EU Regulatory Update & GMP Deficiencies

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Outline

Update on changes in EU GMP Guide

- Summary of GMP changes to the Guide
- Important details of changes over the last year
- Other EU GMP Regulatory Changes

Deficiencies

- Where does this information come from - references
- Deficiencies associated with the Quality System and Annex 1
- Reminder of why deficiency data may be important for you

Why look at EU GMP Changes ?

- Parts of EU GMP and PIC/S GMP are similar
- What happens today in EU GMP is usually in other GMPs tomorrow
- EU GMP may offer a different way of looking at GMP issues
- Those who are producing for the EU market will need to ensure they are aware of and manufacture to current EU GMP guidelines

Regulatory Update

YEAR	YEAR	YEAR	YEAR
2014	2015	2016	2017
Regulation Prior to this date - **FMD** - various legislation to be implemented over coming years	**Regulation** **Chapter 3 / 5**: dedicated facilities **Chapter 5:** starting material controls **Chapter 8:** clarifies reporting responsibilities **Annex15:** validation	**Regulation** **Annex 16** certification by QP **Annex 17** parametric release **Annex 21** importation control	**Regulation** **Annex 1** sterile products **Annex 17 –**parametric release **Annex 21** importation **Safety Features - FMD** **Dedicated Facilities** **Chapters 3/5** Q & As (comment only)

Safety Features and HBELs

Dedicated Facilities

Q & As on the use of the guideline for setting health based exposure limits (HBEL) for use in risk identification in the manufacture of different medicinal products in shared facilities.

Safety Features

Unique identifier and data repository have to be in place by 9th Feb 2019, some way to go yet.

Annex 1, Annex 17 & Annex 21

Annex 1 – Manufacture of Sterile Medicinal Products

Public consultation in Q3 2017, aim is to incorporate Q & A guidance on WFI from Reverse Osmosis into new Annex

Annex 17 – Parametric Release

Expect revised annex to be published this year once comments reviewed

Annex 21 – Importation of Medicinal Products

Current guidance aimed at conventional manufacture, this guidance will clarify expectations for importers – public consultation in 2017

Other GMP Regulatory Changes

Reflection Paper on MAHs

- Reflection Paper being developed on the relationship between GMP compliance and the responsibilities and activities of MAHs and manufacturers.

MRA with USA on GMP Inspections

- Signed 19th January 2017 (ahead of TTIP) for implementation later in 2017, for products for human use initially with potential to widen in future

ATMPs and Changes to Annex 2 & 13

- EC guidelines on GMP for ATMPs and IMPS (replacing Annex 13) will be available later in 2017. The new Annex 13 will be limited to the responsibilities of manufacturers. The new ATMPs guide will require changes to Annex 2. EC intention is that both guidelines will be stand alone.

MHRA as an example of an EU NCA

Some examples of what MHRA & their Inspectorate do (in addition to inspections!):

- Communicate to all stakeholders
  - Publish Inspection findings
  - Hold regular consultation meetings with industry representatives
  - Hold their own conferences (on a regular basis) and present at others
  - Publish Blogs for guidance

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Blogs – GMP deficiencies 2015 & 2016

MHRA recognizes the importance of appropriate interaction and provision of guidance to Industry as an aid to compliance: A range of blogs from all parts of GxP are published;

The deficiency slides in the rest of this presentation have been provided by MHRA and are reproduced with their permission.

The intent is to allow stakeholders to perform their own assessment against the deficiency findings as part of self-inspection and continuous improvement.

Data trending is incorporated to help 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

GMP Inspections conducted in 2016 (compared to 2015)

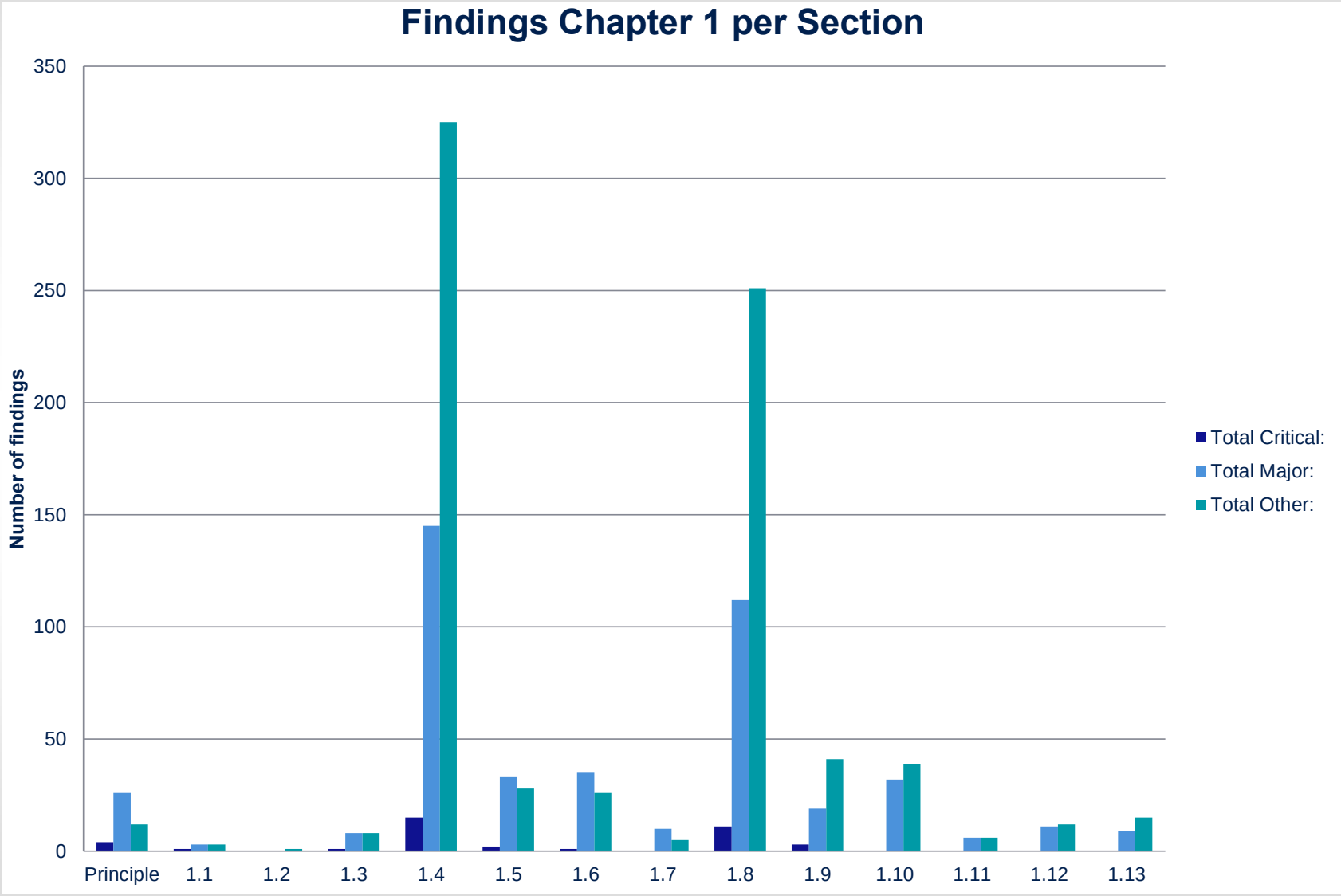
	2016	2015
Total number of inspection	324	303
UK inspections	242	224
Overseas inspections	82	79

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



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.

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.

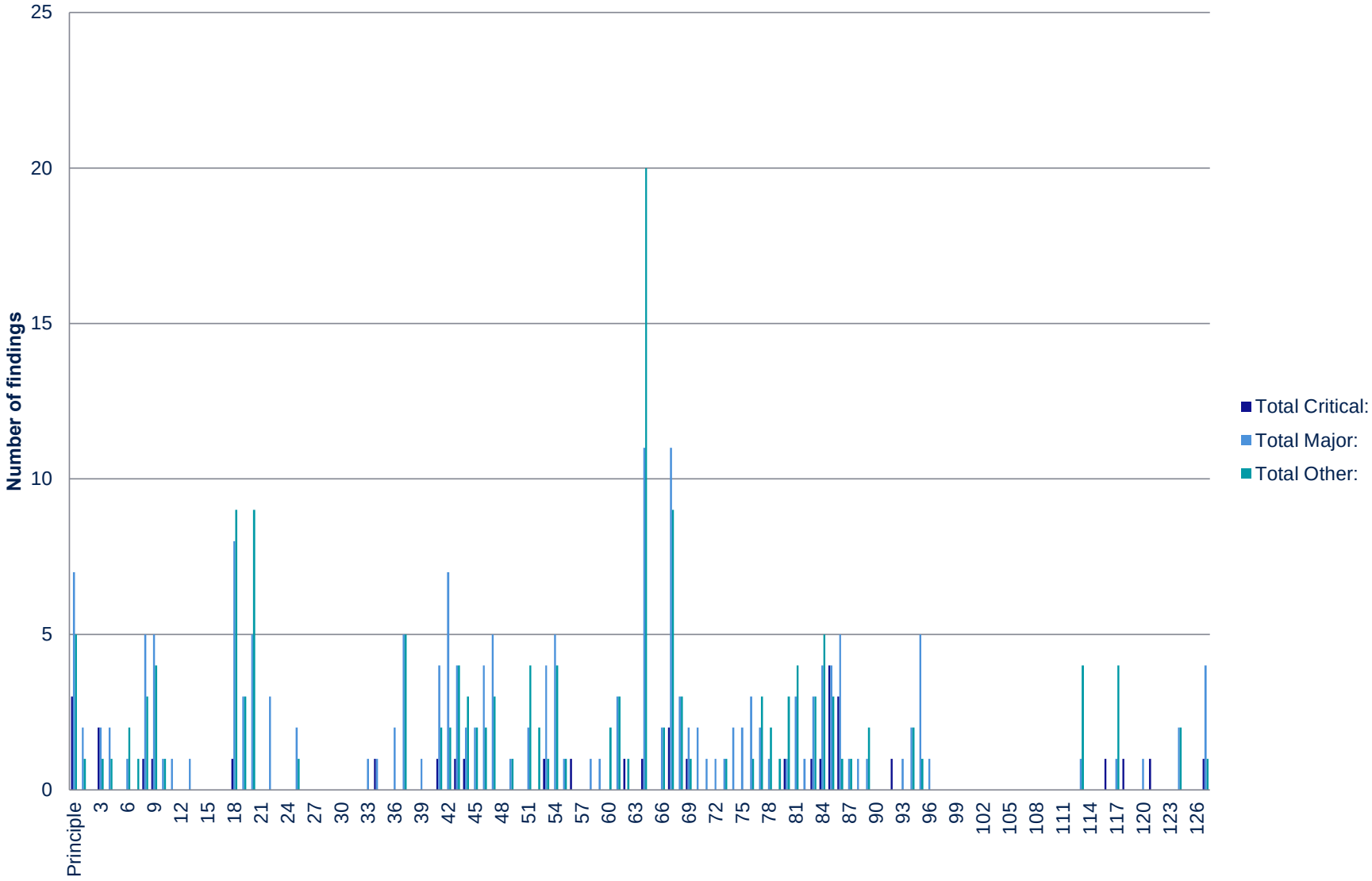
Chapter 9 - Deficiency examples

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.

Conclusions

- Deficiency data bases are important and can be used to help improve your pharmaceutical quality system
- Maintaining a focus on regulatory change is an important aspect of any PQS

Useful links

EU GMP Guide, Changes to Chapters 3 & 5 & Annex 17

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Safety Features & Q & As

https://ec.europa.eu/health/human-use/falsified_medicines_en

https://emvo-medicines.eu

Concept and Reflection Paper for MAHs

www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?...

MRA with USA

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/usa.jsp&mid=WC0b01ac058006e186

MHRA Blog & Deficiencies

https://mhrainspectorate.blog.gov.uk/2017/04/21/2016-gmp-inspection-deficiency-data-trend/

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Thank you for your time. Questions?

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