements and audits were not in place for a number of suppliers

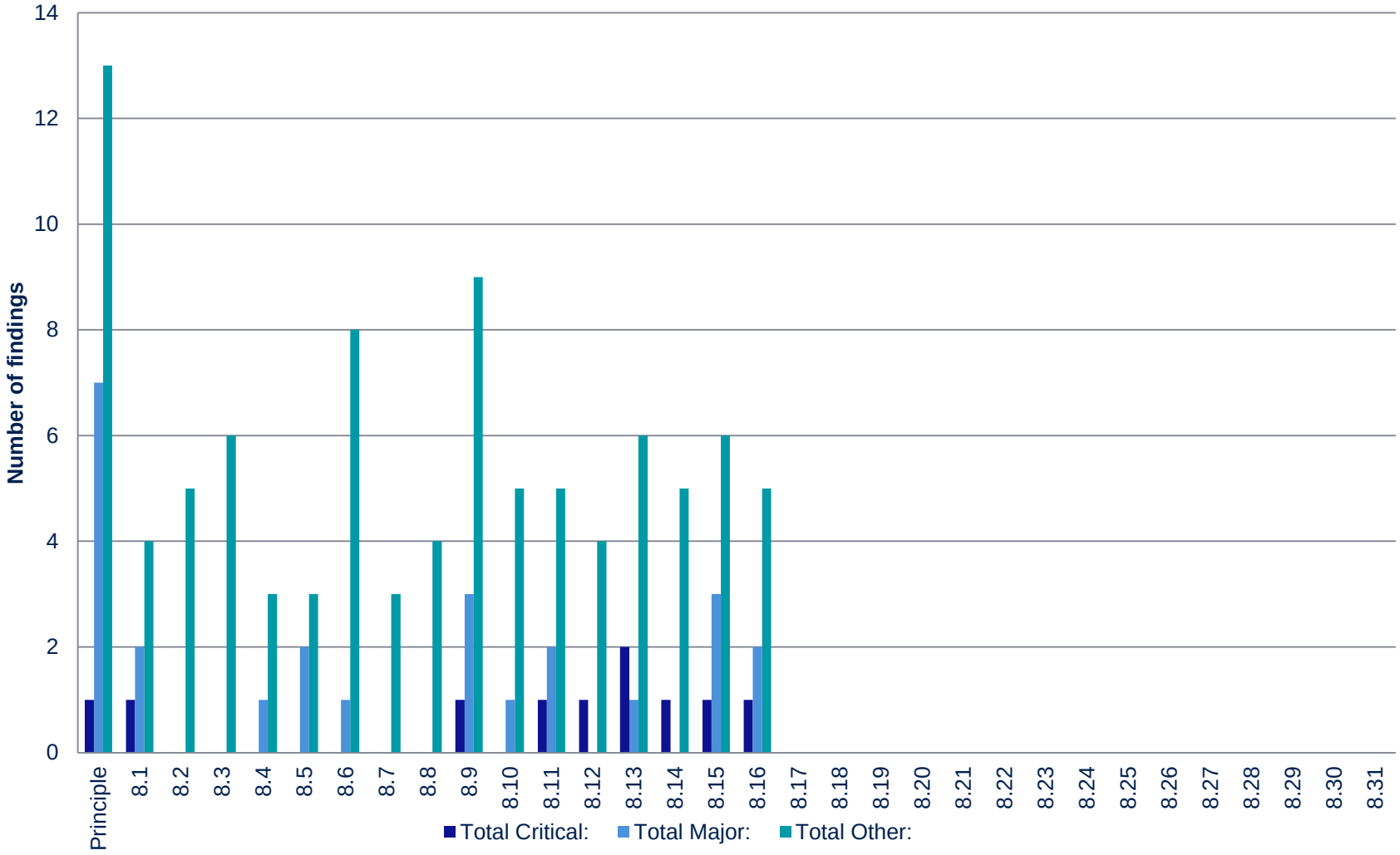
The technical agreements had not been signed by the companies

The technical agreement with Company X was contradictory in regard to the responsibility for assuring API compliance with EU GMP and TSE requirements

There was no inventory of Technical Agreements (TAs) for outsourced activities and no review period

Assessment of the competence of outsourced service providers was not always completed

Findings Chapter 8 per Section



Examples Deficiencies – Chapter 8

The company did not perform robust root cause investigation for complaints to ensure that only product of suitable quality, efficacy and safety were certified and available to the patients, for example:

- There had been several complaints for products failing to work and delivery failures in addition to several batches that had been previously rejected for delivery time and delivery volume
- There had been no assessment as to the impact of these failures on the product on the market, specifically into the safety and efficacy of the product

Examples Deficiencies – Chapter 8

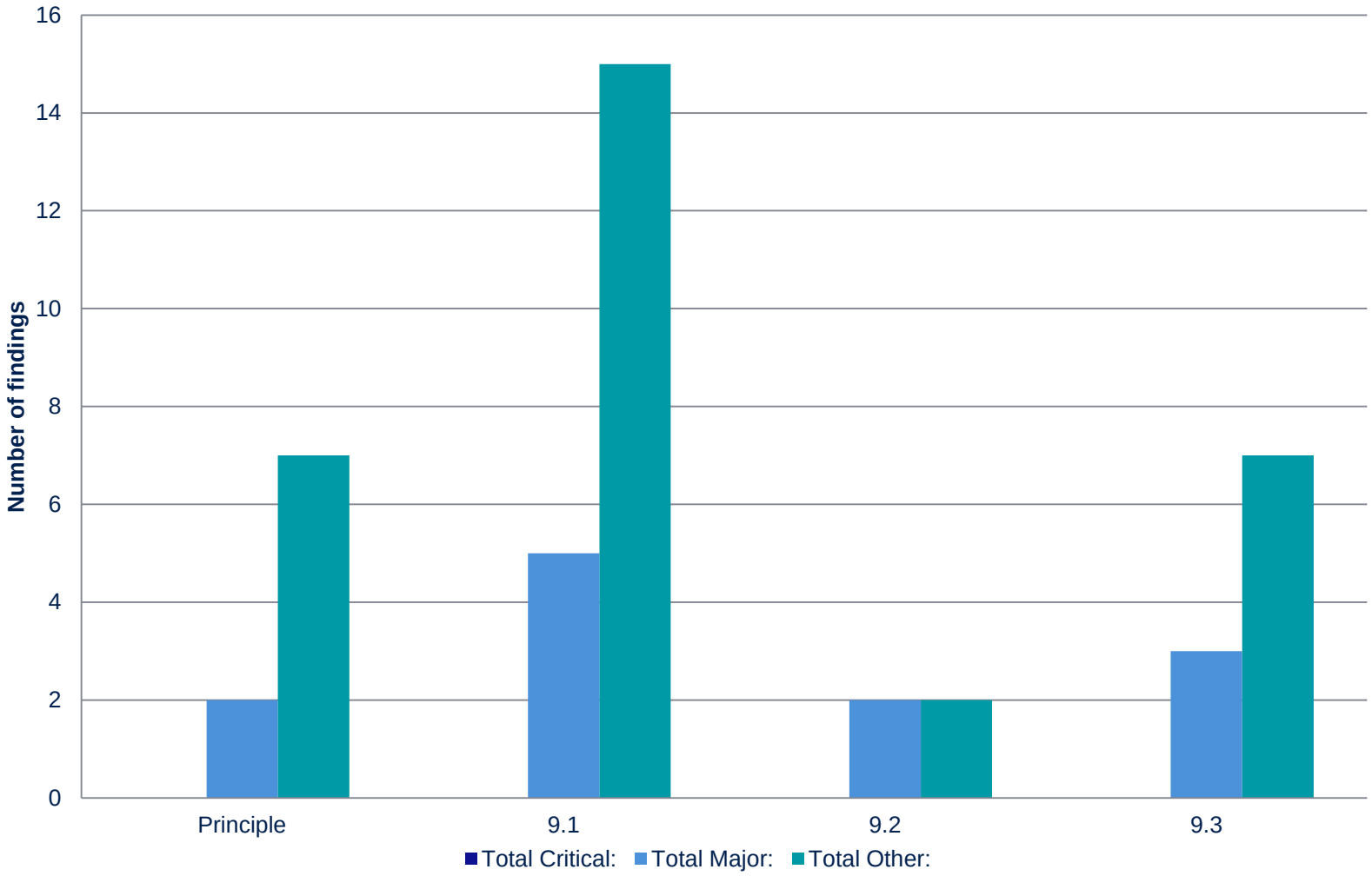
- A complaint was received for batch ABC with regards to the product not working in July 2014. As a result of this, an investigation was raised
  - Retained samples were pulled and tested and were out of specification for dimensional testing. At the time this was assessed as no product impact
  - The company had subsequently failed to consider this additional information whilst investigating the similar failures identified in stability tests and therefore did not make a robust product impact assessment

Examples Deficiencies – Chapter 8

Recall records were inadequate for example:

- Missing out of hours check of the recall procedure
- No requirement to record the learning points of a recall
- The recall records did not contain any evidence of what occurred between receipt of the complaint on 25/11/15 and confirmation with DMRC on 1/12/15
- No written recall correspondence with customers
- Recall record xx-xx/xx did not contain a record of when the company assessed whether any stock was handled/supplied by company X

Findings Chapter 9 per Section



Examples Deficiencies – Chapter 9

Training of individuals carrying out self-inspection was limited to a review of the SOP and verbal discussion, no list of approved internal auditors was held confirming areas of competence

The self-inspection SOP focused on the use of checklists without wider scope or guidance on assessment of responses

There was no schedule in place for internal audits

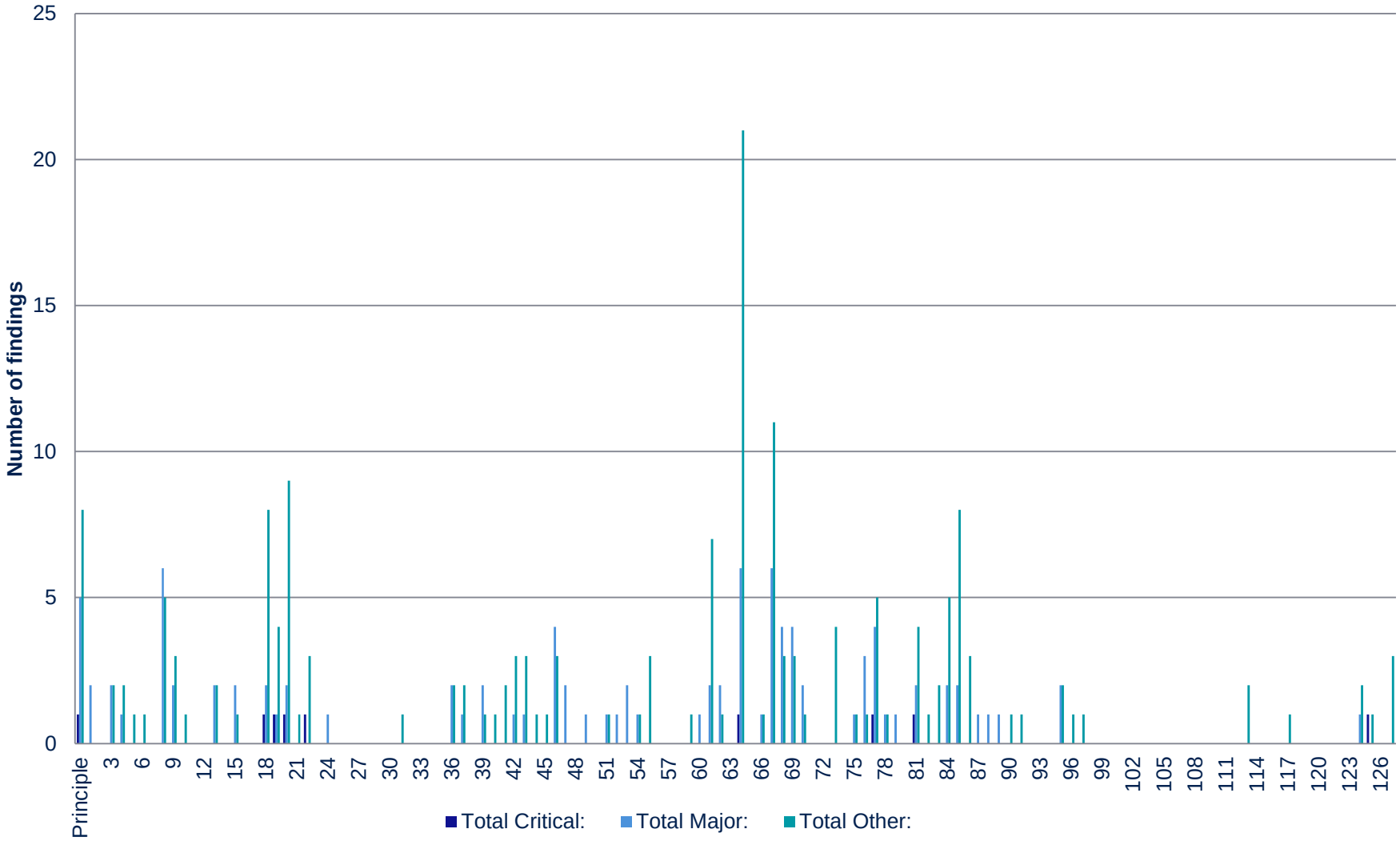
Self inspection has not been conducted since 2011

Examples Deficiencies – Chapter 9

Self-inspections were deficient in that;

- There was no schedule for the self-inspections to be carried out
- Not all areas were covered by the self-inspections
- Actions from previous self-inspections were not confirmed as being completed and were not entered into any tracking system

Findings Annex 1 per Section



Examples Deficiencies – Annex 1

There was a risk to patient safety as a result of continued aseptic preparation of radiopharmaceuticals while significant and repeated evidence of breaches of microbiological control in the critical zone during production sessions had been identified:

- Organisms associated with the continued environmental failures were only identified to genus level and not to species level with Staphylococcus and Bacillus commonly reported
- There was no process to requalify personnel involved in sessions with gross microbiological monitoring failures
- The spray and wipe technique demonstrated (although not a batch related sanitisation run) during the inspection was not adequate or conducted according to site procedure in that insufficient spray was applied and not all surfaces were wiped
- There had been no validation of the media fill method and no positive controls run

Examples Deficiencies – Annex 1

The controls regarding sterility assurance were deficient in that:

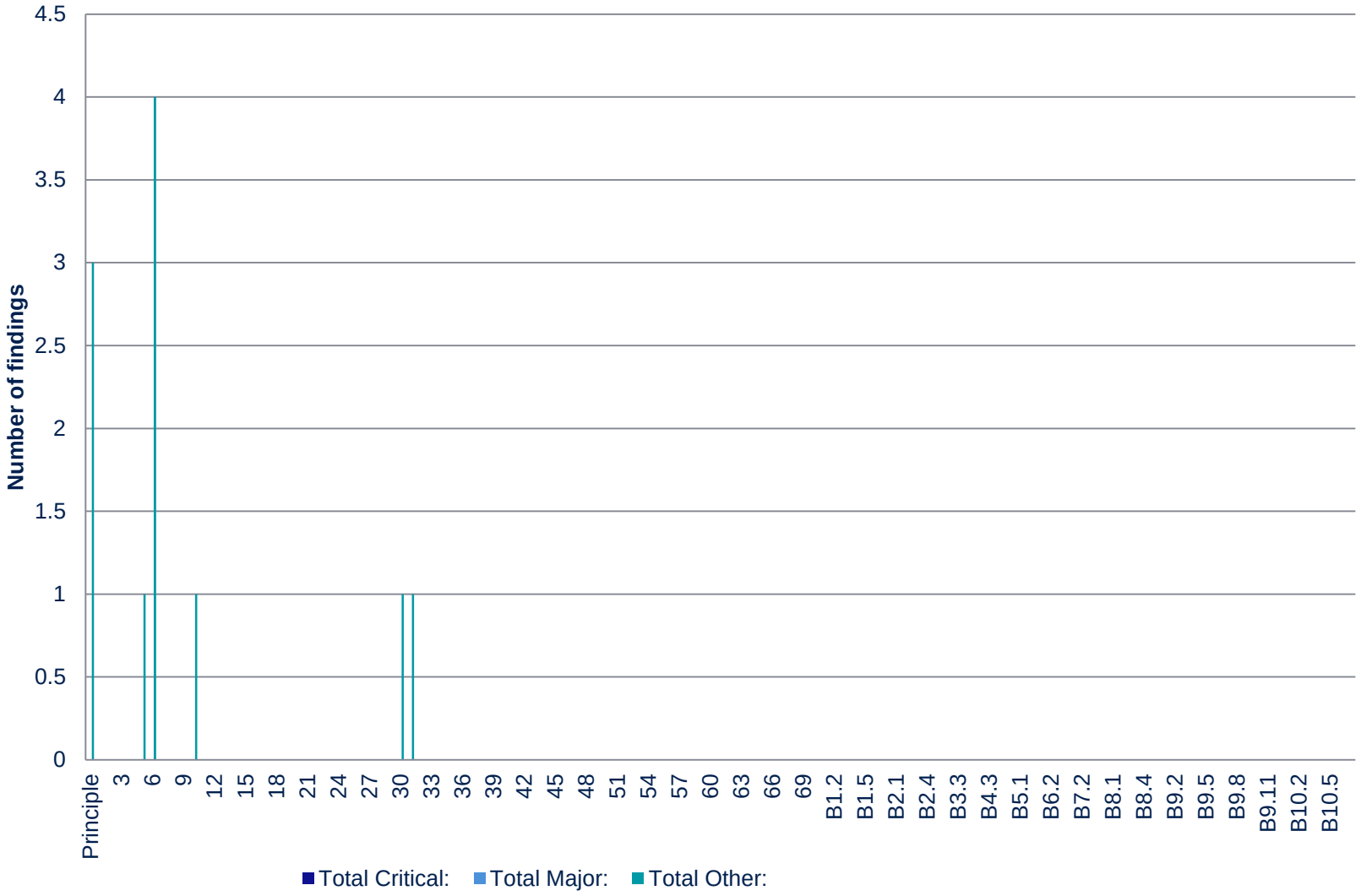
- The transfer of material across zones of different air classification was inadequate in that all sterile components are not kept in the grade A area at all times or alternatively protected via an outer layer of packaging removed before transfer into Grade A
- There is no indication that all components and supporting equipment or tools have been sterilised and the date of sterilisation written on the wrapping, nor the length of time the items have been held in the Grade B zone
- Dedicated tooling required for interventions were not all sterilised into the Grade A environment for adjustments as needed (e.g. manifold tool), resulting in opening of panels unnecessarily

Examples Deficiencies – Annex 1

There were issues found regarding positioning of the environmental sampling points within the grade A zone, for example:

- There were no settle plates located close to the point of fill to provide adequate assurance during exposure periods that EU GMP Annex 1 grade A limits were being met
- There were no settle plates located in the zone where samples were taken for IPC weight checks
- The continuous particle monitoring sample points were located too high in relation to the relevant work zones to provide meaningful data to demonstrate that EU GMP Annex 1 requirements were being met

Findings Annex 2 per Section



Examples Deficiencies – Annex 2

The control of microbial risks and environmental monitoring had the following weaknesses:

- Not all phases of production were subject to microbial monitoring, e.g. activities with no cellular product present such as preparation of equipment, which has a similar potential for contamination of product
- At decontamination of items for transfer into the isolator it was noted that not all areas of potential contact on the trolley were subject to decontamination
- The clean room was only monitored after cleaning. There was no periodic monitoring before cleaning to monitor for potential microbial changes or for the continuing effectiveness of cleaning

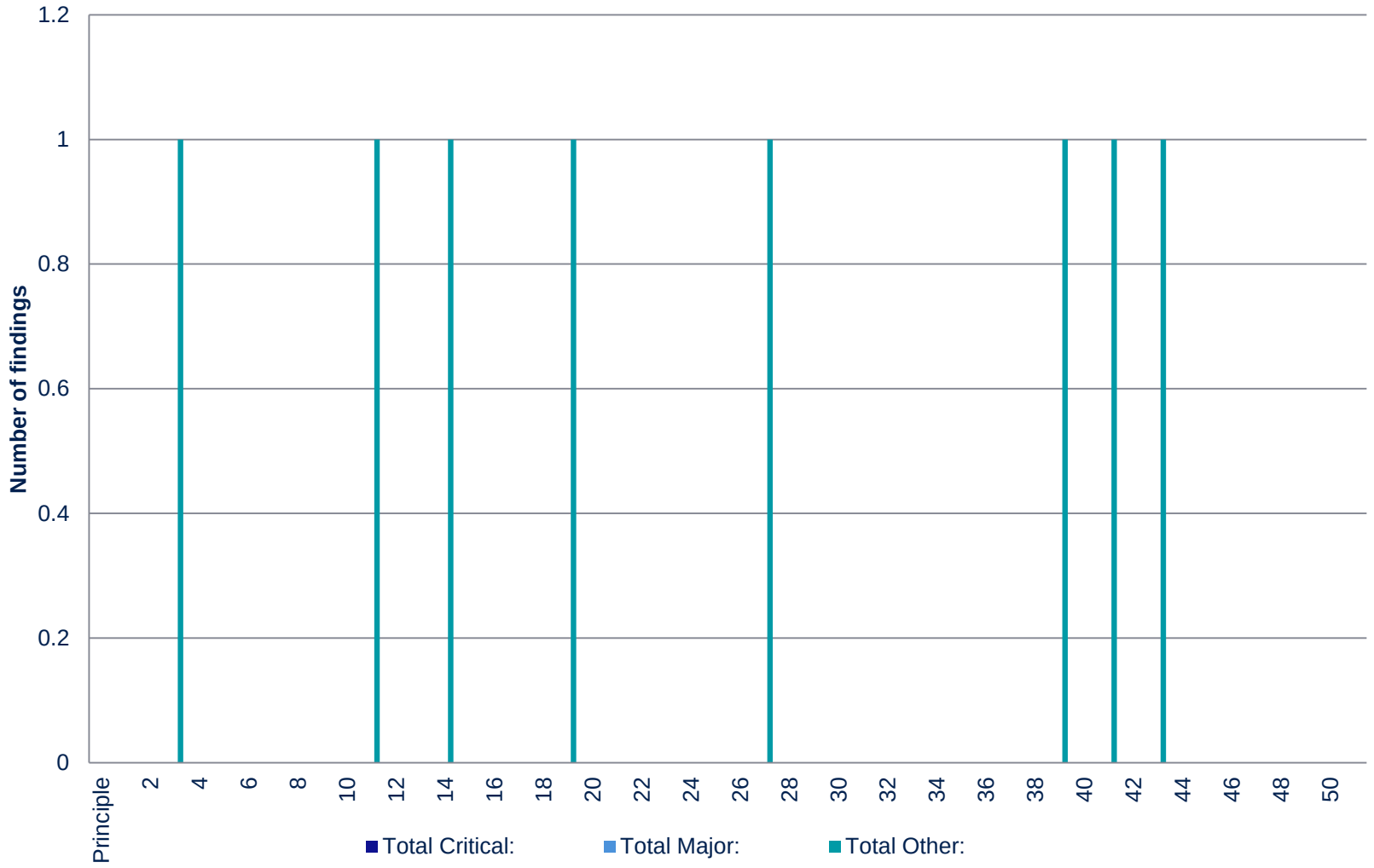
Examples Deficiencies – Annex 2

Clean room equipment was not designed, controlled or maintained to minimise the risk of contamination in that:

- Maintenance activities on incubators in the global cell banking area did not include changing internal tubing on the humidification system at an appropriate frequency, so creating a potential biofilm generation risk
- It was noted that particle counters and viable air monitoring samplers had been brought back into the microbiology laboratories from production areas without any consideration of the risk of contamination

Materials were being stored in an area where the acceptable temperature range was outside the storage range defined by the kit manufacturer without a documented justification being in place

Findings Annex 3 per Section



Examples Deficiencies – Annex 3

The product release process was not appropriate in that:

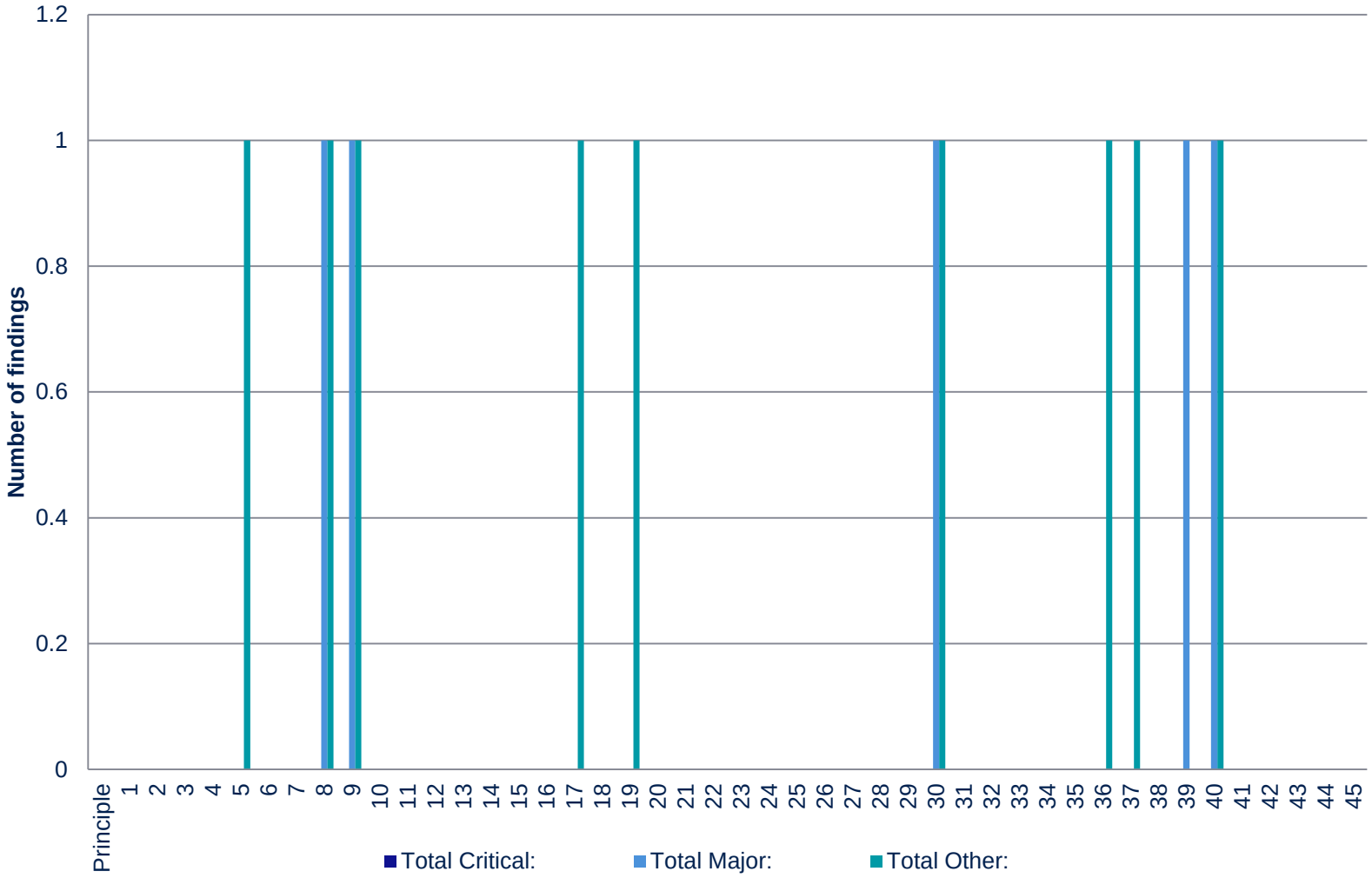
- The release statement on the batch in the dispatch area appeared to indicate that the product was packed and dispatched at 0645 which was before the formal QC release at 0655
- The release statement stated that the batch was ‘fit for human use’ rather than being manufactured to GMP
- The parameters in the production report to be reviewed at batch release were not formalised

Examples Deficiencies – Annex 3

The batch release process was deficient in that:

- Batch release does not include a review of either a printed or electronic copy of the synthesis record
- Testing for residual solvents is not always performed as a pre-release test for all F18 products when there is adequate time to perform this test prior to release

Findings Annex 6 per Section



Examples Deficiencies – Annex 6

The company's arrangements for Quality Control of finished product were deficient in that:

- The instrument used for analysis of carbon monoxide was unavailable for an extended period. The company continued to manufacture and release batches during this period without any suitable justification (e.g. written risk assessment) for not performing the registered carbon monoxide test
- There was no requirement for periodic moisture analysis of medical oxygen batches or suitable justification for not doing so

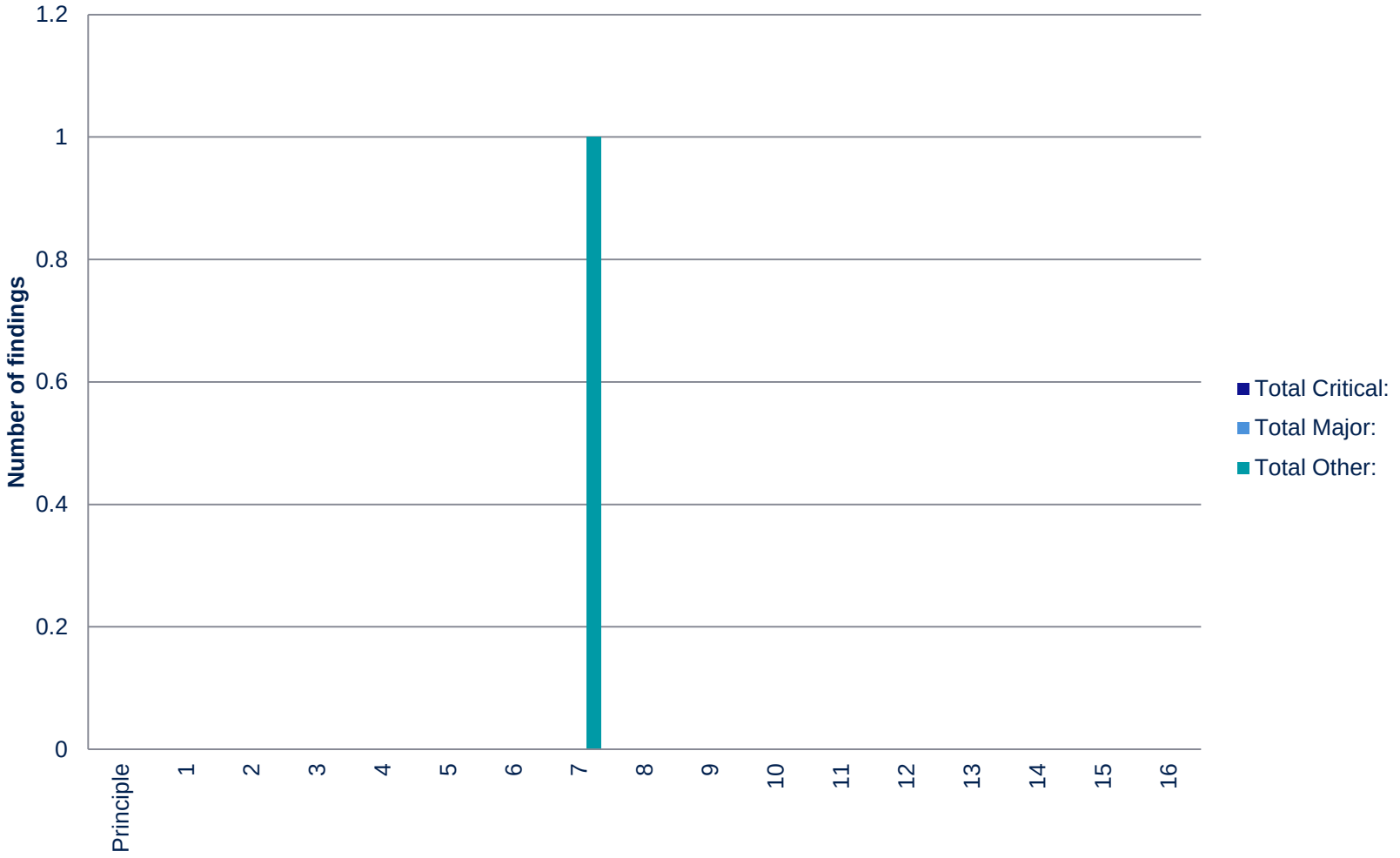
Examples Deficiencies – Annex 6

Segregation of medical gas cylinders at various stages of processing was inadequate:

- A pallet of empty cylinders was seen to be stored in the area designated for rejected oxygen/nitrous oxide starting material cylinders
- Cylinders awaiting inspection in the workshop were not identified as such and were noted to be empty
- The quarantine area in the workshop was not suitably delineated

There was no system for confirming that returned cylinders had retained a positive pressure prior to refilling

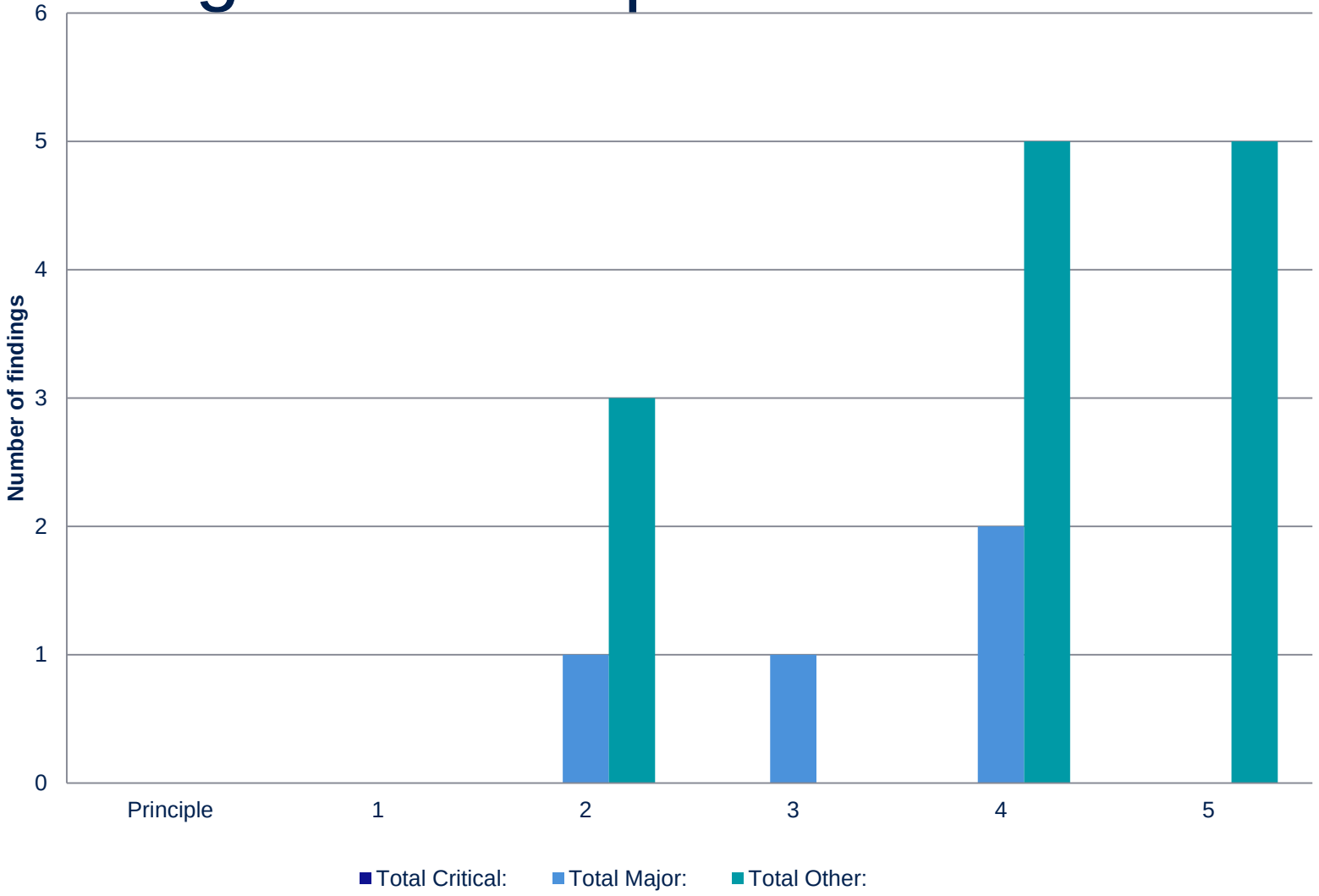
Findings Annex 7 per Section



Examples Deficiencies – Annex 7

The checks in place to confirm that materials were received from an approved supplier were insufficient to confirm that the materials had been received from a specific address of each approved supplier

Findings Annex 8 per Section



Examples Deficiencies – Annex 8

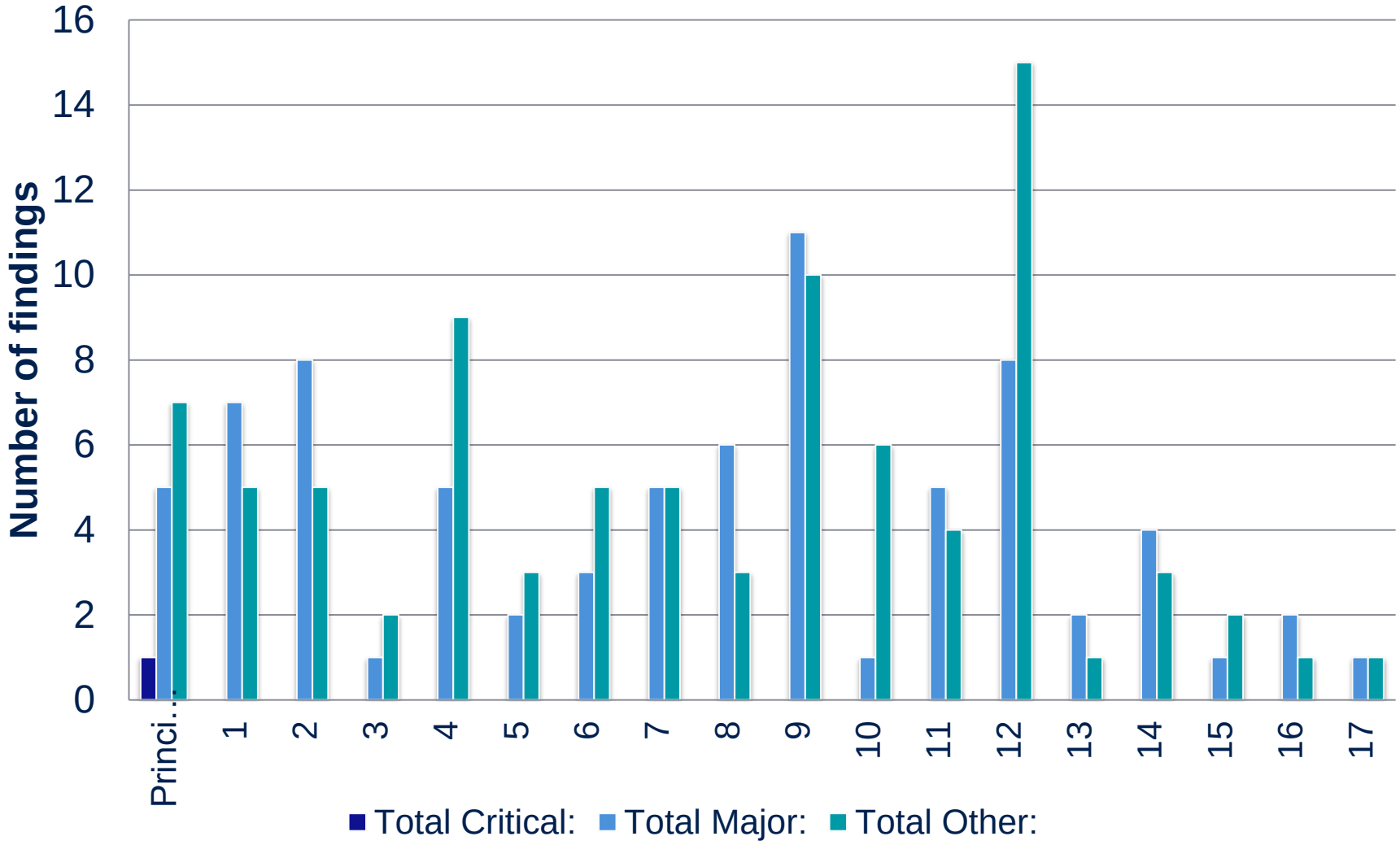
Samples of raw materials were only taken from the surface

Sampling of APIs and high risk excipients did not require core representative sample to be taken

Identification testing was not completed on each container of starting material

There was no requirement to perform any incoming ID testing for development materials that were subsequently approved for use within the GMP areas

Findings Annex 11 per Section



Examples Deficiencies – Annex 11

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

Examples Deficiencies – Annex 11

- Manual integration was permitted routinely without additional review or permission
- The clock used for determining time/date for the HPLC software could be adjusted therefore allowing the option to alter the true time and date in the printed paper records
- There were no audits to address the data integrity controls within the laboratory, data integrity was not included within the scope of audits of contact laboratories

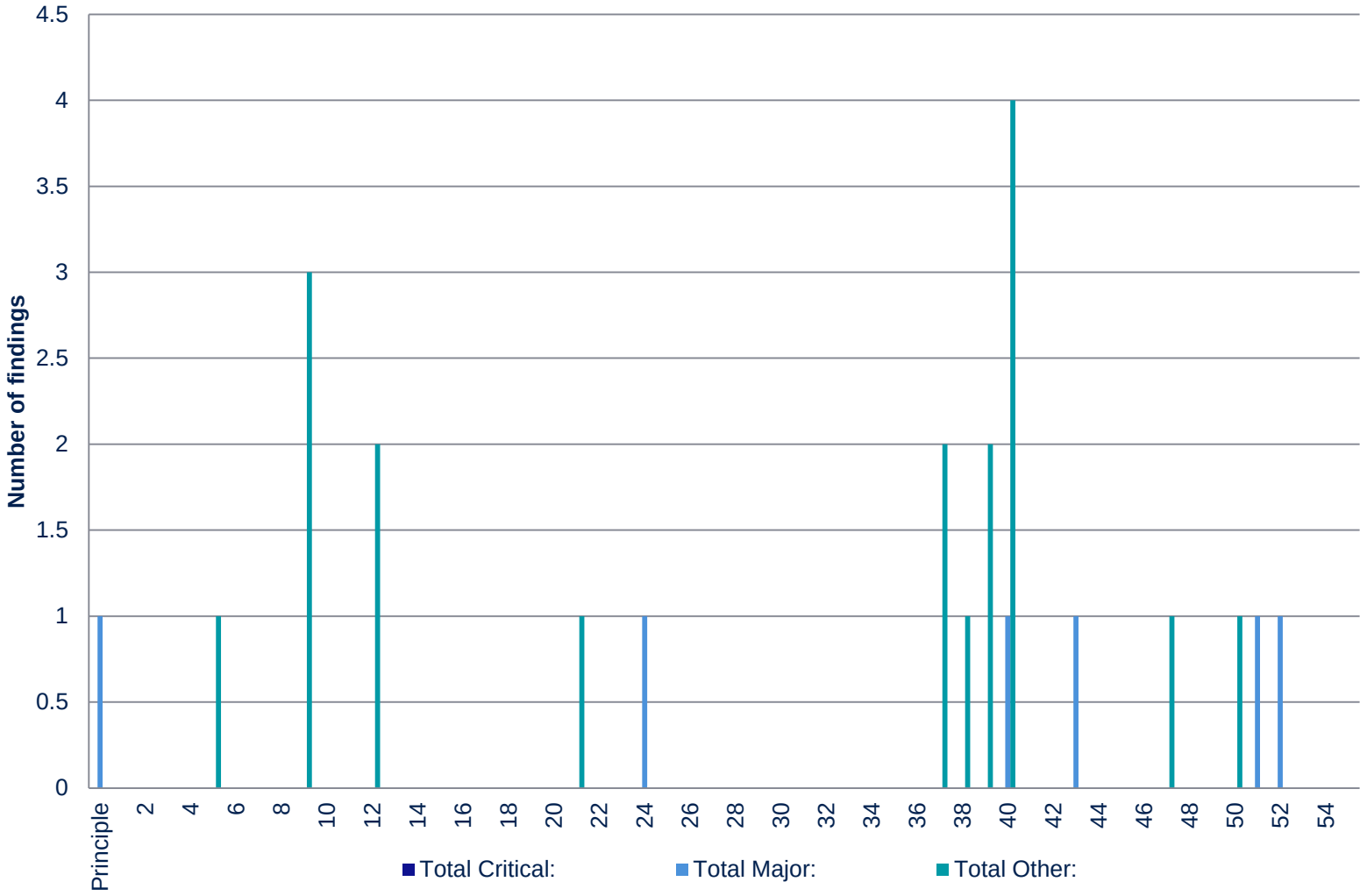
Examples Deficiencies – Annex 11

There were no overall risk assessments of electronic systems within the company in order to define data integrity control strategies

The listing of all relevant GMP systems and their GMP functionality is deficient in that:

- The list is not a current, accurate list and the GMP functionality of the systems is not included / apparent
- The access control system has been defined as not a GMP system and as a consequence has not been validated. The computer registration document states that this is not the system which controls entry to GMP areas. It is understood that there is no other system to control entry to GMP areas

Findings Annex 13 per Section



Examples Deficiencies – Annex 13

Control of the generation and approval of labels was weak in that:

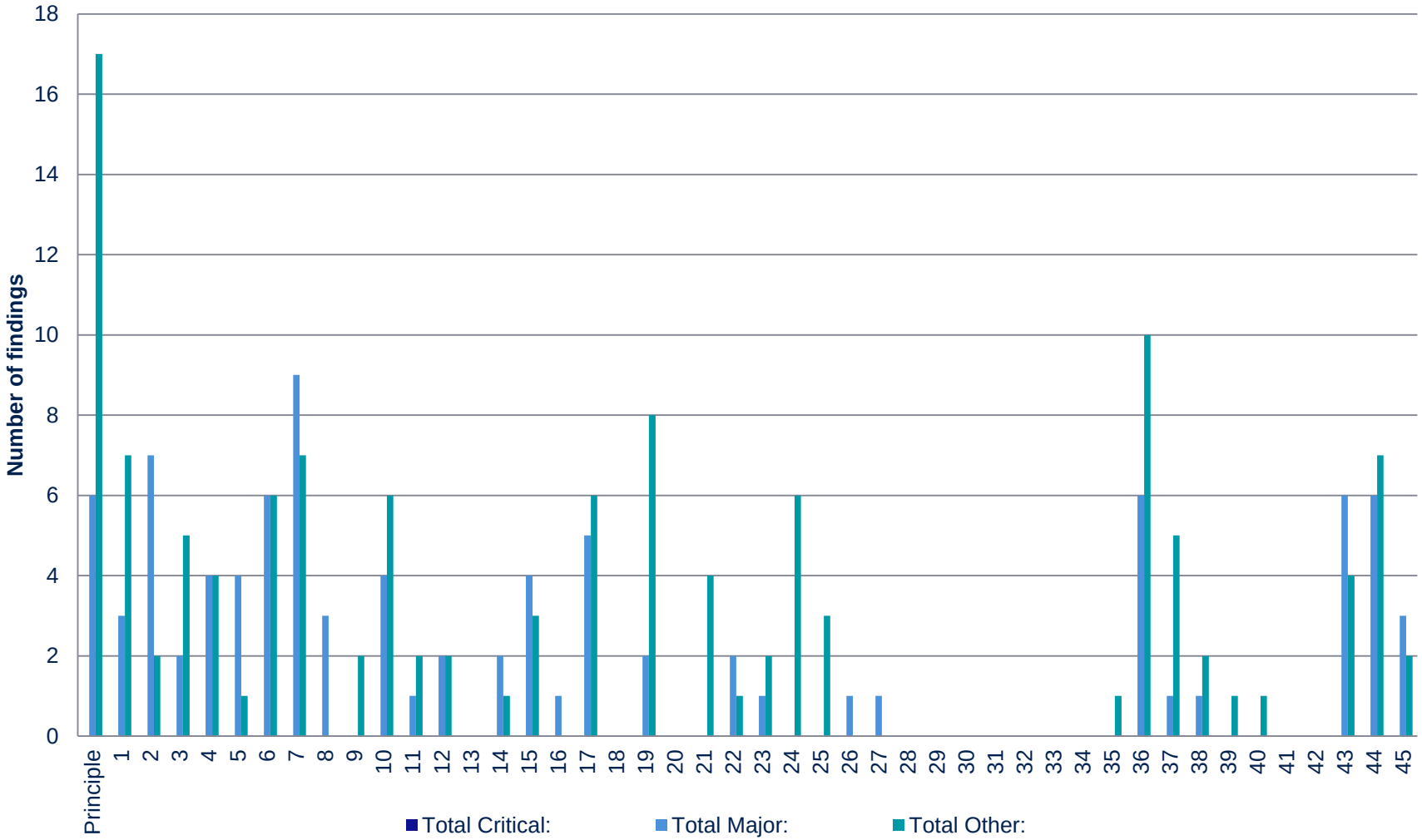
- There was no formal process for controlling the reissue of labels in the event that these were required, in particular for labels including a patient number
- The procedure was not clear regarding the checks performed when labels were printed
- Labels were printed from a ‘Master Template’ generated in MS Word which was fully editable at the time of printing

Examples Deficiencies – Annex 13

Batch ABCDE related to an expiry update operation however there was no formal QP certification of this, only a statement from the QP that the finished product had been previously certified, with no confirmation that the revised expiry date was acceptable under the provisions of the CTA

Prior to the certification of aseptic batches manufactured in August 2014 there was a series of environmental failures and media fill failures. There was no formal mechanism for the QPs to be made aware of these events before the bimonthly product quality meeting that took place in September. It was therefore not clear that the QP had adequately assessed the impact of these events prior to certification

Findings Annex 15 per Section



Examples Deficiencies – Annex 15

Not all new equipment qualification included the design phase of qualification e.g. Design Qualification or User Requirements

Qualification documents provided by equipment suppliers were not adopted into the company's Pharmaceutical Quality System to ensure appropriate review

The heat tunnel equipment Operational Qualification was not fully complete with omissions noted

Whilst the OQ protocol for the HVAC system was supplied by the third party, there was no evidence that the company had confirmed the suitability and compared that with the company procedures prior to approval

Examples Deficiencies – Annex 15

The cleaning validation programme was deficient as evidenced by:

- The cleaning validation / verification was deficient and did not assure the effective removal of organic compounds
- The effectiveness of sprayballs used for vessel cleaning have not been demonstrated or adequately controlled
- Permitted limits for carryover of organic molecules have not been set or adequately risk assessed
- Swab samples have not been taken, in particular no swabs have been taken from difficult to clean areas where other methods or determining residues may not be effective
- The cleaning of open vessels has not been verified

Examples Deficiencies – Annex 15

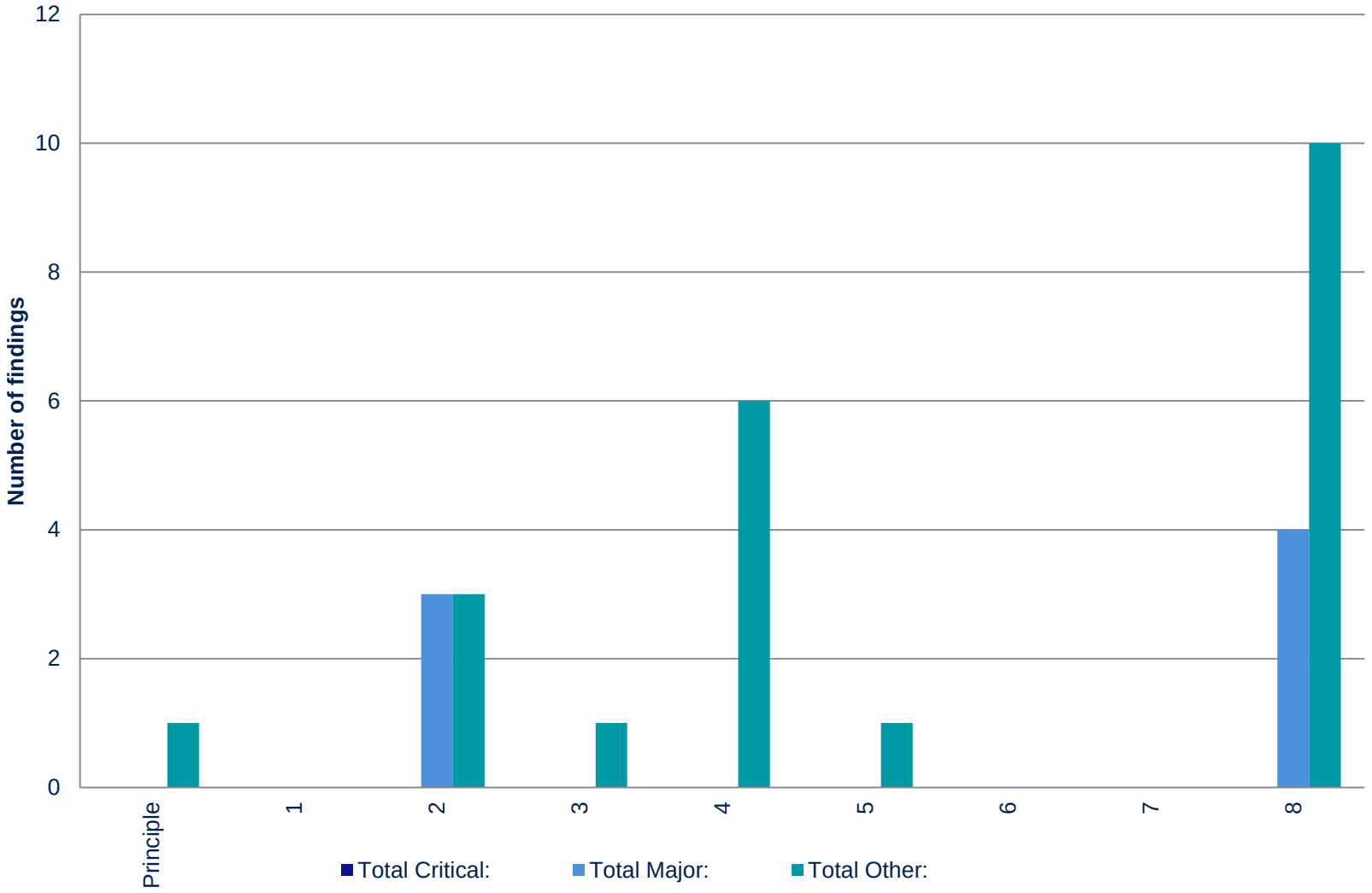
Performance and Process validation activities did not include assessment of all critical parameters e.g. tablet dimensions and embossing

Not all aspects of manufacturing were covered by process validation e.g. the use of the small coating pans as opposed to the validated automated system

Batches of product were validated contemporaneously without justification for release prior to completion of the qualification process

There was no clear scientific rationale to support the selection of products used for cleaning validation matrix or qualification limits

Findings Annex 16 per Section



Examples Deficiencies – Annex 16

The Qualified Person did not have visibility of the Overall Risk Assessments which were used to manage the project and formed part of the change control process

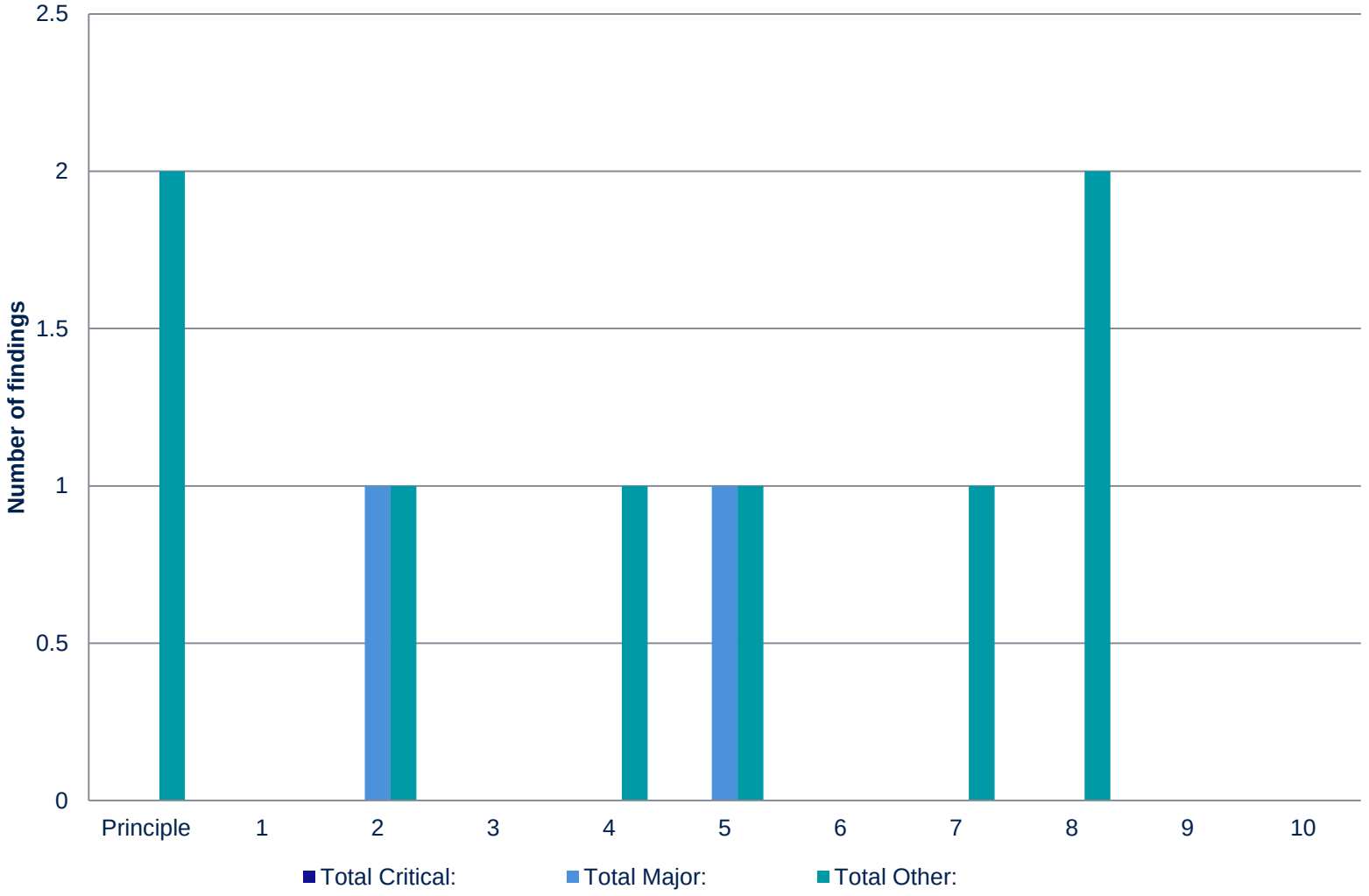
Product release certificates for a non-licensed product (for export) inappropriately referenced the MIA number and GMP certificate number, neither of which was applicable to this product. The statement also referenced compliance with local regulatory authority requirements that would not be applicable to the products in question

Examples Deficiencies – Annex 16

The QP Batch Certification Checklist did not include a check that the Qualified Person had reviewed the Quality Impact Assessment and found it to be acceptable or otherwise for certification of the batch

The QP named on the licence was not being used for batch release and was not keeping up to date with site systems and had not visited the site in approximately 2 years

Findings Annex 19 per Section



Examples Deficiencies – Annex 19

A retained sample selected as an example could not be found during the inspection

The stability protocol operating procedure did not ensure adequate reconciliation of the samples stored and used with a 5% reconciliation/tolerance limit in operation at the end of the stability programme

There were no storage facilities, monitoring devices or associated procedures for the intended storage of the reference/retention samples at the site