Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

MHRA GMP Inspection Deficiency Data Trend 2016

Introduction

The GMDP Inspectorate has improved the way of gathering the inspection deficiency data for 2016. The new data trending can allow industries to identify:

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

The purpose for publishing the inspection deficiency data is to allow industries to perform their own assessment against the deficiency findings as part of self-inspection and continuous improvement.

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

Deficiency Data Trending 2016 (Dosage Forms)

GMP Inspections conducted in 2016 (compared to 2015)

	2016	2015
Total number of inspection	324	303
UK inspections	242	224
Overseas inspections	82	79

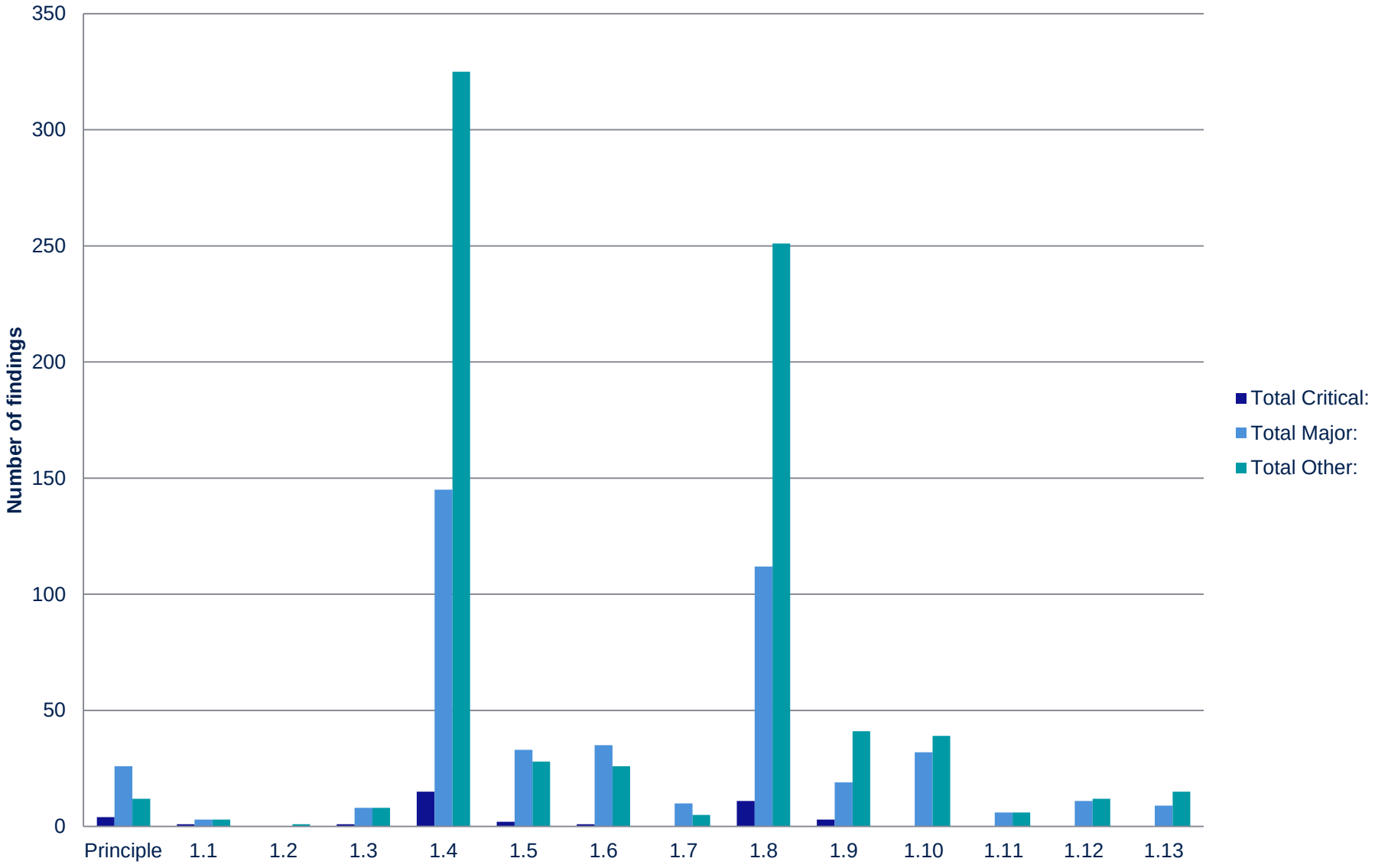
Top 10 Most cited deficiency groups 2016

Ranking	Groups	Critical	Major	Others
1	Quality System	38	449	772
2	Sterility Assurance	34	190	162
3	Production	20	191	543
4	Complaints and Recall	11	80	110
5	Qualification/Validation	10	123	232
6	Premises & Equipment	9	113	464
7	Computerised Systems	9	44	120
8	Personnel	8	42	150
9	Documentation	2	166	646
10	Quality Control	2	42	192

Comparison of top 10 most cited deficiency groups between 2016 and 2015

	2016	2015
Ranking	Groups	Groups
1	Quality System	Quality System
2	Sterility Assurance	Complaints and Recall
3	Production	Documentation
4	Complaints and Recall	Quality Control
5	Qualification/Validation	Computerised Systems
6	Premises & Equipment	Production
7	Computerised Systems	Premises & Equipment
8	Personnel	Validation
9	Documentation	Personnel
10	Quality Control	Materials Management

Findings Chapter 1 per Section



Chapter 1 - Deficiency examples

Deficiencies related to incident investigations and corrective and preventive action (CAPA) implementation:

- Deviation reports did not contain sufficient information to describe the investigations conducted or demonstrate the evidence that supported the proposed root cause.
- In some cases there were no formal CAPA raised and in others the CAPA were not adequate. There was no review of repeated deviations which would indicate a trend or failure of CAPAs to resolve the issue.
- The site had not established and maintained an effective control system to monitor process and product quality, and had not applied an appropriate level of investigation or fully documented all potential serious incidents, with the objective of determining the root cause and implementing appropriate corrective and preventive action.

Chapter 1 - Deficiency examples

The deviation procedure lacked sufficient detail to ensure that investigations were appropriately thorough:

- There was no requirement to identify the impact of the deviation on the batch.
- There was no process to escalate deviations in a timely manner in the event of an issue having the potential to present a patient safety impact.
- There was no procedural requirement to consider if the deviation had occurred previously.
- There was no requirement to ensure that process, procedural or systems based errors had not been overlooked prior to identifying ‘Personnel Error’ as a root cause.
- There was no timeline for completion of the deviations in the procedure (other than ‘in a timely manner’).
- The root causes recorded were not always those identified in the procedure.

Chapter 1 - Deficiency examples

- At least 8 overdue CAPA (ranging from 59 days to 242 days overdue) were observed to have been closed the day before the inspection.
- Two overdue CAPA were open at the time of the inspection (186 days and 60 days overdue).
- Where134 deviations were raised between November 2015 and February 2016, no CAPA were raised.
- Effective monitoring of CAPA was not in place as numerous CAPA with different due dates could be recorded on a single form but only the latest date was tracked.
- The review of effectiveness of CAPAs was identified as being part of Management Review, however there was insufficient detail describing this process and the process was not risk based as the Management Review was only carried out once a year.

Chapter 1 - Deficiency examples

Deficiencies related to lack of senior management oversight on effective implementation of pharmaceutical quality system (PQS) and continuous improvement:

- There was no formal Management review process.
- A number of process improvements had been identified across the company yet not logged or tracked in the PQS.
- The management team was not seen to be reacting effectively to poor key performance indicators.
- Senior management had failed to ensure an effective Quality Management System was in place as evidenced by the fact that a number of the CAPA from the previous MHRA inspection had not been completed on time.
- There was no written procedure for the Quality Monthly Meetings attended by the departmental managers to review the effective implementation of the quality system.

Chapter 1 - Deficiency examples

- The management team failed to ensure an effective implementation of the quality systems and to identify opportunities for continual improvement of components, processes and system itself.
- The current reporting method on quality metrics did not sufficiently identify and allow monitoring and assessing the effective implementation of the quality systems. For example, the open and overdue items were not reported for discussion.
- The outstanding quality items reported in the management review meetings were not challenged to identify the root cause for the delay. Risk assessments had not been performed or formally documented to assess the impact on patient safety and the effectiveness of the PQS as a result of choosing to delay addressing the overdue actions.

Chapter 1 - Deficiency examples

- The management review process was deficient, for example, the meeting minutes stated that all environmental monitoring results were satisfactory; despite there being an obvious adverse trend increase in clean room environmental monitoring results.

- The monthly quality system metrics generated do not include the status of supplier audits and do not show site performance over time to allow an effective review of performance changes and to confirm that the quality system is in a state of control.

Chapter 1 - Deficiency examples

Deficiencies related to change control management:

- There was insufficient detail recorded to describe the nature of the change and the actions to be carried out.
- There is no definition of which moderate level change controls would require a risk assessment and regulatory affairs review and which would not.
- There is no post implementation review of the effectiveness of change control actions.
- Changes were implemented outside of the company's Change Control procedure.
- Procedures for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification were not robust.
- There was no documented requirement for a post implementation effectiveness check to be performed.

Chapter 1 - Deficiency examples

Deficiencies related to Product Quality Review (PQR):

- The PQR procedure did not require a review of the supply chain traceability of active substances taking into account the full supply route and manufacturers (including intermediates).
- The completed PQR did not identify that all the relevant technical agreements were in place.
- There was no confirmation that the ongoing stability studies showed no adverse trends and would be expected to remain within specification for the proposed shelf life.
- The review of critical parameters did not present data to determine if there was a trend and no comment was made on whether there was a trend.

Chapter 1 - Deficiency examples

- There was no consideration of the purified water results to determine if the system was performing as required.

- PQRs were not being completed in a timely manner:
  - 9 PQRs were open that were more than 6 months overdue with some up to almost a year overdue.
  - At least 29 closed PQRs that had gone beyond the 3 month due date with a number over 6 months beyond their due date.

Chapter 1 - Deficiency examples

Deficiencies related to the lack of monitoring of regulatory updates and implementing appropriate actions:

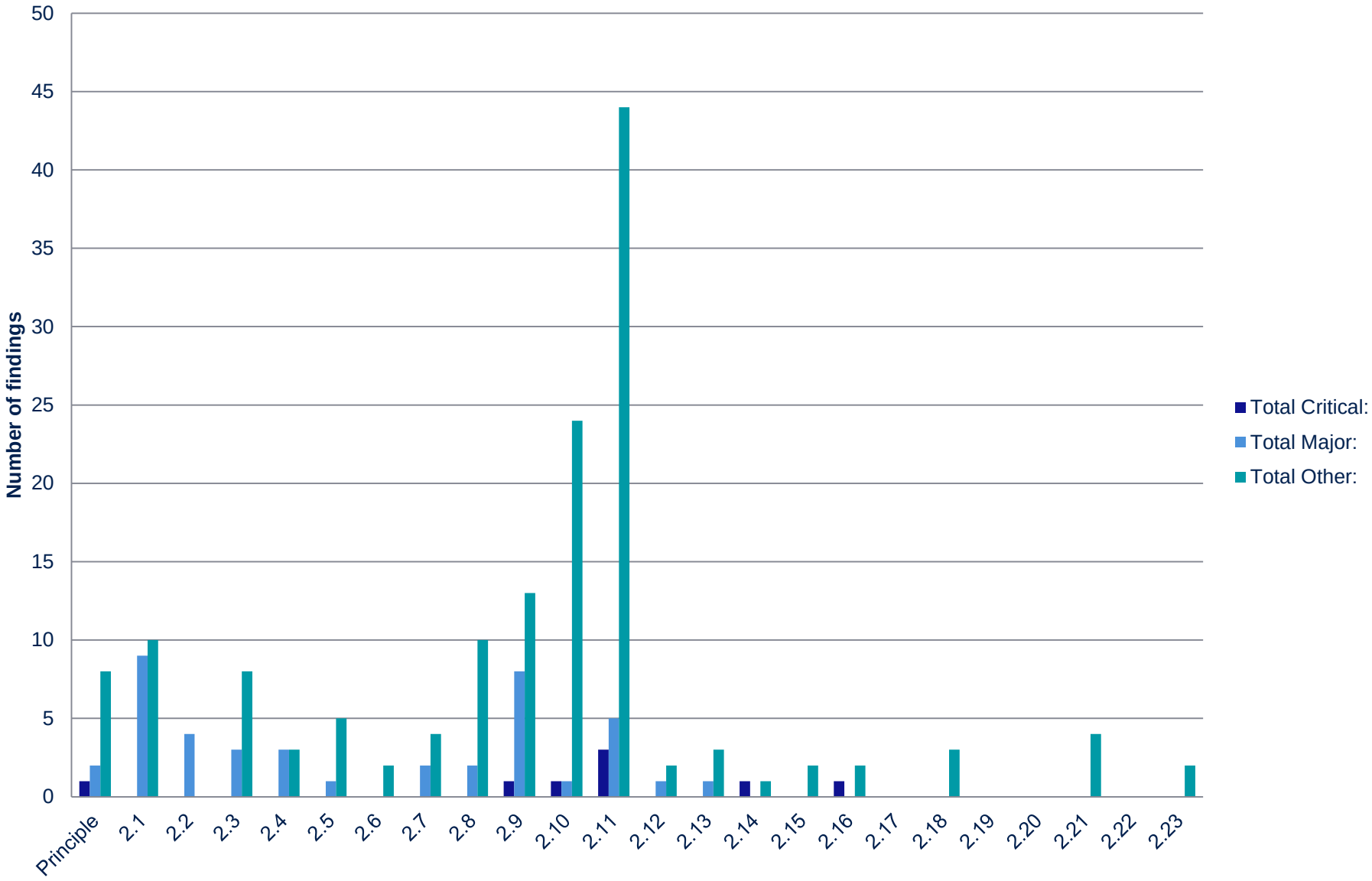
- There was no mechanism to ensure that changes to regulatory requirements were captured and the impact to the site considered.
- There was no formal system for the review, assessment and where appropriate, implementation of EU GMP updates.
- There was no formal system to review regulatory updates.

Chapter 1 - Deficiency examples

Deficiency related to the return of products:

The returns procedure did not require verification that the returned goods had been stored under appropriate temperature conditions by the customer prior to the return.

Findings Chapter 2 per Section



Chapter 2 - Deficiency examples

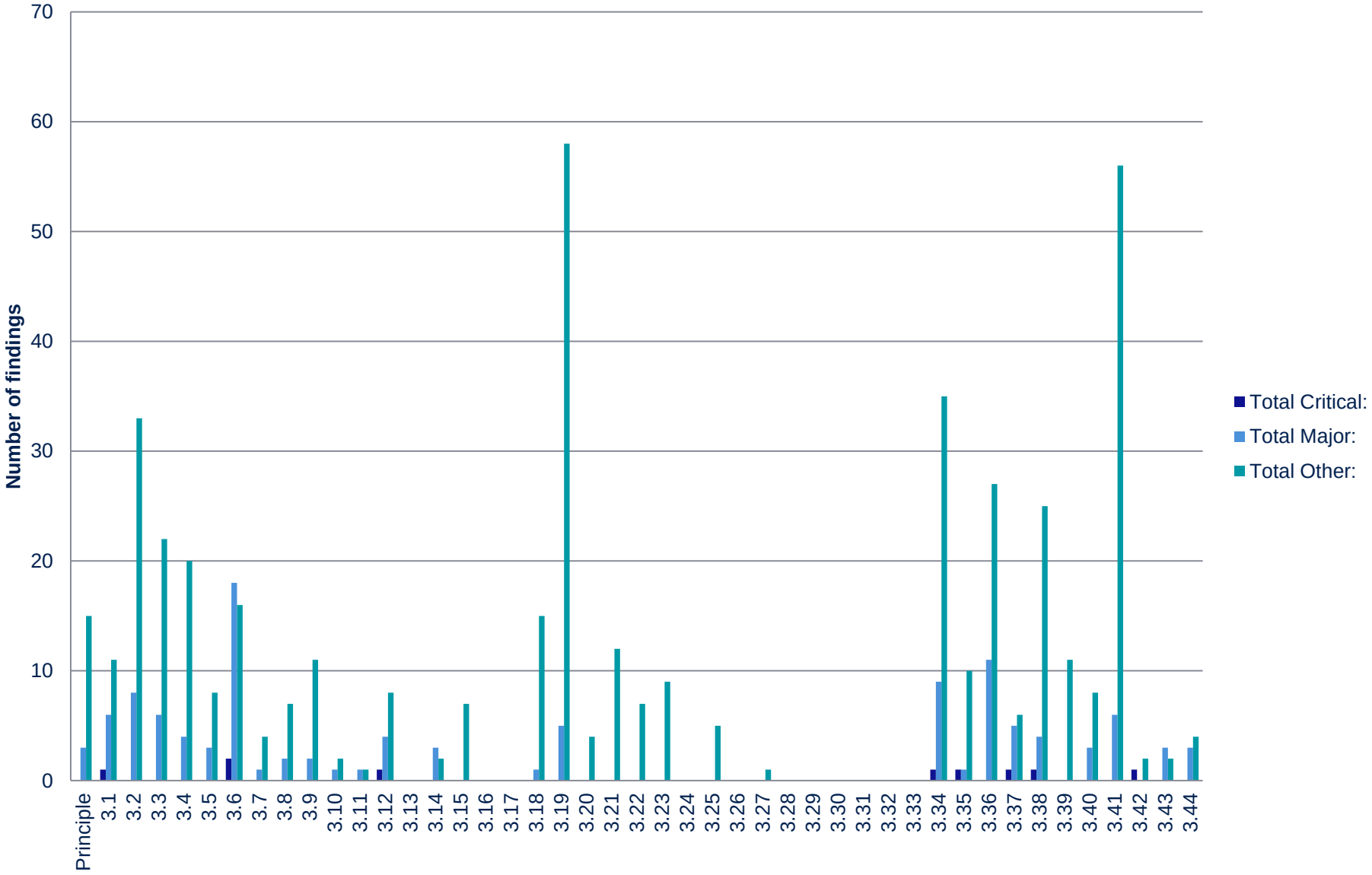
Deficiencies related to staff training:

- The production operative was signed off as trained in raw material assessment based on read and understand questionnaire with no practical assessment.
- The production operative was signed off as competent for manufacture of solutions and suspensions had not completed training in all associated duties such as cleaning of compounding equipment.
- Procedure awareness assessment forms were not all signed off by the trainer as required by the training procedure.
- There was no system for confirming that all personnel that required training had been trained.

Chapter 2 - Deficiency examples

- No evidence was seen for competency assessment for the GMP training of a recently recruited QA Officer.
- The training record of production operator did not show they were trained in the operation of the isolator despite being signed off for aseptic manufacturing.
- There was no control to ensure that only trained contract cleaners enter the manufacturing facilities.
- There was no robust process for the monitoring of analyst training and qualification.
- When an analyst was qualified on one chromatography system, he was considered qualified on the other two systems used on site without any further competency checks performed related to understanding of differences between the systems.

Findings Chapter 3 per Section



Chapter 3 - Deficiency examples

Deficiencies on failure to minimise the risk of contamination and cross contamination:

The arrangement of gloves and components during hydrogen peroxide sanitisation created occluded surfaces e.g.

- isolator gloves were creased
- a bunch of plastic ties were pinned tightly together
- isolator gloves lying against product bags
- small equipment such as scissors and spoons were lying horizontally on metal racking

This would prevent effective sanitisation of the items.

Chapter 3 - Deficiency examples

- There had been no calculation of health based exposure limits or PDE values for the molecules used on site, and no assessment of the organisational or technical measures required within the production facilities.
- There was no drawing showing the pressure cascades within the facilities available.
- There was no documented assessment of the clean status of the product contact equipment, or the potential for contamination from product residues.
- Equipment had not been cleaned beyond the standard approach for a product changeover.

Chapter 3 - Deficiency examples

Deficiencies related to premises:

- The warehouse was allowed to store mixed pallets of materials including same material, different lot numbers giving rise to the risk of mix up.
- There was no canopy over the goods-in / goods-out to provide cover whilst loading/unloading material.
- There was no demarcation between clean and dirty sides of the change room entering the formulation area.
- A pool of liquid was observed in the corner of the formulation area corridor, indicating poor maintenance (leak) or poor cleaning (spill) practices.

Chapter 3 - Deficiency examples

Deficiencies related to equipment:

- Several clean sifting screens were stored together in a single plastic bag. It was confirmed that the bag was opened to remove a single screen for use, and then resealed with the potential risk of contamination of the other clean screens.
- There is no usage history of a sifting screen, such as the identity of the previous product in which it was used for manufacturing.
- The door seal on the coating machine was not intact and had sections missing.
- Equipment was not always being stored covered as required by procedure.
- Sticky tape was being used to hold the sight glass on to the tablet hopper on packing line.

Chapter 3 - Deficiency examples

Deficiencies related to temperature controlled storage facilities:

- The temperature alarms within the manufacturing areas were set at 18°C to 26°C, yet some raw materials and finished products required storage between 2°C and 25°C. The site would thus not be notified of excursions between 25°C and 26°C.
- Temperatures and relative humidity were only captured twice per day throughout manufacturing as instantaneous measurements. No maximum/minimum data was available to provide assurance of temperature and relative humidity requirements at all times.

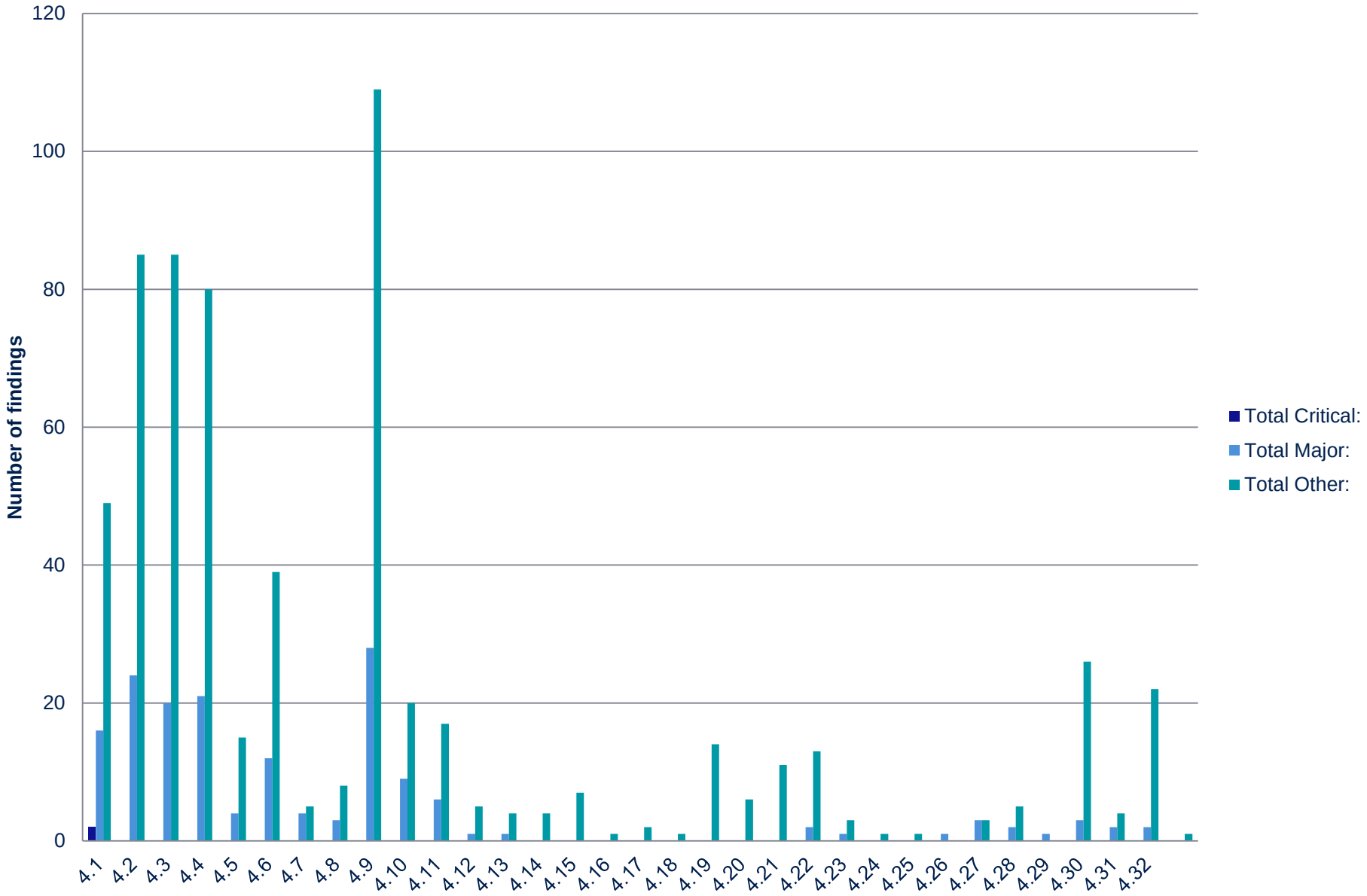
Chapter 3 - Deficiency examples

- The company had not assessed the methodology used by contractor to test HEPA filters within classified areas.

- There were no predetermined acceptance criteria documented for the external calibration activities including the warehouse temperature and humidity probes and the purified water flow meter.

- There was no requirement for a check of the delivery vehicle to ensure vehicles were suitable for transport of medicinal products/materials.

Findings Chapter 4 per Section



Chapter 4 - Deficiency examples

Deficiencies related to document control and completion:

- Document retention policy was inconsistent e.g. the document control procedure identified that documents should be kept for the lifetime of the company, but the complaints procedure stated a retention period of 3 years for complaints.
- Non-contemporaneous recording was noted during placebo manufacture as the date completed for the process step on the batch production record had already been entered before that process step had actually been completed.
- The QC Preventive Maintenance and Calibration tracker had gaps and additions without appropriate explanation.

Chapter 4 - Deficiency examples

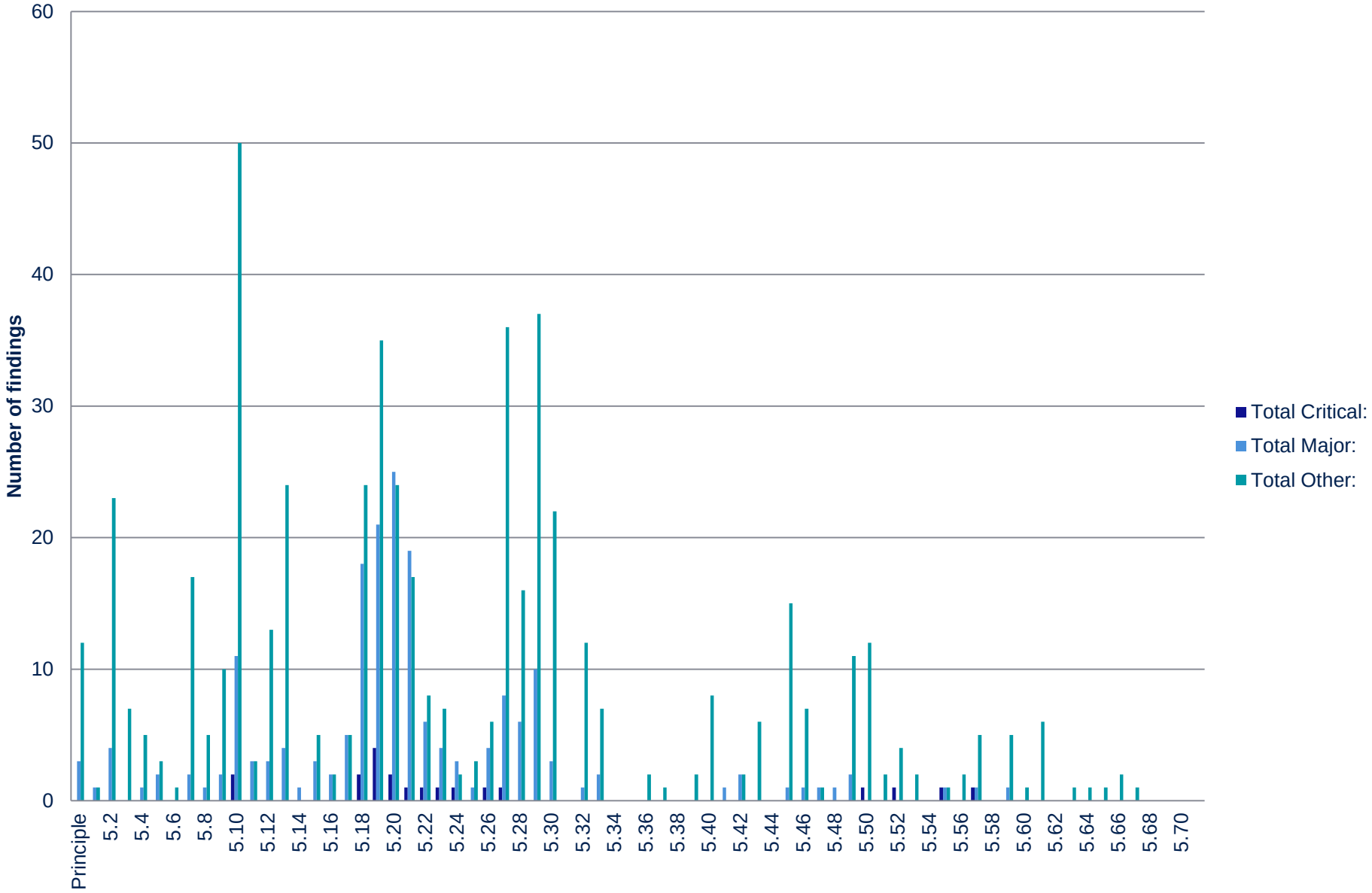
- A photocopy of a batch sheet page related to pallet stacking pattern seen in the trash container outside the bottle packing line was indication of an unacceptable practice of uncontrolled photocopying of pages of the batch record during use.
- There were no log books in place for each compounding workstation to ensure traceability of operations.
- Uncontrolled documentation was noted throughout: production engineering notebooks with set up details and passwords, crib notes on the wall of the goods in area, scraps of paper containing numbers of components brought onto line.

Chapter 4 - Deficiency examples

Deficiencies related to integrity of data:

- Data integrity assessments were focused on system compliance and failed to consider the impact of business processes on the integrity of data, for example manual transfer of data between electronic systems.
- The investigation relating to a data integrity failure, whereby fictitious utility monitoring data was recorded, lacked sufficient detail to demonstrate whether willful intent was suspected.
- Printouts of particle count data from HEPA filter testing were not transferred from thermal paper to non-volatile media to ensure the integrity of the record throughout the retention period.

Findings Chapter 5 per Section



Chapter 5 - Deficiency examples

Deficiencies related to material management and controls:

- The supplier qualification and audit procedure lacked sufficient definition of a critical material or supplier.
- Product containers were being over-labelled so GMP data was being obscured.
- The warehouse receiving area was not being temperature monitored so the acceptable temperature limit of <32°C could not be verified.
- Only the top layer of large dry powder chemical drums was being sampled so this material was not representative of the bulk material.

Chapter 5 - Deficiency examples

- API shipped from the supplier in India were not subject to temperature monitoring or control despite requiring storage at ≤25°C.
- The approved supplier list does not include the address of the manufacturer. The site is therefore unable to confirm that the material is received from both the correct supplier and manufacturer.
- There was no requirement to confirm that the tamper evident seal numbers were as expected upon receipt of APIs.
- There were no TSE certificates obtained for the reagents added to the purified water system.
- The warehouse receiving and unloading bays did not provide sufficient protection to materials during bad weather.

Chapter 5 - Deficiency examples

Deficiencies related to inadequate control to prevent cross contamination:

- No cleaning validation had been performed on the dispensing isolator.
- The justification for not doing cleaning validation was weak and the risk mitigation factors considered in the associated risk assessment did not reflect actual practice.
- There was no data to show that the cleaning of the mist shower was effective in removing any residual contamination.
- There was no diagram to show how drums would be loaded into the mist shower. This could lead to drums being packed to closely together which would create occluded surfaces which would not be wetted by the shower.

Chapter 5 - Deficiency examples

- There was no instruction to prevent the use of the raw materials dispensing booth whilst the dispensing isolator was being used.
- There were cracks in the vinyl around the mist shower drain. This would create a trap point which could cause the accumulation of chemical and microbial contamination.
- Equipment used to manufacture high potent materials was not verified as clean prior to removal to the general storage area.
- The FMEA risk assessment had failed to demonstrate adequate risk mitigation by referring to SOPs without detailing or assessing how controls were implemented.

Chapter 5 - Deficiency examples

- Where health based exposure limits were conducted, these had not been adequately integrated into the risk assessment process and the opportunities for retention in the equipment train at the ADE level had not been recorded in the context of the risk assessments.
- Cleaning failures identified at visual inspection by the second production inspector were not logged as deviations or similar to allow trending.
- There was no written instruction on rules of use of cleaning bays to ensure the risk of cross contamination between cleaned and un-cleaned items was controlled.

Chapter 5 - Deficiency examples

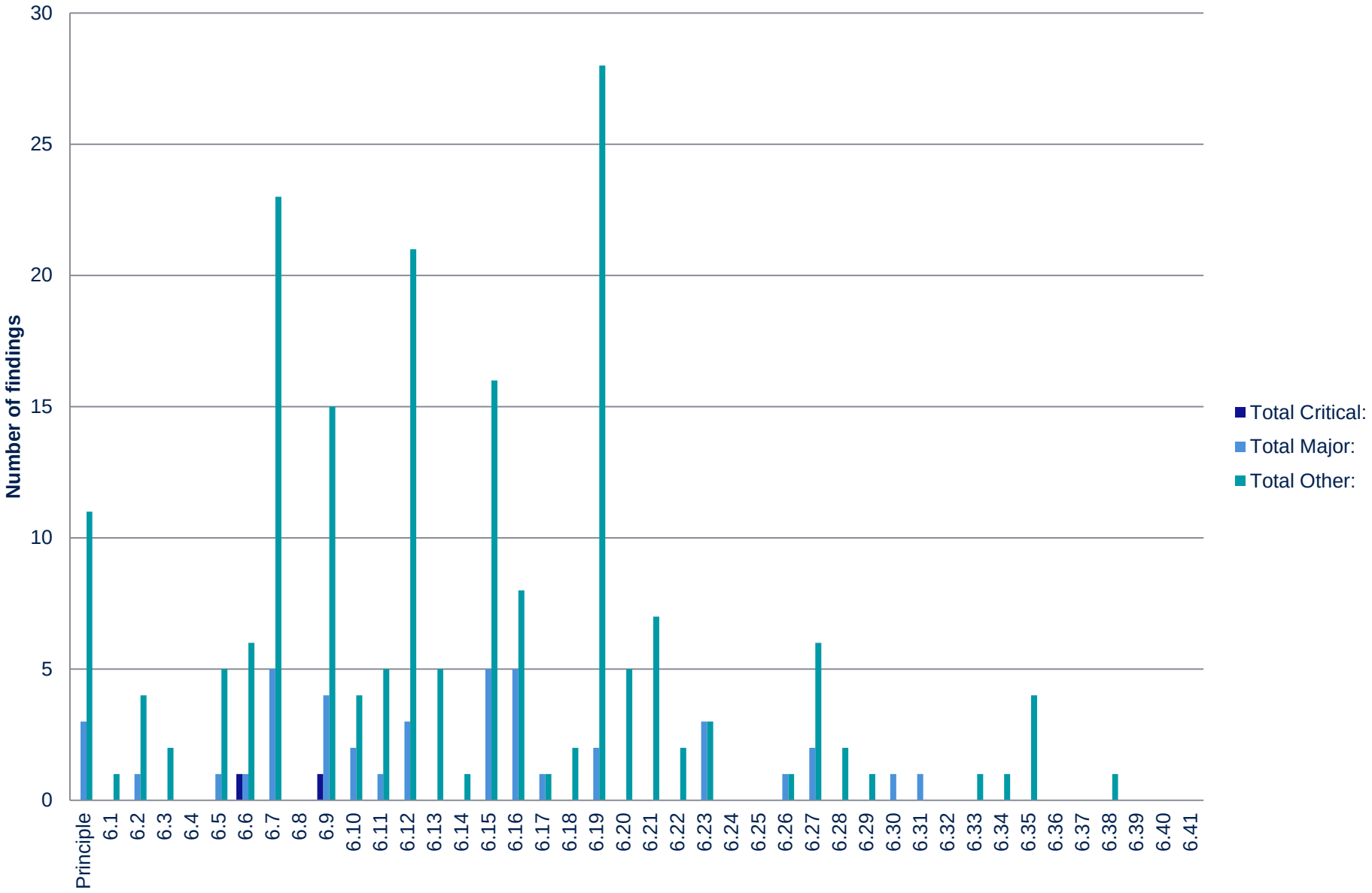
- There was no procedure to define how cleaning methods should be developed (i.e. by use of technical drawings and physical examination of the equipment) and verified to ensure a consistent approach was taken.
- The new product introduction procedure required products to be banded but not subject to development of health based exposure limits (PDE’s) and hazard assessments although it was acknowledged by the inspector that these had been generated for some products.

Chapter 5 - Deficiency examples

Deficiencies related to production:

- Different labels were not adequately segregated in the labels store in the packaging site as multiple different labels were stored in the same location.
- Capsule shells are not stored at the manufacturer’s recommended humidity conditions (35 - 65%RH) in the warehouse.

Findings Chapter 6 per Section



Chapter 6 - Deficiency examples

Deficiencies related to QC Laboratory activities:

- The sample receipt logbook in the QC laboratory was completed when a test request was received and not when the sample was received into the laboratory which could occur several days later, therefore sample traceability was not maintained and the data entry was not contemporaneous.
- One of the stability chambers was poorly labelled with the incorrect temperature and relative humidity.
- Clean glassware was not covered to prevent recontamination and a clean expiry date had not been defined.
- Grade B glassware was used in the laboratory for GMP testing.
- The Microbiology laboratory did not have a microbiological plate reader with magnifying glass to ensure an accurate colony count.

Chapter 6 - Deficiency examples

- There was no justification for the twelve month expiry assigned to reagents.
- There was no consideration of the chemical stability of the reagents when setting the shelf life for the opened chemicals.
- The mobile phase expiry period of 2 months for aqueous solutions could not be supported with data.
- The risk to product was not minimised as the laboratory balances were on an annual calibration and they were only challenged with a single weight once a week.
- There was only weekly checking of the temperature of the standards fridge and the probe had no maximum/minimum read outs.

Chapter 6 - Deficiency examples

Deficiencies related to out of specification (OOS) and out of trend (OOT) investigations:

The laboratory incident report (LIR) for bulk product that failed moisture analysis by titration was re-sampled as part of the Phase II investigation without first re-testing the original sample or proving beyond reasonable doubt that it had been compromised.

The agreed retest plan included the equivalent sample already taken for Hardness and Friability (H&F) as part of hypothesis testing. The H&F and re-sample passed and the OOS was overturned, however the LIR did also not record how the re-sample was to be conducted and record of resampling suggested the sample was not taken representatively from the run.

Thus overall there remained an element of doubt over whether the batch homogeneity was adequate.

Chapter 6 - Deficiency examples

The laboratory incident report (LIR) for an unknown impurity failure on batch 123 of API XYZ was re-sampled in support of the phase II investigation without first establishing adequate evidence to determine that the original sample had been contaminated.

The re-sample testing was not included in the LIR report and there was no comment to explain what had been done with the re-sample.

Chapter 6 - Deficiency examples

- An OOS result was averaged with two in-spec results to generate a passing result.
- Where re-sampling and re-testing was to be carried out, a maximum of three sets of analyses was permitted. This number of retests was not deemed to be statistically significant.
- The Out of Specification procedure did not contain adequate controls relating to the resampling of material.
- There was no requirement for an investigation to be conducted by Manufacturing to identify potential contributory factors.

Chapter 6 - Deficiency examples

- Investigations did not include hypothesis for test failure before retesting.

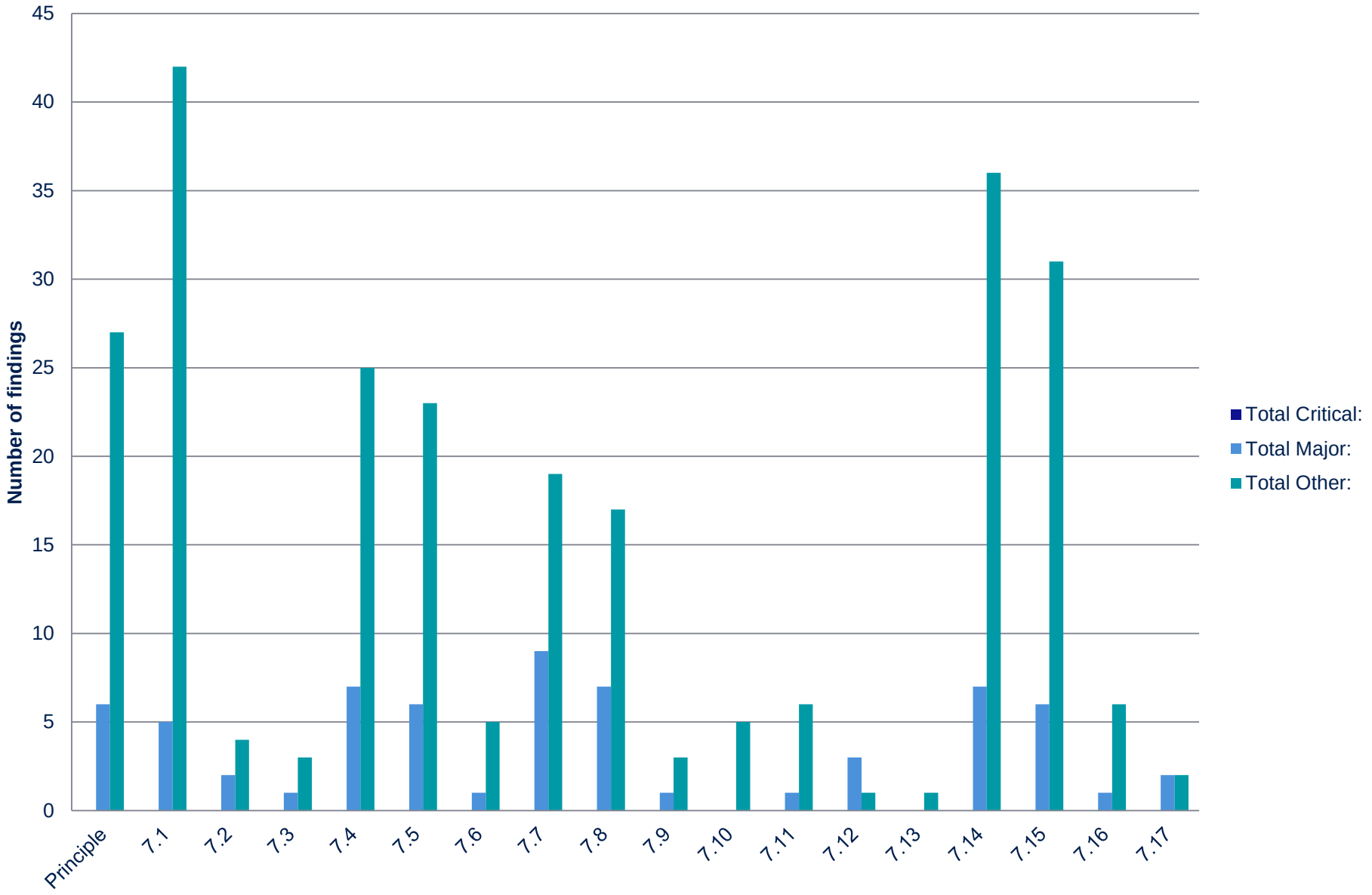
- Investigations which identified laboratory error did not always include preventative actions to ensure that the same laboratory error would be avoided in future.

Chapter 6 - Deficiency examples

Deficiencies related to the management of stability studies:

- There had been numerous stability failures (including pre-shelf life expiry) identified but these had not been formally assessed by the QPs or the impact on continued certification considered.
- The contract manufacturer did not notify the stability failures to the Marketing Authorisation Holders.

Findings Chapter 7 per Section



Chapter 7 - Deficiency examples

Deficiencies related to the management of outsourced activities:

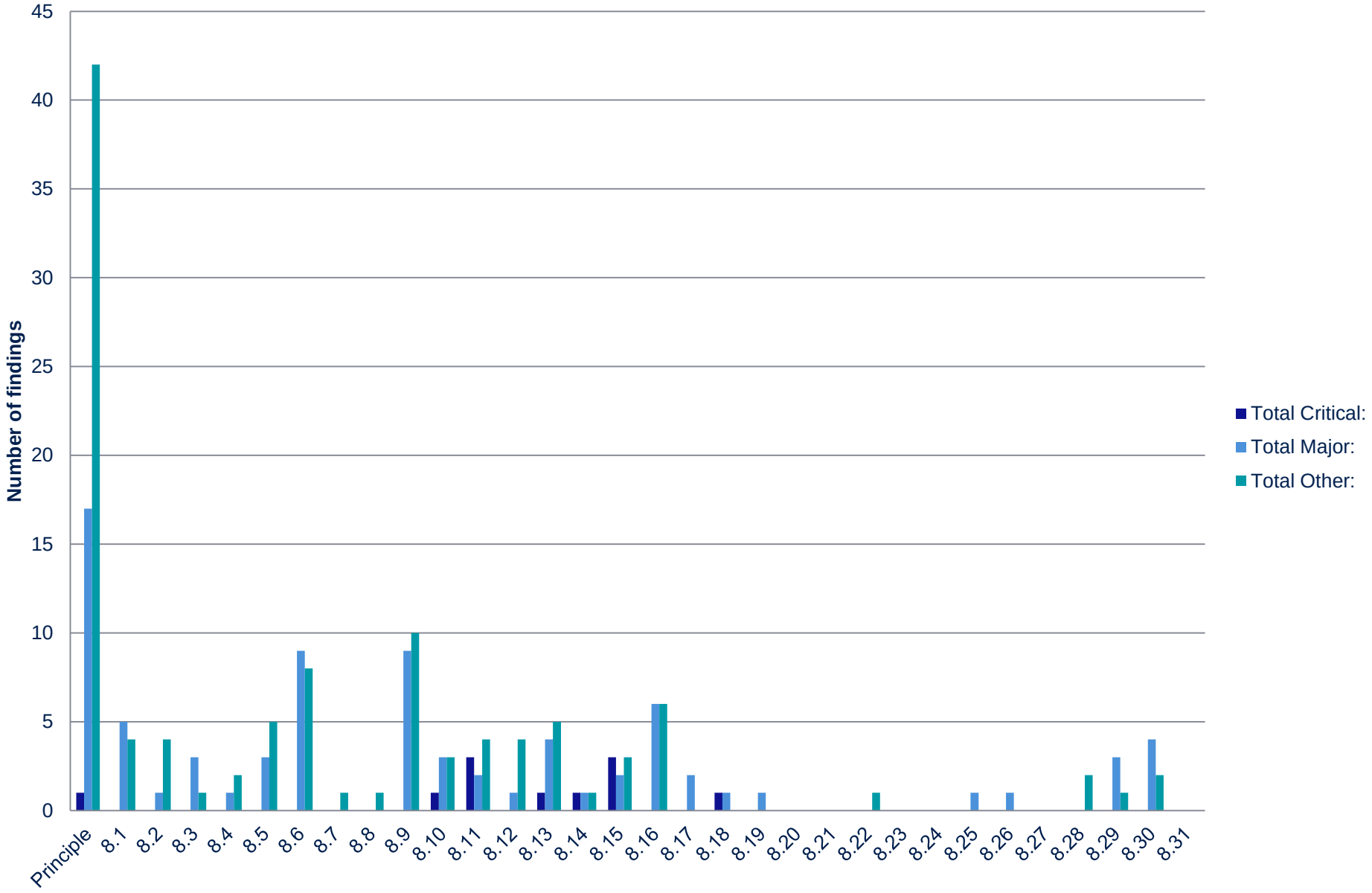
- There was no procedure in place for the management of critical service suppliers and there was no mechanism in place to enable the qualification and monitoring of supplier performance.
- There was no evidence of a review by company personnel of the audit report conducted by a third party auditor.
- There was no procedures that describe the training and competency assessment required for company auditors.
- Procedures did not describe the basis for accepting an audit report prepared by a third party.

Chapter 7 - Deficiency examples

Deficiencies related to technical agreements:

- The technical agreement between Company A and Company B was insufficiently detailed. It only contained a series of bullet points covering Company B's activities, and did not describe the responsibilities of Company A.
- The technical agreement between Company A and Company C contained conflicting statements regarding the responsibility for customer verification.
- The technical agreement with Company D did not identify the products that were to be within the scope of the agreement.
- The technical agreement with Company E did not identify which party was the Contract Acceptor and which was the Contract Giver. Additionally there was no explicit requirement for temperature monitoring devices to be used for shipment of goods to Company F.

Findings Chapter 8 per Section



Chapter 8 - Deficiency examples

Deficiencies related to handling of complaints and investigations:

- There was no consideration of whether the complaint referred to a falsified medicine.
- There was no requirement to obtain the product implicated by the complaint.
- There was no requirement to consider if any other batches were implicated.
- The complaint process did not require a check to consider if complaints were due to counterfeits.
- The procedure did not include contact details for the Defective Medicines Report Centre (DMRC) or requirements for the reporting of potential falsified medicines.

Chapter 8 - Deficiency examples

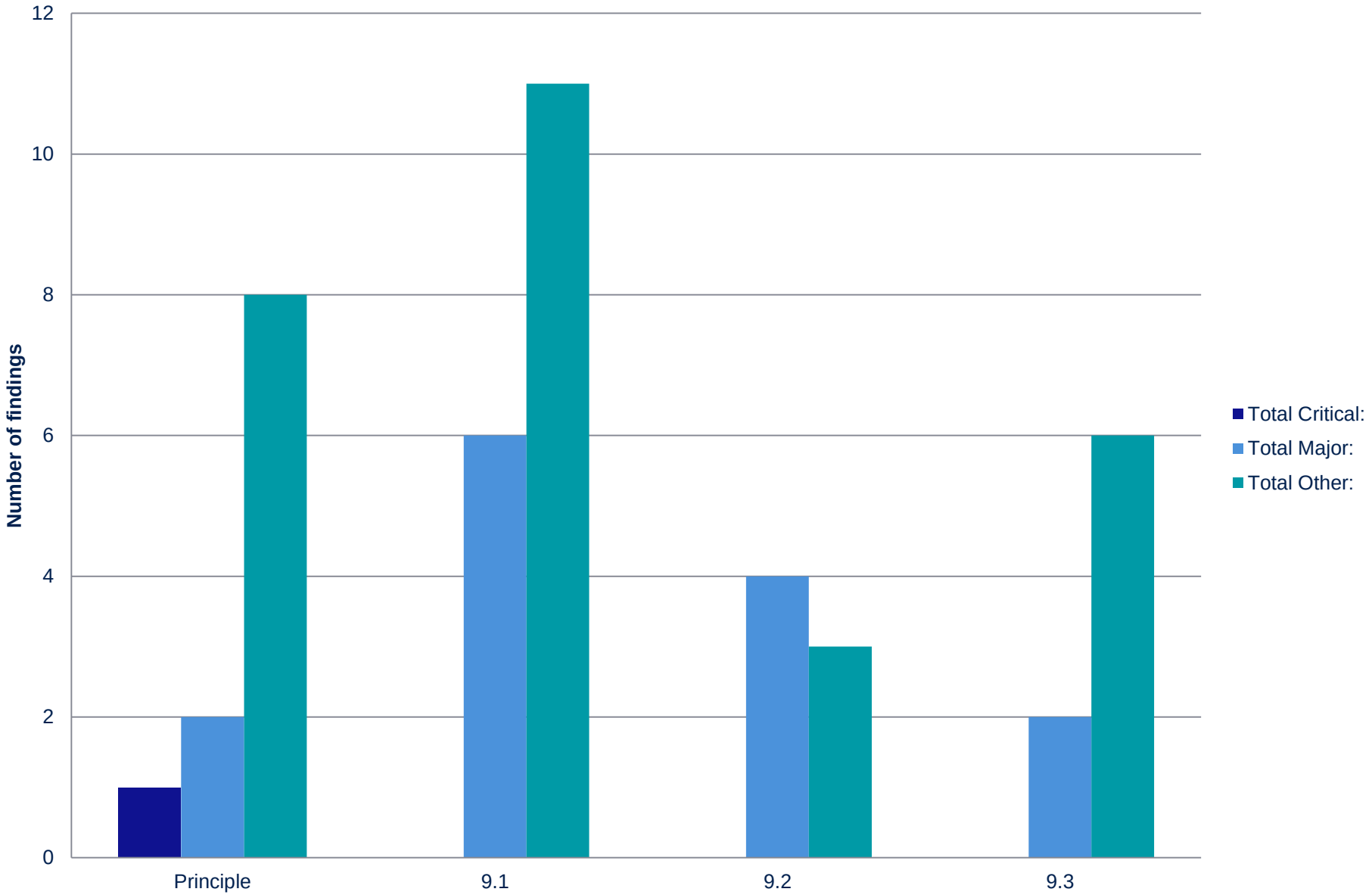
- Inadequate investigation was performed on site. For example, not reviewing manufacturing and other data available and also not considering the wider implications of the complaint on other batches.
- Complaint investigations were not always documented contemporaneously.
- Due to the lack of site investigation, CAPA were not always considered or effective to prevent reoccurrence.

Chapter 8 - Deficiency examples

Deficiencies related to product recall:

- The recall procedure did not define maximum timelines for key steps to ensure the recall process was completed in a timely fashion.
- There is no requirement to perform an out of normal working hour test of the recall system.
- The mock recall challenge was not completed in a timely manner and no final formal assessment report was generated.
- There is no procedural instruction to ensure that any in-house stocks of product potentially affected by a recall are quarantined.
- The mock recall process did not effectively challenge the supply chain and did not require a reconciliation or report to consider the effectiveness of the recall.

Findings Chapter 9 per Section



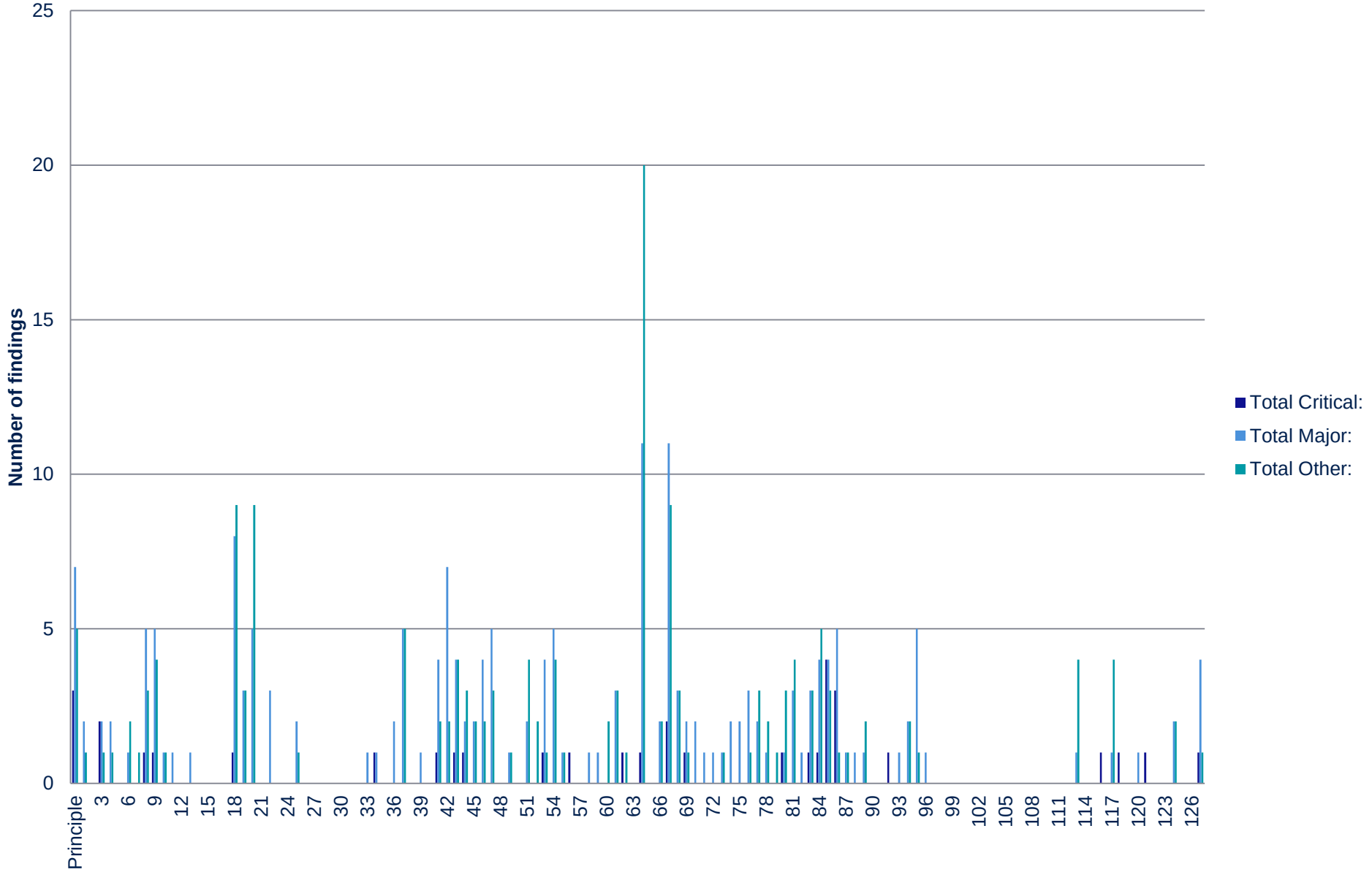
Chapter 9 - Deficiency examples

Deficiencies related to Self-inspection program:

- Although two self-inspections had been performed these had not covered key aspects of the Quality Systems.

- There was no self-inspection schedule in place.

Findings Annex 1 per Section



Annex 1 - Deficiency examples

Deficiencies related to increased risk of microbial contamination and failure to ensure sterility assurance:

- Bags containing filling equipment (for example filling needles) were opened by tearing the bag which presented a risk of introducing fibres to the equipment/line and subsequently the product.
- The innermost bag containing the stopper track was damaged prior to loading into the filling line which presented a risk of fibres being transferred to stoppers and subsequently the product.
- There was insufficient evidence documented to demonstrate that the number of aseptic connections after sterilisation had been minimised.
- There is no sanitisation of hands after each individual garment is touched and put on.

Annex 1 - Deficiency examples

- Operators wore outdoor clothes under aseptic gowns in the Grade B zone.
- Gowning procedures required operators to remove their shoes when entering grade D and C areas. The nature of the foot coverings used would not prevent microbial contamination passing from the operator's feet onto the clean room floors.
- In the main office of Block B manufacturing operators appeared to be allowed to wear flip flops, shoes with over-shoes or socks.
- During gowning into the manufacturing area the bench was not sanitised prior to sitting on it.
- While donning sterile gloves prior to entering a grade B area an operator was observed touching the outside of sterile gloves on several occasions.

Annex 1 - Deficiency examples

- Only the surfaces which are touched by the operator or are in contact with components on the compounder are sanitised before manufacture, rather than all surfaces as expected.
- The hooks used for hanging bottles and bags were not cleaned appropriately as they were held together with the operator’s hand and sanitised as a group rather than individually to ensure that all surfaces are sanitised.
- The wipes used for sanitisation did not appear to be wetted sufficiently as only the area in the centre appeared to be wet rather than the whole area to ensure effective surface coverage.
- A gap between the hood and mask was seen for some operators resulting in exposed skin at the side of the face with the potential for product contamination especially when working in a LAF cabinet.

Annex 1 - Deficiency examples

- There are currently no drawings or diagrams which define the positioning of components in the laminar air flow (LAF) cabinet or isolators to ensure that unidirectional airflow is maintained.
- Operators do not wear goggles even though compounding is conducted in an open LAF cabinet and ampoules may be used in the compounding process which is an open rather than a closed manipulation.
- Sanitised rather than sterile googles were permitted to be worn in EU Grade B areas.
- The sequence of installing the filling needles and connecting tubing did not minimise contamination risks; the sequence used resulted in contact between fingers of the restricted access barrier system (RABS) glove and the exposed tops of needles on several occasions.

Annex 1 - Deficiency examples

Deficiencies relating to media fill process:

- The investigation into the media fill failure did not include a full chronology of events and did not include full details of all the corrective actions taken at each event. e.g. operator assessments, re-training of operators.
- A sample of the contaminated bag was not kept and therefore the contaminating organism was not able to be identified to species level which would have aided any investigation.
- The media fill batch size was 60 bags, however these were not labelled in the order of filling and therefore the position of the contaminated container could not be determined.
- The media fill and process validation studies did not capture the full complexity of the aseptic manufacturing processes used and therefore did not closely imitate the production process and were not representative of worst case.
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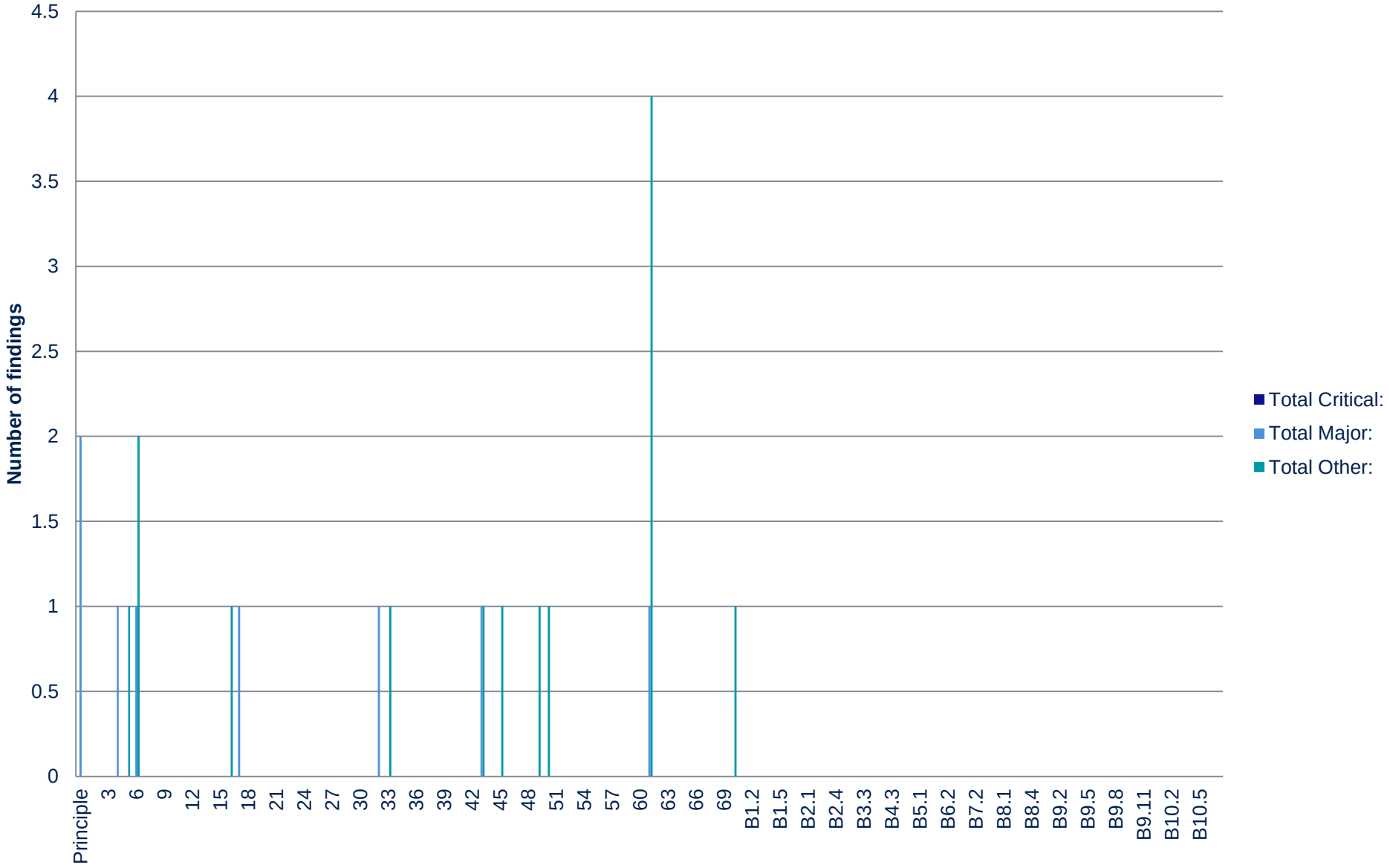
Findings Annex 2 per Section



Annex 2 - Deficiency examples

Deficiencies related to risk of contamination and inadequate control:

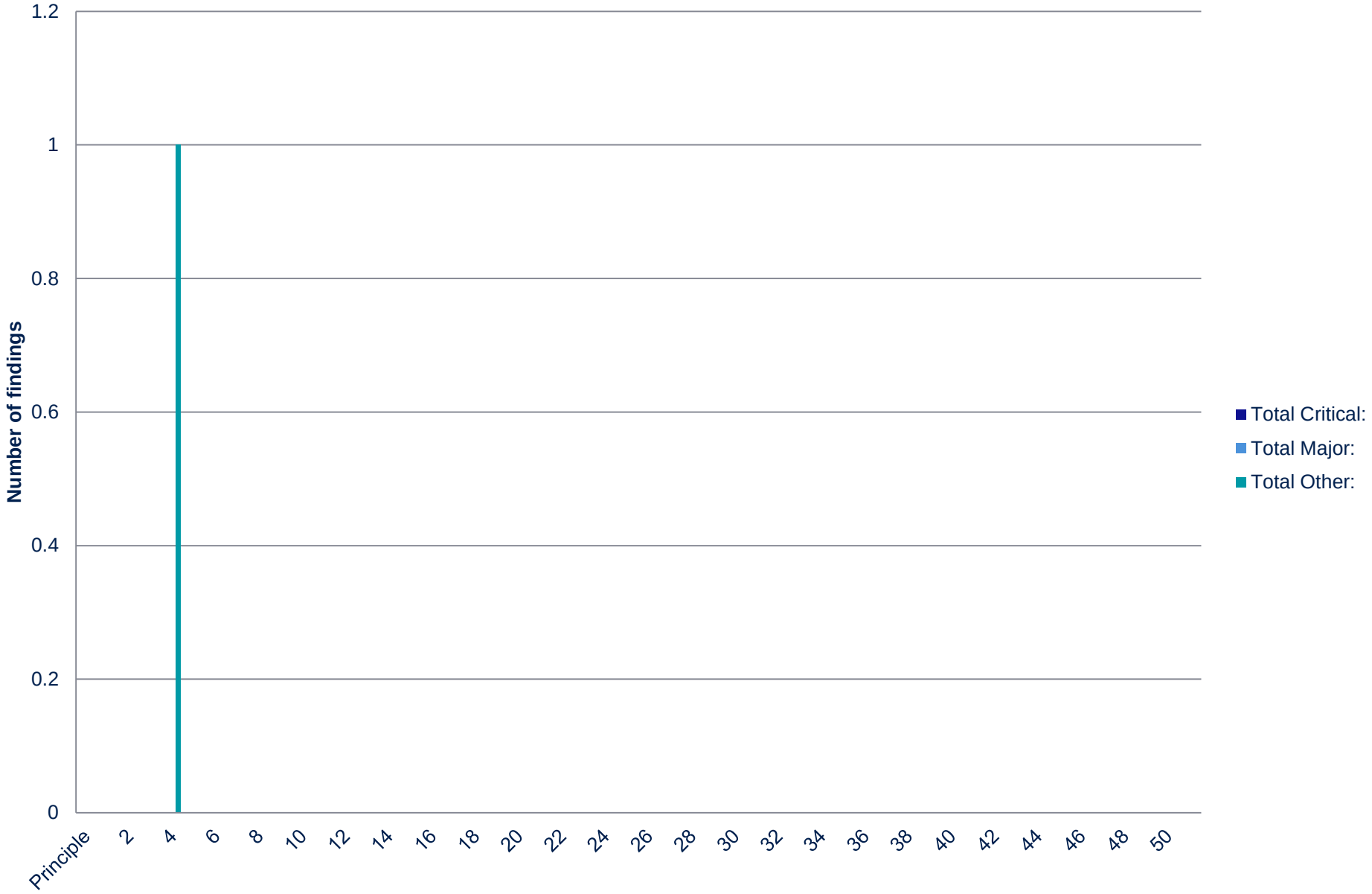
- Sanitisation contact times were not being monitored and the five minutes contact time for the sporicide was not as defined by the sanitising agent manufacturer or validated by the Company.
- Building Management System alarm cables were not being unclipped to aid effective end of campaign cleaning.
- Gowns worn in EU Grade B rooms were not sterile and skin was exposed as googles were not worn.
- Sterile gloves were not being worn by the operator sanitising materials into the transfer hatch to the EU Grade B area.
- Outdoor clothing was worn in EU Grade B areas.

Annex 2 - Deficiency examples

The facilities were inadequate for EU Grade A/B aseptic processing operations:

- Airlock doors were not either interlocked or a door open warning system installed.
- There was not a change lock between each individual air classification.
- There was no local alarm in EU Grade B rooms to indicate a failure in the air supply.

Findings Annex 3 per Section



Annex 3 - Deficiency examples

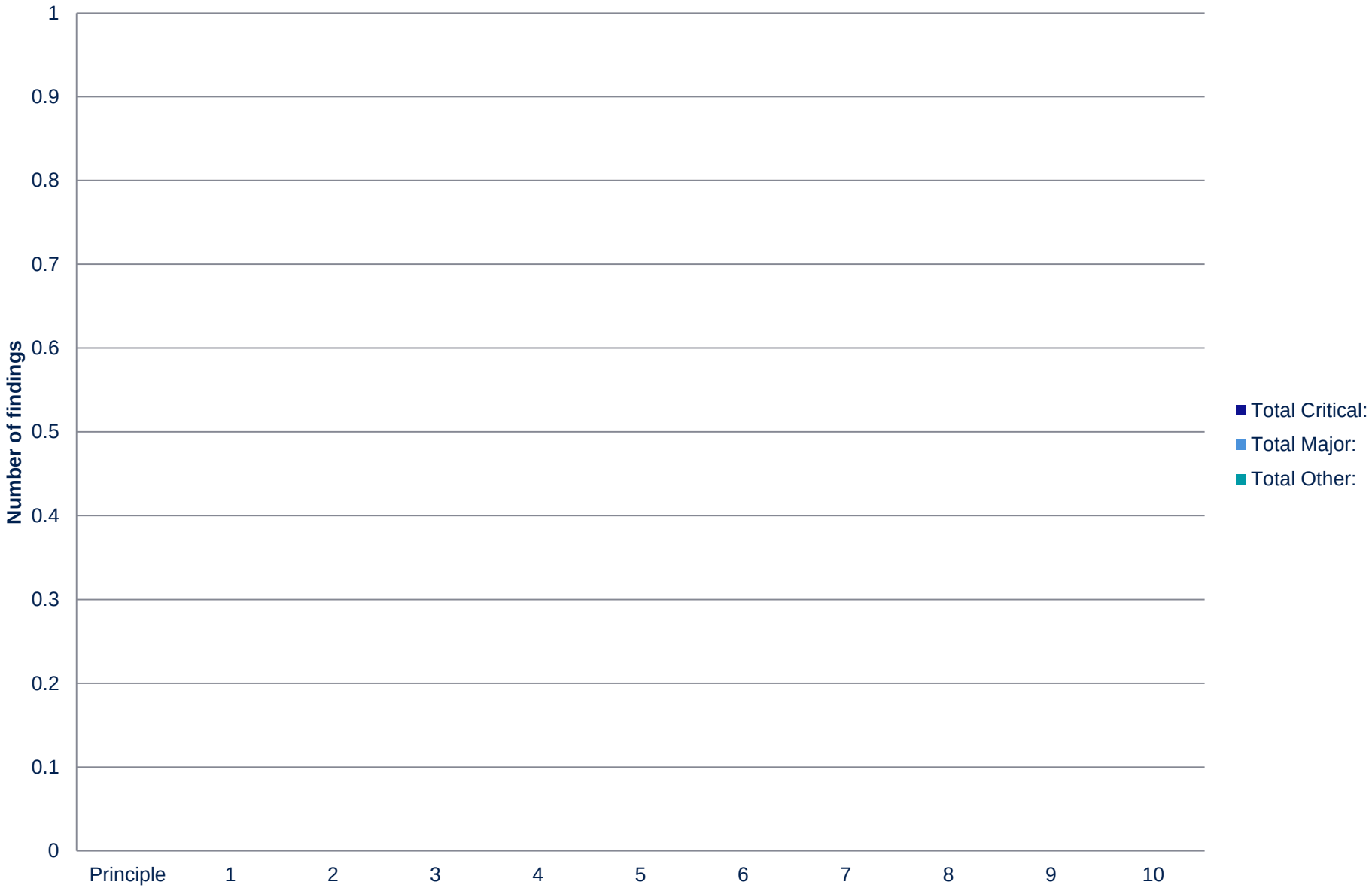
Deficiencies related to controls for cleaning, verification and validation:

- Records of visual inspection of cleaned disassembled equipment were not retained to confirm they were clean and available for re-use.
- The risk assessment conducted prior to the inspection on suitability of organisational and technical measures in limiting risk of cross contamination did not apply an adequate challenge of current controls to confirm suitability or identify potential failure opportunities in the controls.
- New equipment had not been fully and adequately assessed for design and construction and the required disassembly for cleaning purposes.

Annex 3 - Deficiency examples

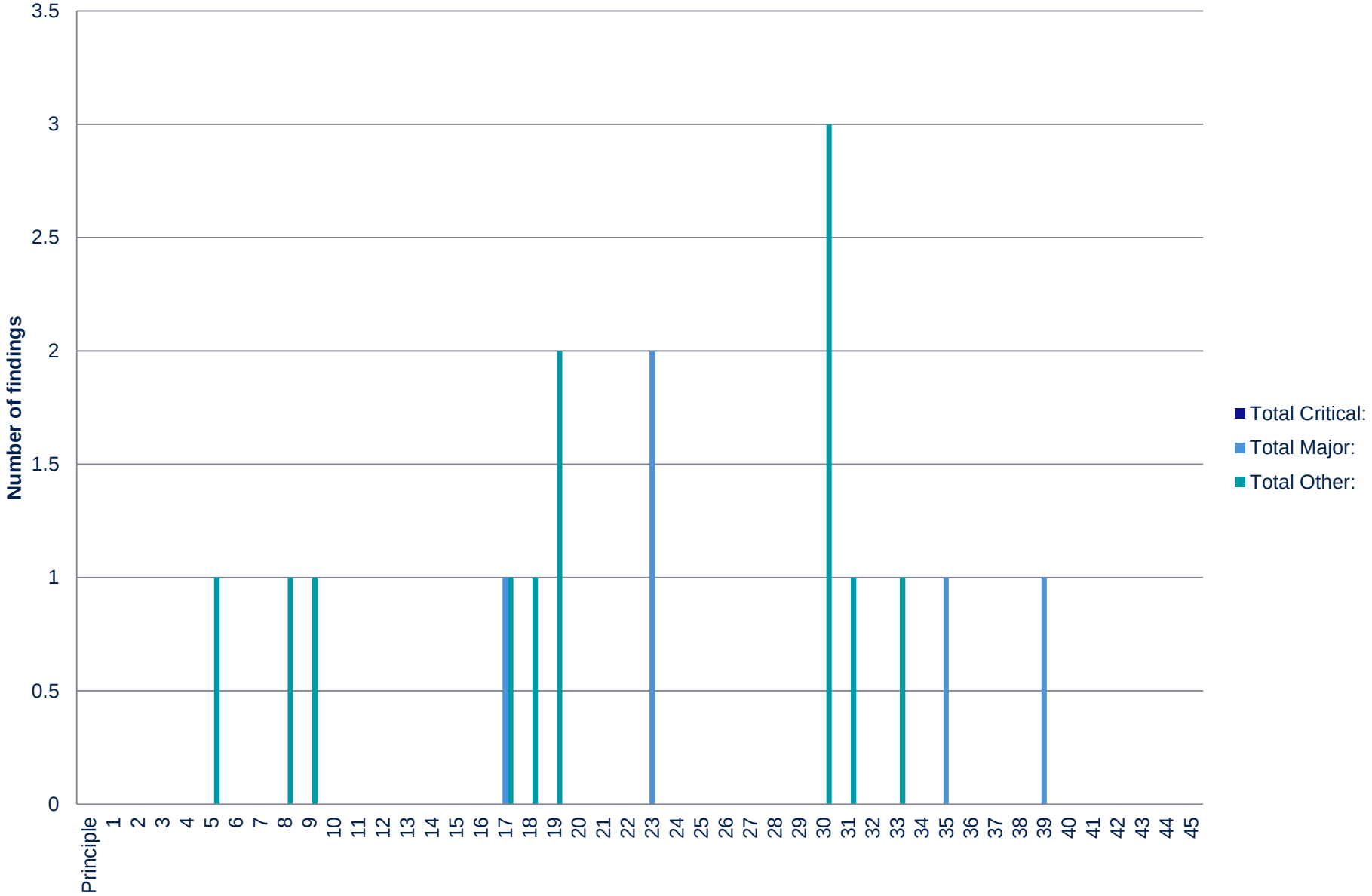
- There was no procedural requirement for how cleaning and disassembly of equipment should be developed.
- There was no record of failures seen at visual inspection stage that could be tracked for trend and validation review purposes.
- There was a large powder deposit in the wash bay floor at the clean equipment out door that was attributed by site personnel to be product X. Gross clean should have been completed prior to equipment reaching the washroom so this appeared to indicate a breach of required practice. Additionally, a washroom should not be left with gross contamination.

Findings Annex 4 per Section



Findings Annex 5 per Section

Findings Annex 6 per Section



Annex 6 - Deficiency examples

Deficiencies related to batch release and receipt and storage:

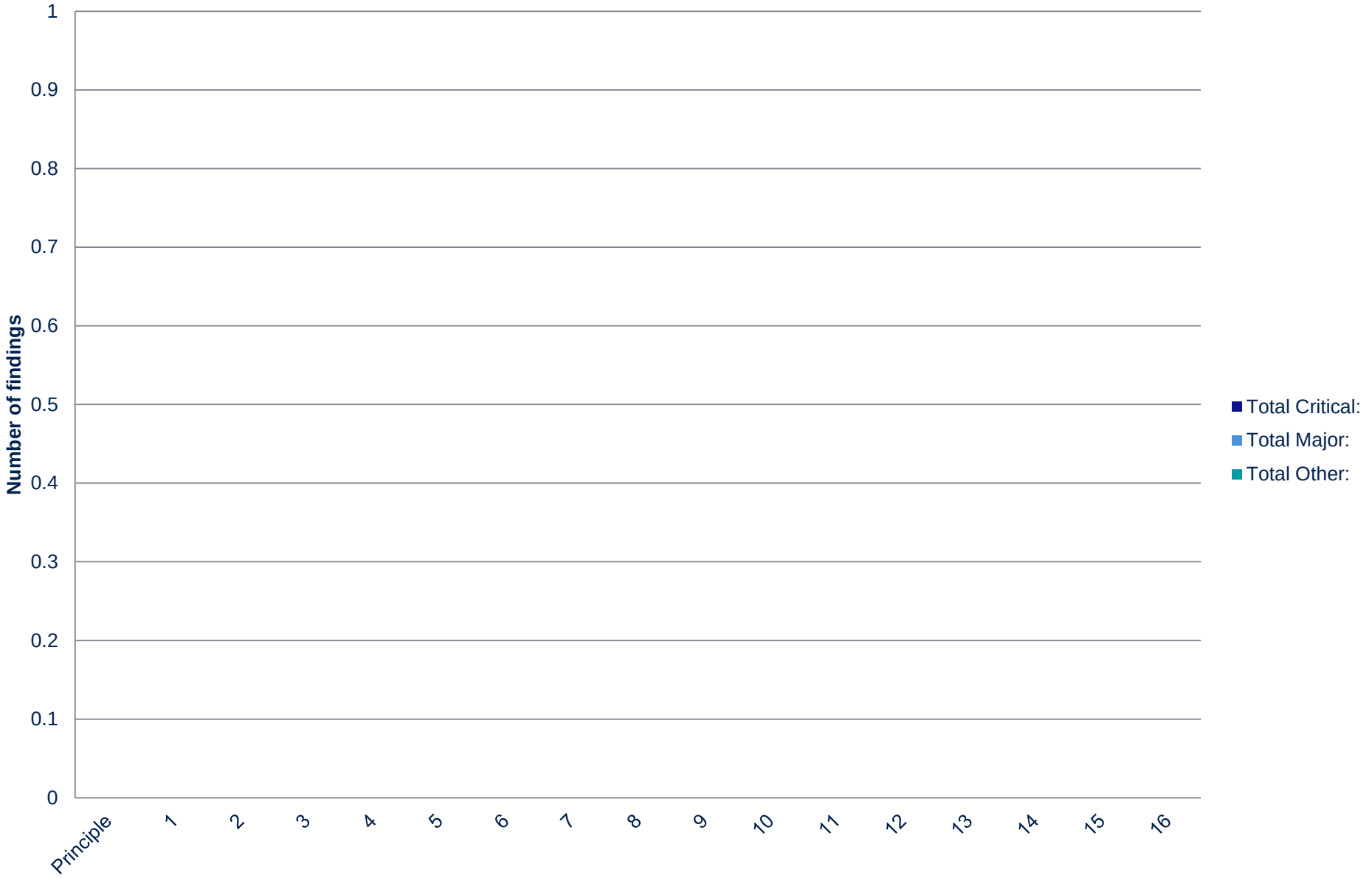
Release of batches was inadequately managed with a recorded out-of specification oxygen content:

- Neither the authorised Quality Controller or Qualified Person detected that an OOS result had been recorded and this was only picked-up during preparation of the Product Quality Review.
- An assumed root cause of human error was assigned however no attempt was made to verify this.
- No consideration was given to informing the competent authority (via the Defective Medicines Reporting Centre) of the potential risk of defective product being on the market.

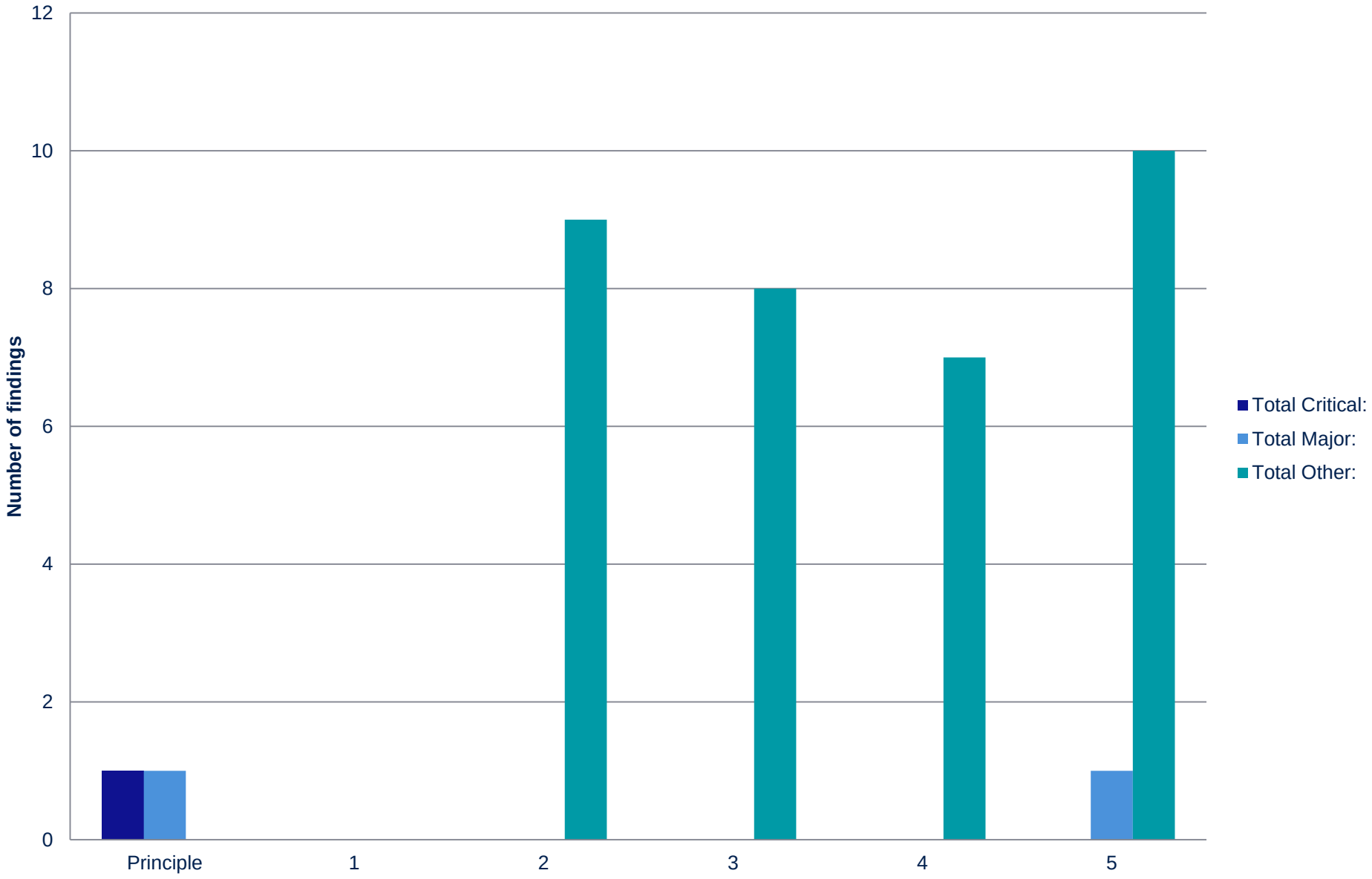
Annex 6 - Deficiency examples

- Filled medical oxygen Dewars were not stored under cover in a manner that ensured that they would be delivered in a clean state, compatible with the environment in which they will be used.
- Product labels on filled Dewars, available for despatch, were defaced such that registered details were not always fully visible.
- The current process for filling tankers did not ensure a prospective independent quality (QC or QP) release prior to delivery to customers or a QP certification.
- The justification for the lack of residual pressure check on incoming Dewars had not been documented and the validation report for the purging process was not available on site and therefore could not be inspected.

Findings Annex 7 per Section



Findings Annex 8 per Section

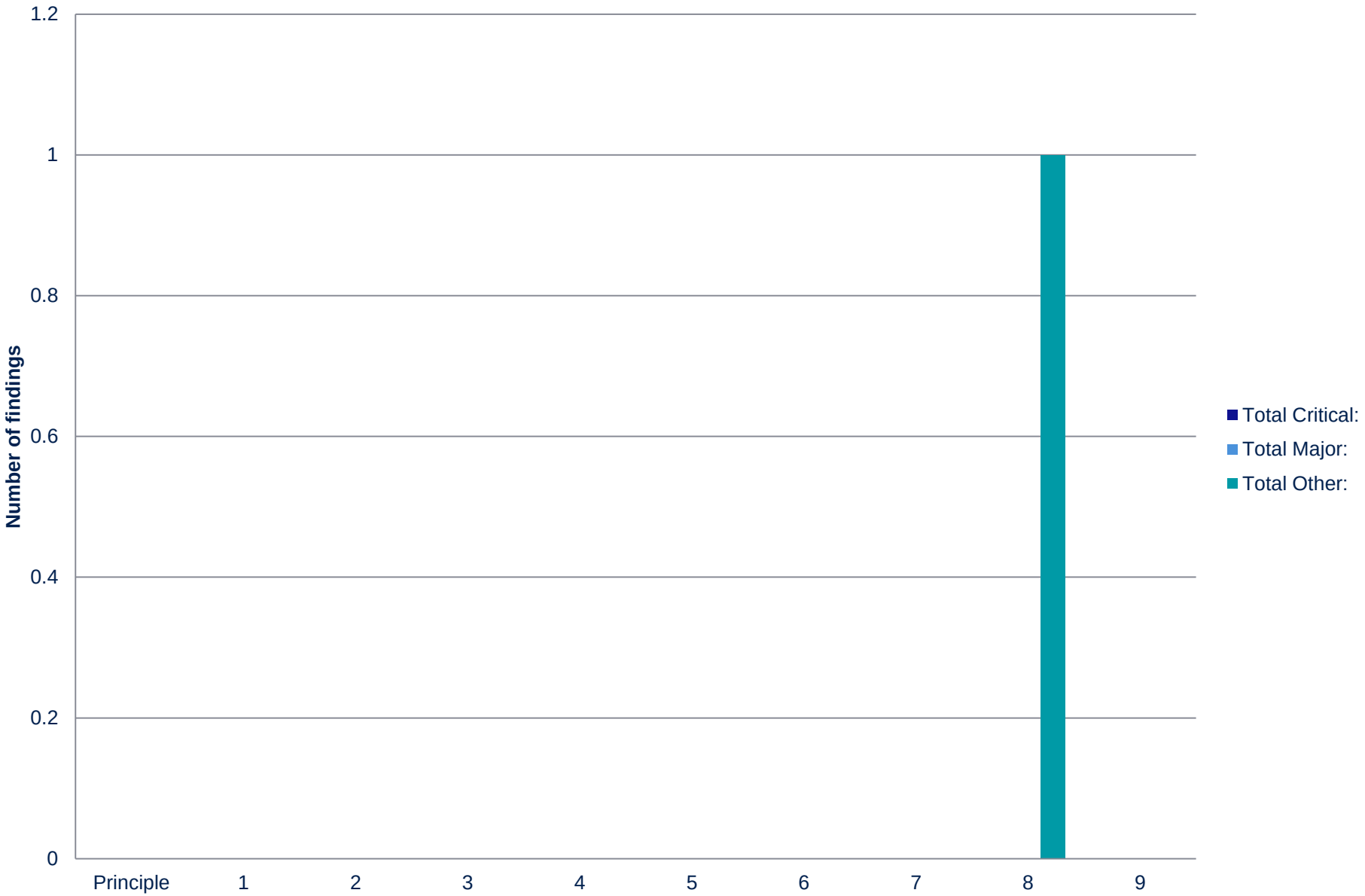


Annex 8 - Deficiency examples

Deficiencies related to controls for sampling and receipt of packaging materials

- Sampling plans for printed packaging components were not statistically based.
- There is no designated sampling location for printed packaging materials; instead they are sampled on the storage pallets in the warehouse.
- Sampling of printed packaging components did not take account of the production method in that there was no requirement to ensure all printing stations from the component printing company were included in the sample.
- Shade cards used for checking printed packaging components were not adequately controlled in that there were no checks performed against a reference standard (e.g. pantone chart).

Findings Annex 9 per Section

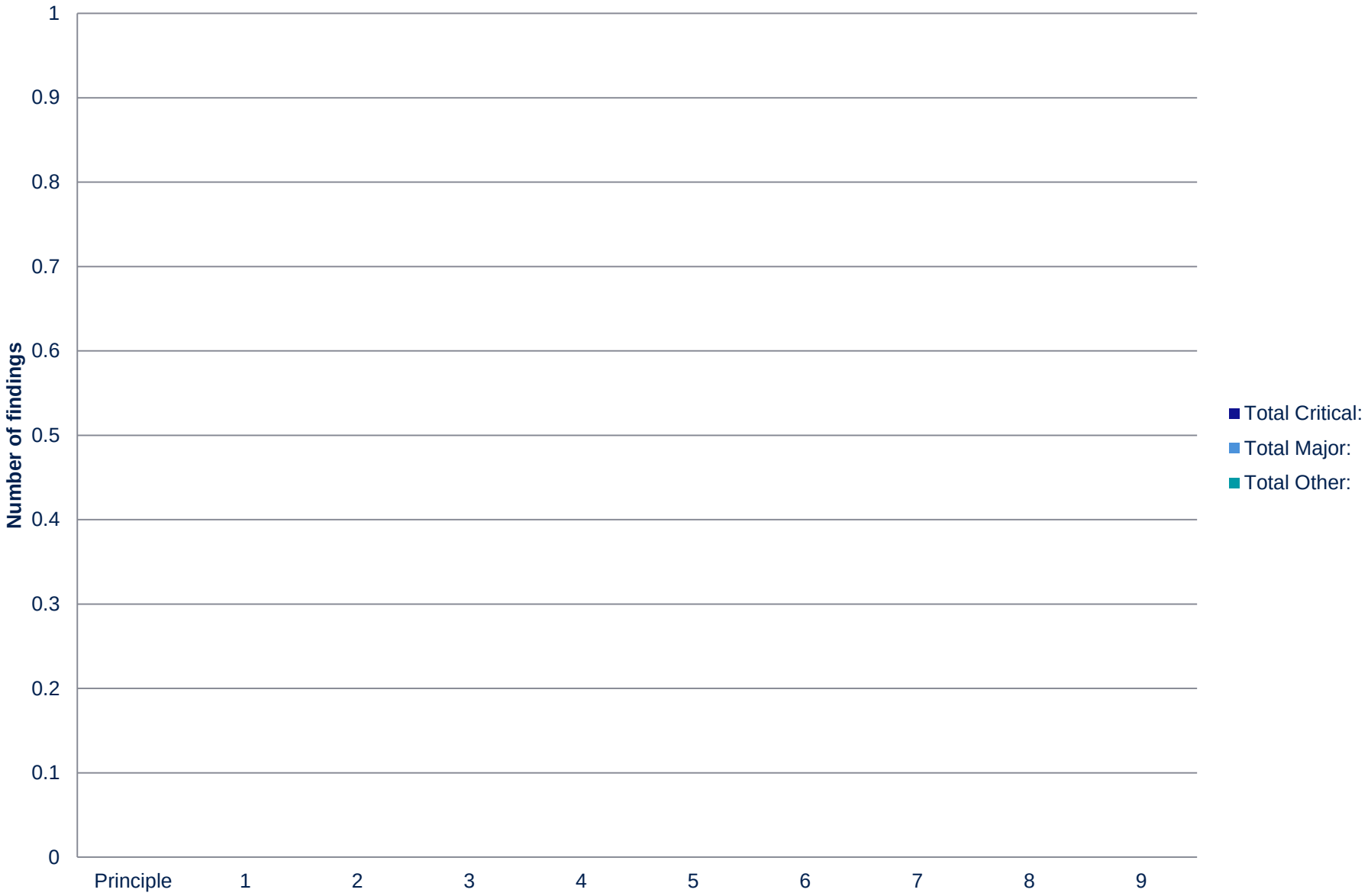


Annex 9 - Deficiency examples

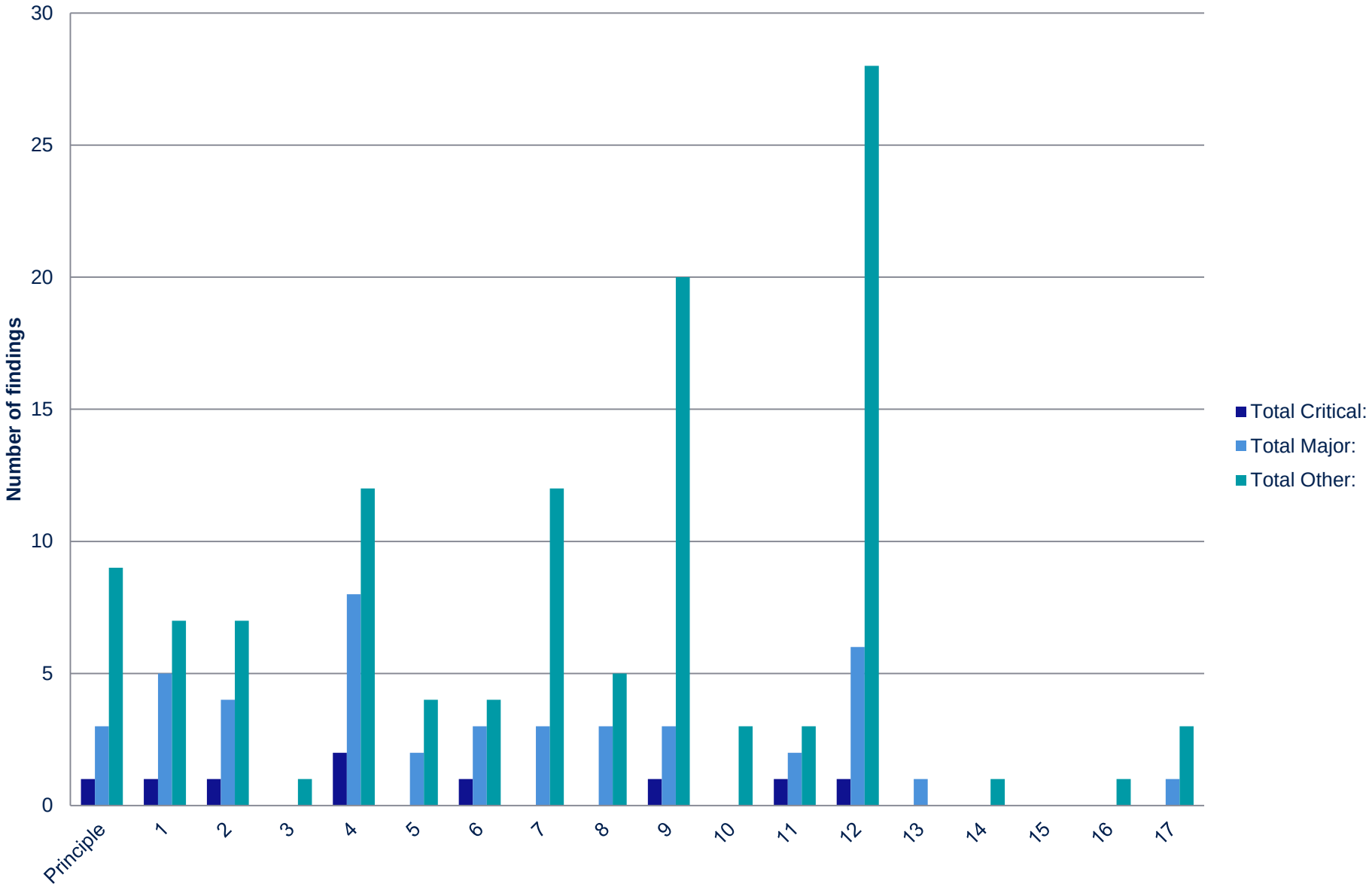
Deficiency related to production controls:

It could not be confirmed that the validated manufacturing process was routinely achieved, as the mixer in manufacturing room 5 was not calibrated and the speed was not routinely verified.

Findings Annex 10 per Section



Findings Annex 11 per Section



Annex 11 - Deficiency examples

Deficiencies related to data backup:

- Following a software update, data was lost from an autoclave control system. The system backup was unable to recover lost data as the backup was only performed on a 3 monthly basis.
- The backup CD/DVD for the autoclave control system was not stored within a controlled environment to assure its integrity.
- Data from the integrity test was not backed up. The system was observed to overwrite previous data.
- Backups were required to be reviewed for accessibility annually for 5 years however this failed to ensure that data that is required to be stored for longer such as validation data, was accessible for its full retention period.
- Backups were permitted to be made on the same computer drive which failed to ensure that a separate copy was available following drive failure or corruption.

Annex 11 - Deficiency examples

Deficiencies related to inadequate control of computerised systems:

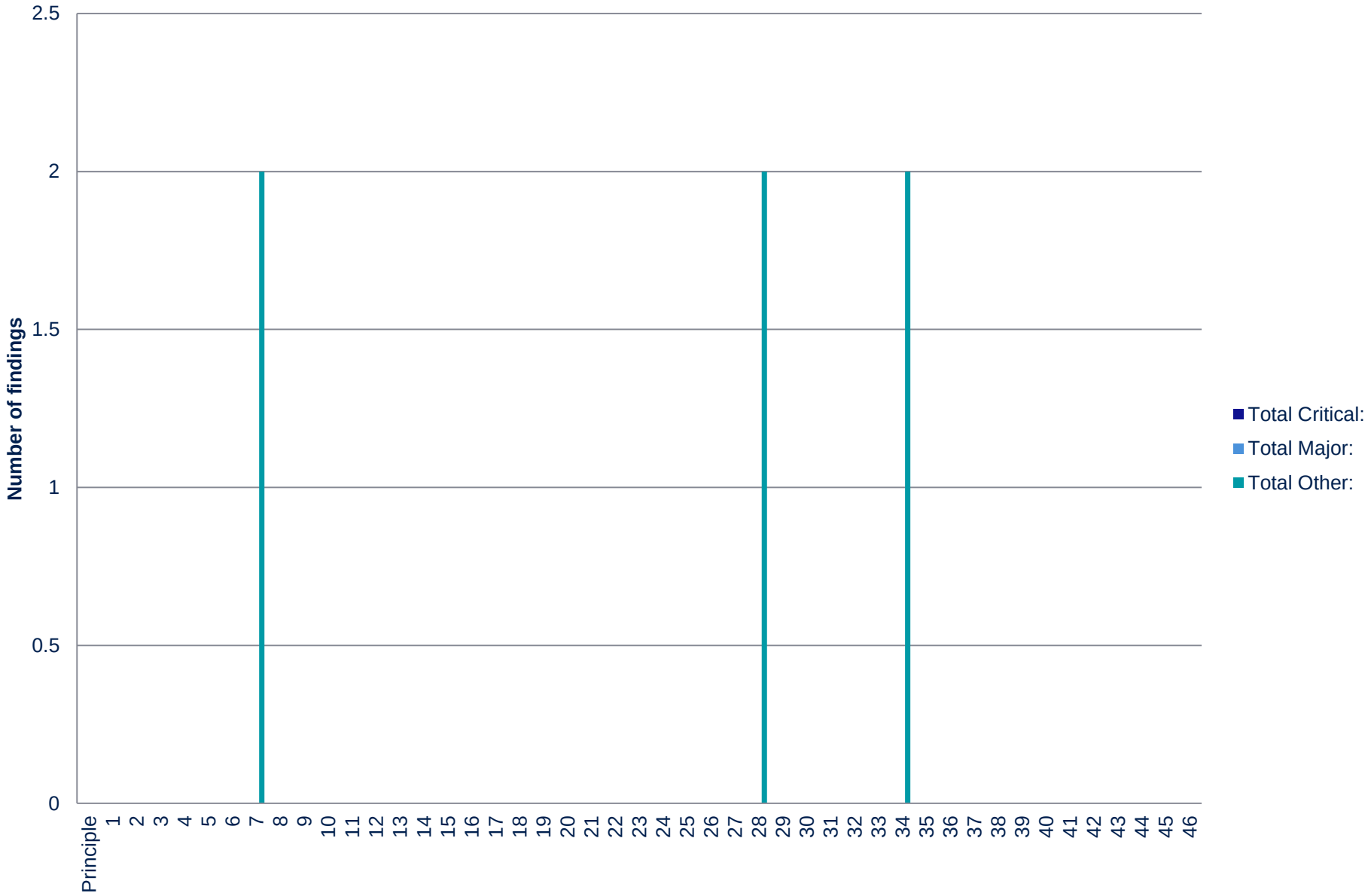
- Access to files and the system clock on the hard drive were available to all users.
- The lock screen used a shared password. If a user had logged into the software behind the lock screen and another user opened the computer, they could perform actions under the initial user's login.
- Users had more authorisation on the chromatography data system than was permitted according to the SOP.
- Access control systems were not considered GMP systems despite their intended purpose to control access to GMP areas.

Annex 11 - Deficiency examples

The HPLC software within the laboratory was not configured for GMP compliance:

- Unique user passwords were not enforced.
- Users were permitted to change the default audit trail.
- Users were permitted to change the default “require user comments”.
- Users were permitted to copy non-related projects.
- Users were permitted to use annotation tools.

Findings Annex 12 per Section

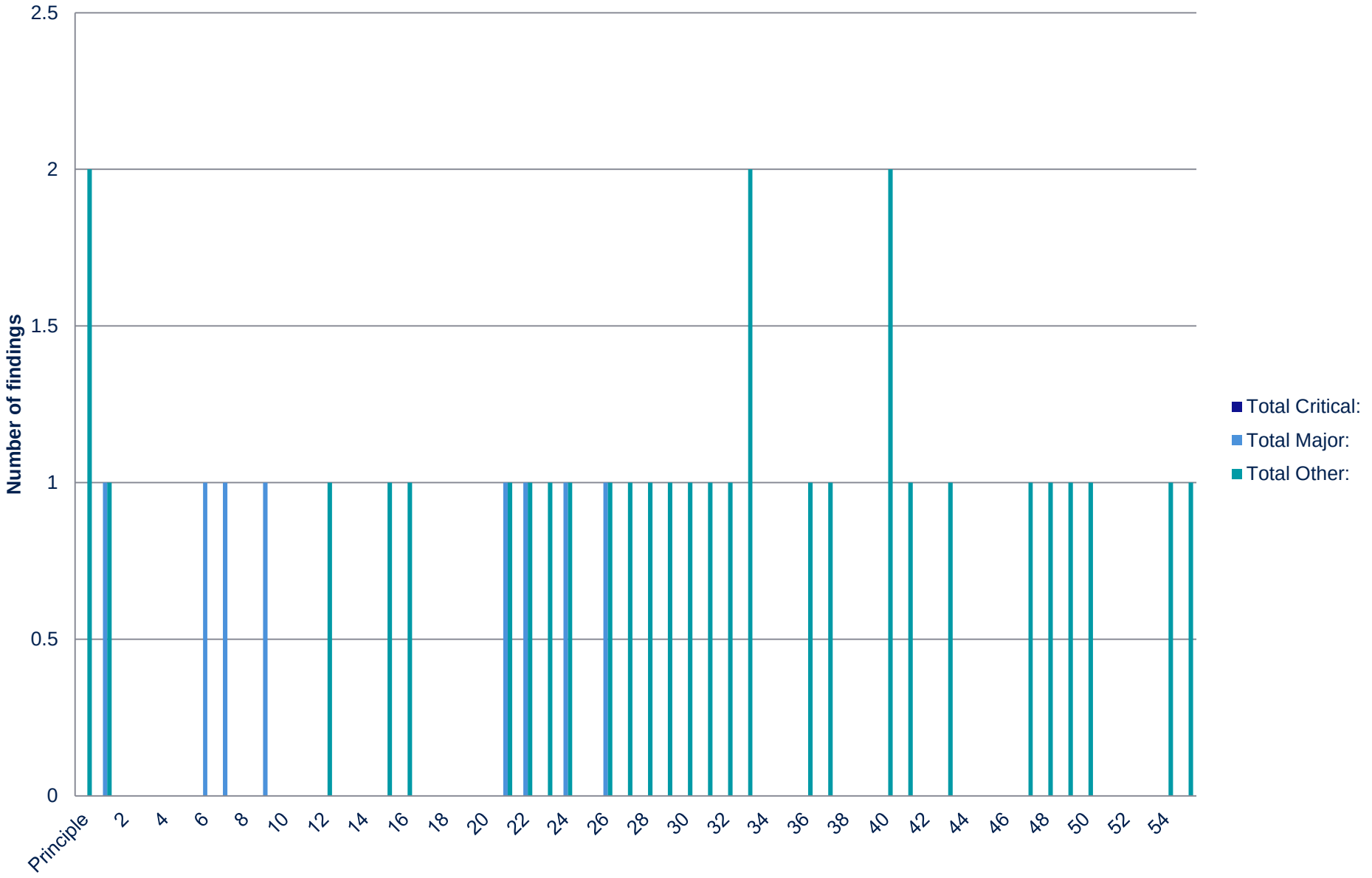


Annex 12 - Deficiency examples

The control of dosimeter readings was deficient:

- Dosimeters could be reread and individual thicknesses be input into the shared-arm dipole array (SADA) system if a variation of 6% was identified for a location, this did not result in a deviation to review the validity of previous acceptable results
- New thickness readings resulting from the scenario had no second person verification to ensure accuracy of the data used.

Findings Annex 13 per Section



Annex 13 - Deficiency examples

Deficiencies related to management of QP Declarations for import of IMPs:

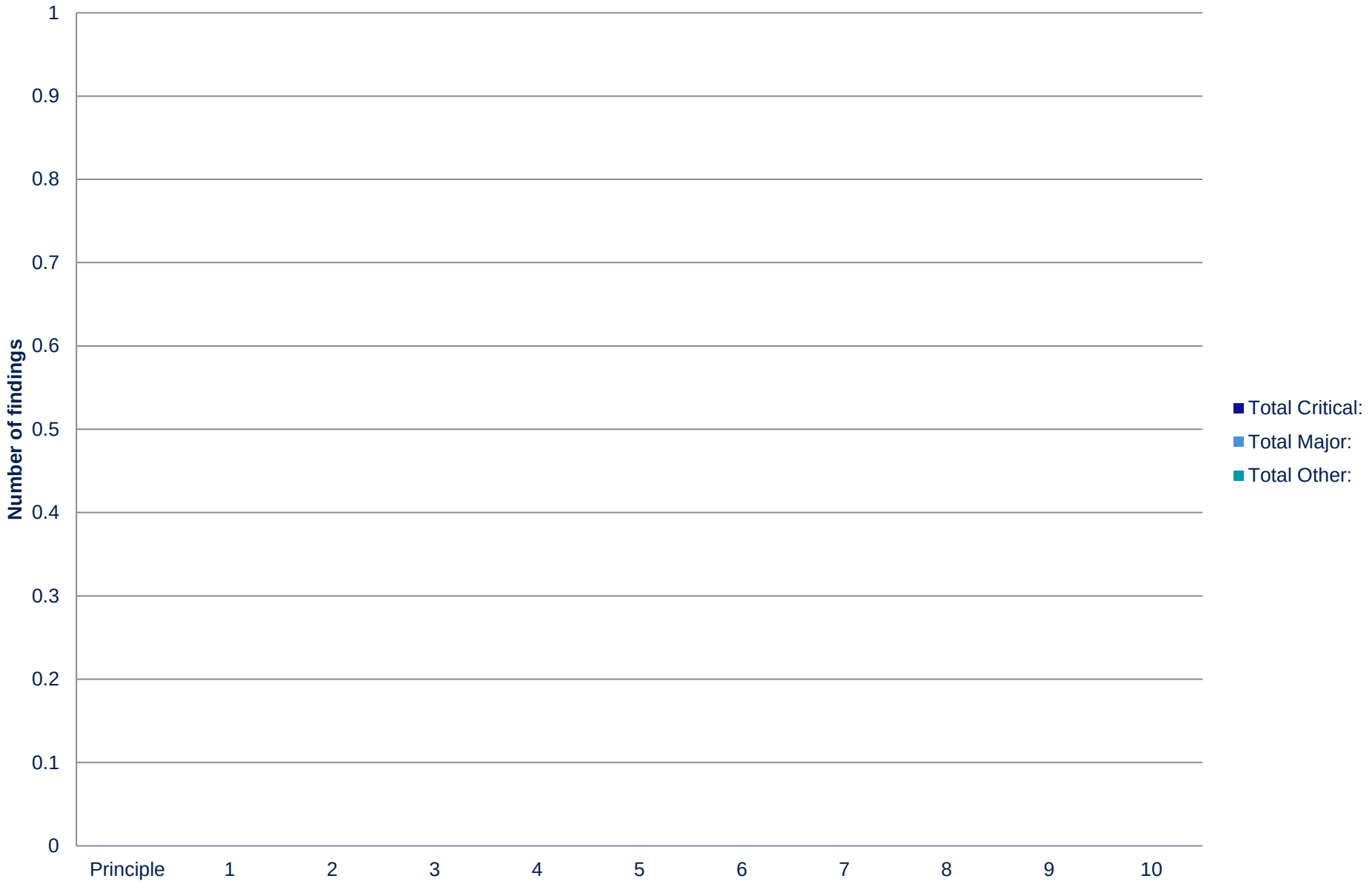
- It was unclear which party was responsible for issuance of the QP Declaration for import for comparator products sourced from non-EU countries.
- A declaration had not been issued for product recently imported and certified for further processing despite this being a requirement within the respective Technical Agreement.

Annex 13 - Deficiency examples

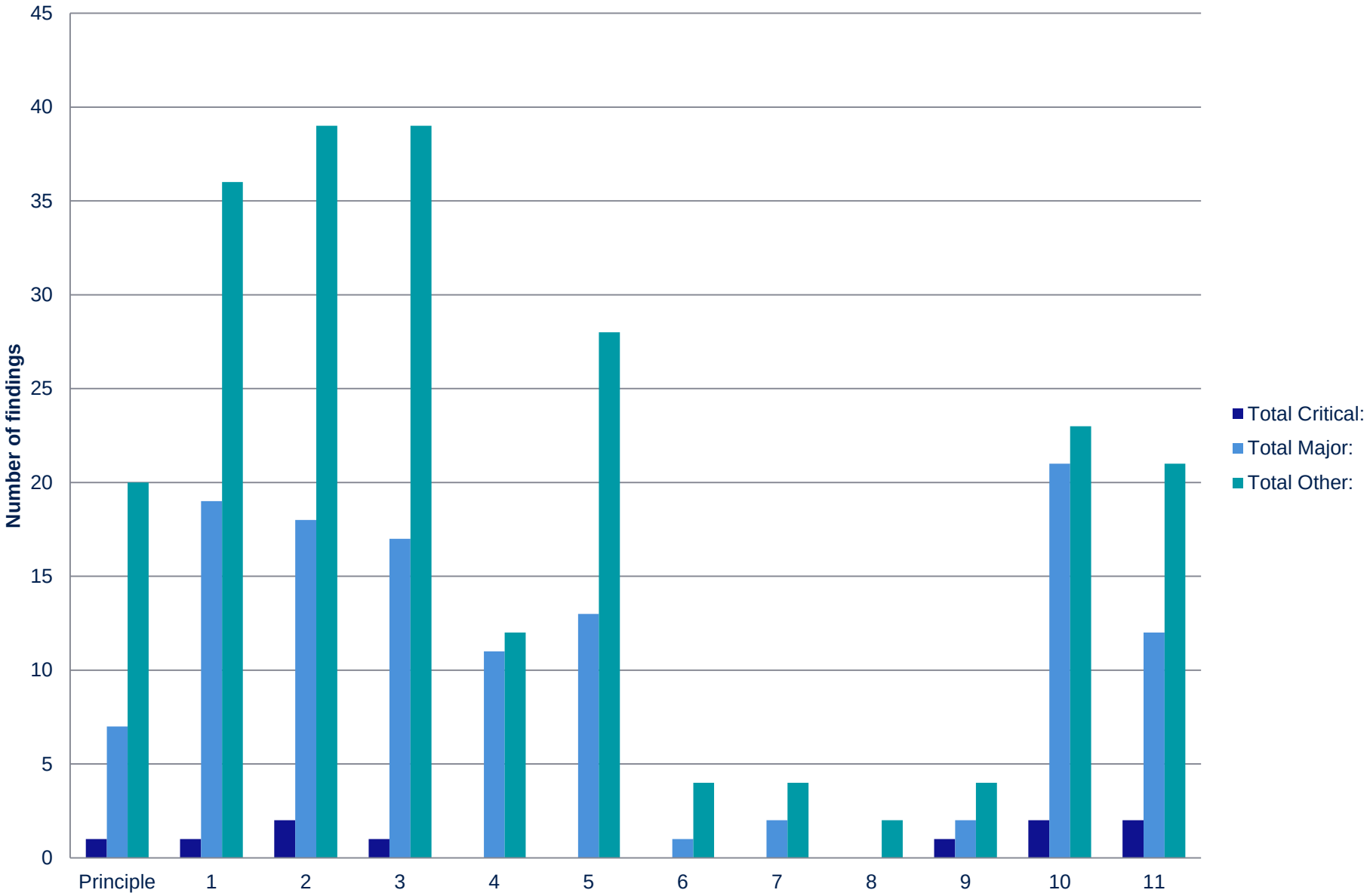
Deficiencies related to the product specification file (PSF):

- The PSF was inadequate as it did not include a summary reference to all documents associated with the clinical trial and current version numbers. The current document ‘manufactured product specification’ which is called the PSF is not appropriate.
- The investigational medicinal product dossier (IMPD) states that plastic vials from Country F should only be used however, vials from another site in Country G are also used.
- The IMPD was not updated following the initial rejection of the Clinical Trial application and subsequent changes to the specification and process.

Findings Annex 14 per Section



Findings Annex 15 per Section



Annex 15 - Deficiency examples

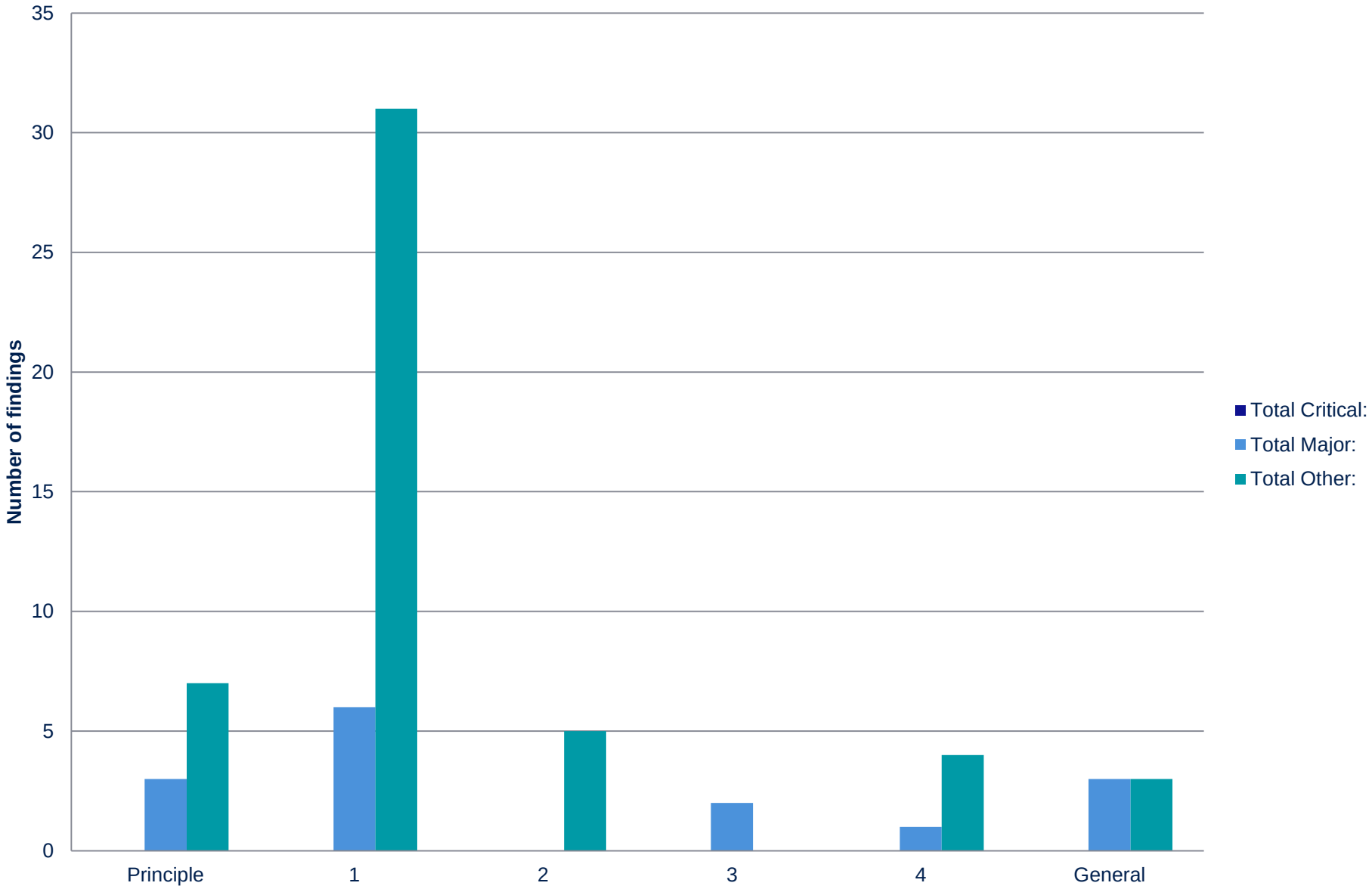
Deficiencies related to qualification and validation:

- There was no change control or overall project plan in relation to the acquisition of the existing site, equipment and materials. There was no user requirement specification (URS) for the A facility, in contrast to the L facility.
- The L facility URS was inaccurate, for example with regard to the number and capacity of manufacturing vessels.
- The re-qualification of the L facility purified water system highlighted two potential action items during the installation and operation qualification reviews. These items were not addressed in the subsequent performance qualification exercise, and were not captured elsewhere in the PQS.

Annex 15 - Deficiency examples

- The Validation Master Plan did not cover all required high level aspects and validation of utilities, process validation and cleaning validation were not considered.
- There was no routine re-validation of manufacturing processes.
- There was no cleaning validation for the non-dedicated sampling tools.
- The method used for isolator leak tests during validation and requalification would not detect leaks.
- Batch processing parameter ranges were not always supported by process validation data, for example the coating flow rate and the granulation chopper speed.
- There is no clear indication in the process validation protocol that validation batches are predefined as potentially releasable for commercial sale.

Findings Annex 16 per Section



Annex 16 - Deficiency examples

Deficiencies related to importation and batch certification of product:

- Procedures permitted samples to be taken in the third country for EU QC testing; there was no requirement for a technical justification for this approach, nor any requirement to take periodic samples of the imported product to verify that samples taken in the third country were representative.
- Arrangements for temperature monitoring of air shipments did not justify why data loggers were not required in every pallet.
- Procedures allowed mean kinetic temperature (MKT) to be used to assess temperature excursions but did not require an investigation to be performed into the cause of the excursion.

Annex 16 - Deficiency examples

- Several products were routinely imported into the EU from the USA and stored at site for onward export to other third countries, however these were not subject to QP certification before being released for this export supply.
- For those batches recognised as imported, there were no provisions implemented for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in third countries.

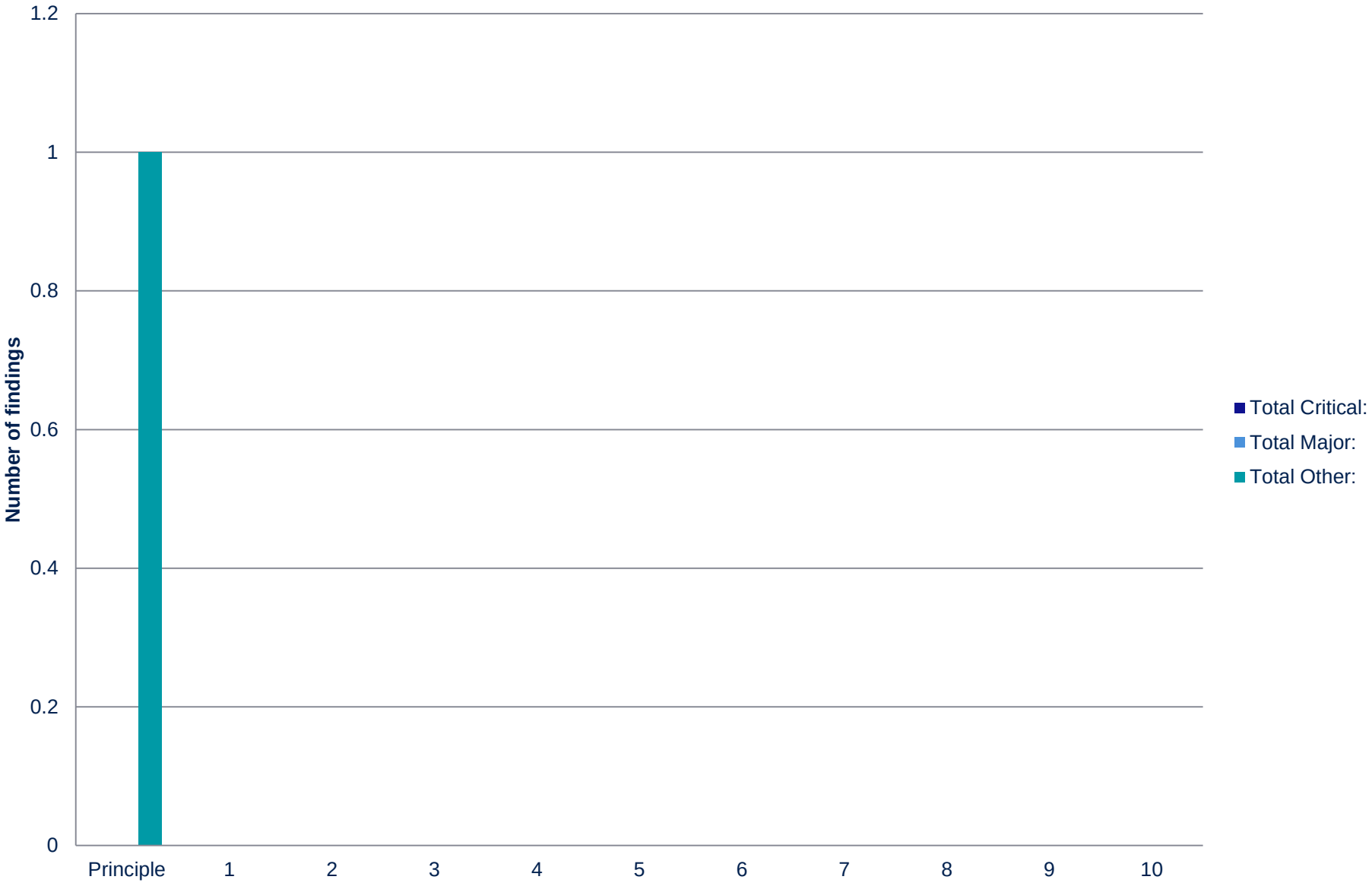
Annex 16 - Deficiency examples

Deficiencies related to failure of QP to fulfill duties:

- The company did not hold any information with regards to the MA for the product which was released under the company MIA.
- The company did not hold any information regarding confirmation of the supply chain.
- There was no detail on the process and management of QP certification.
- The release certification was not documented on company headed paper and did not include all details as per the Mutual recognition Agreement on the content of batch certificate.
- No details of any Certificate of Analysis were held on file.
- The QP did not ensure that he had current knowledge of the company PQS.

Findings Annex 17 per Section

Findings Annex 19 per Section



Annex 19 - Deficiency examples

Deficiency related to procedures and control:

The arrangements associated with retention samples had not been fully defined.