FDA Inspections – QC Laboratory considerations

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National GMP & Validation Forum

Hosted by PharmOut

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Agenda

- Module 1 – Introduction - FDA Trends in QC Lab Deficiencies
- Module 2 – Case Study: What happened and why?
- Module 3 – Remediation strategy
- Module 4 – Moving forward
- Module 5 – Next regulatory inspection

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Introduction - FDA Trends in QC Lab Deficiencies

Where do we look for the answers?

https://www.pharmout.net/services/gmp-consultants/fda-483-inspections-citations-drugs/

https://www.fda.gov/ICECI/Inspections/ucm222557.htm

http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPNonCompliance.do

https://www.tga.gov.au/presentation-data-metrics-and-current-inspection-trends

Book: Validation of Chromatography Data Systems, 2nd Ed., R.D. McDowall

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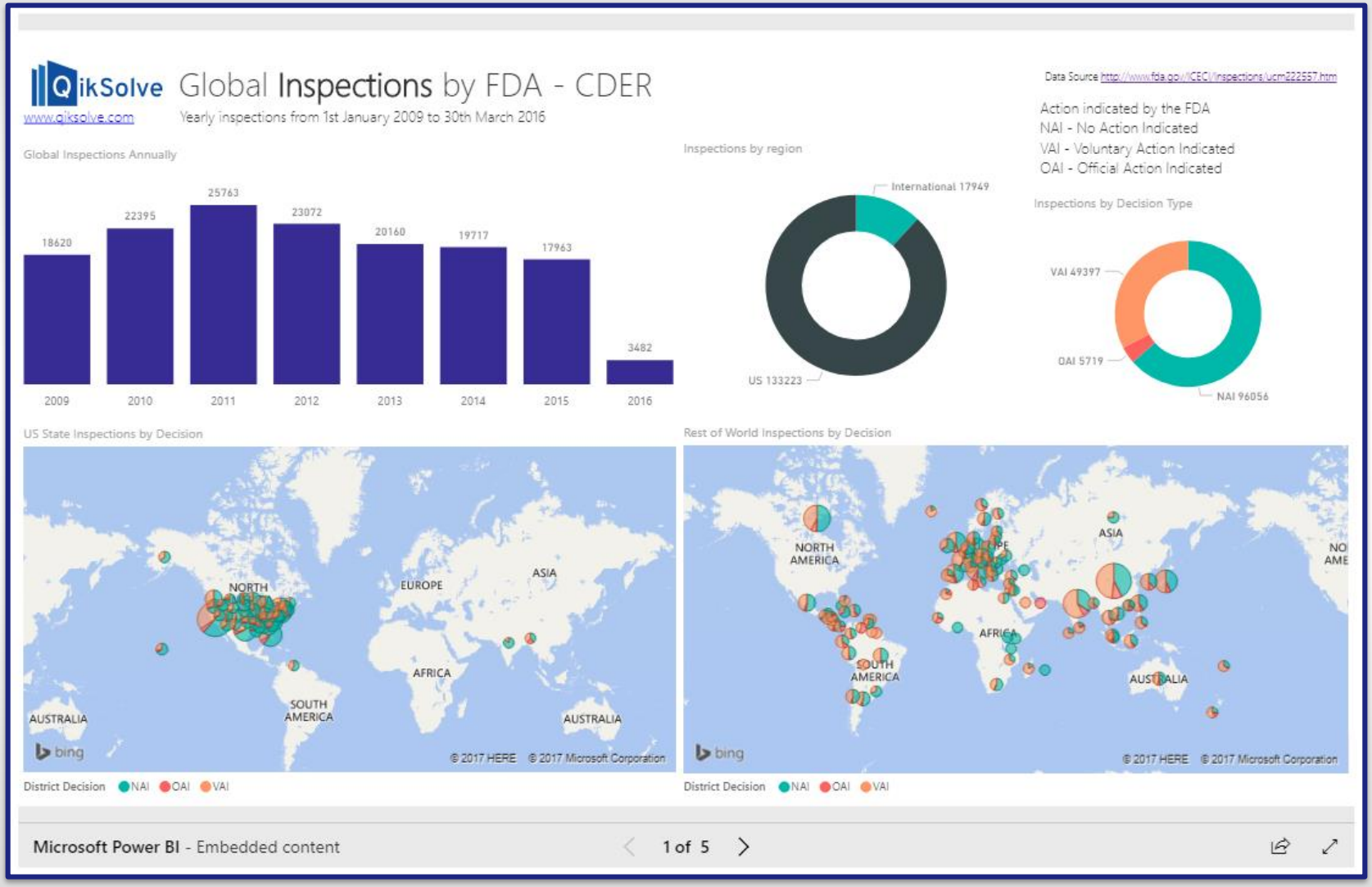
Introduction - FDA Trends in QC Lab Deficiencies



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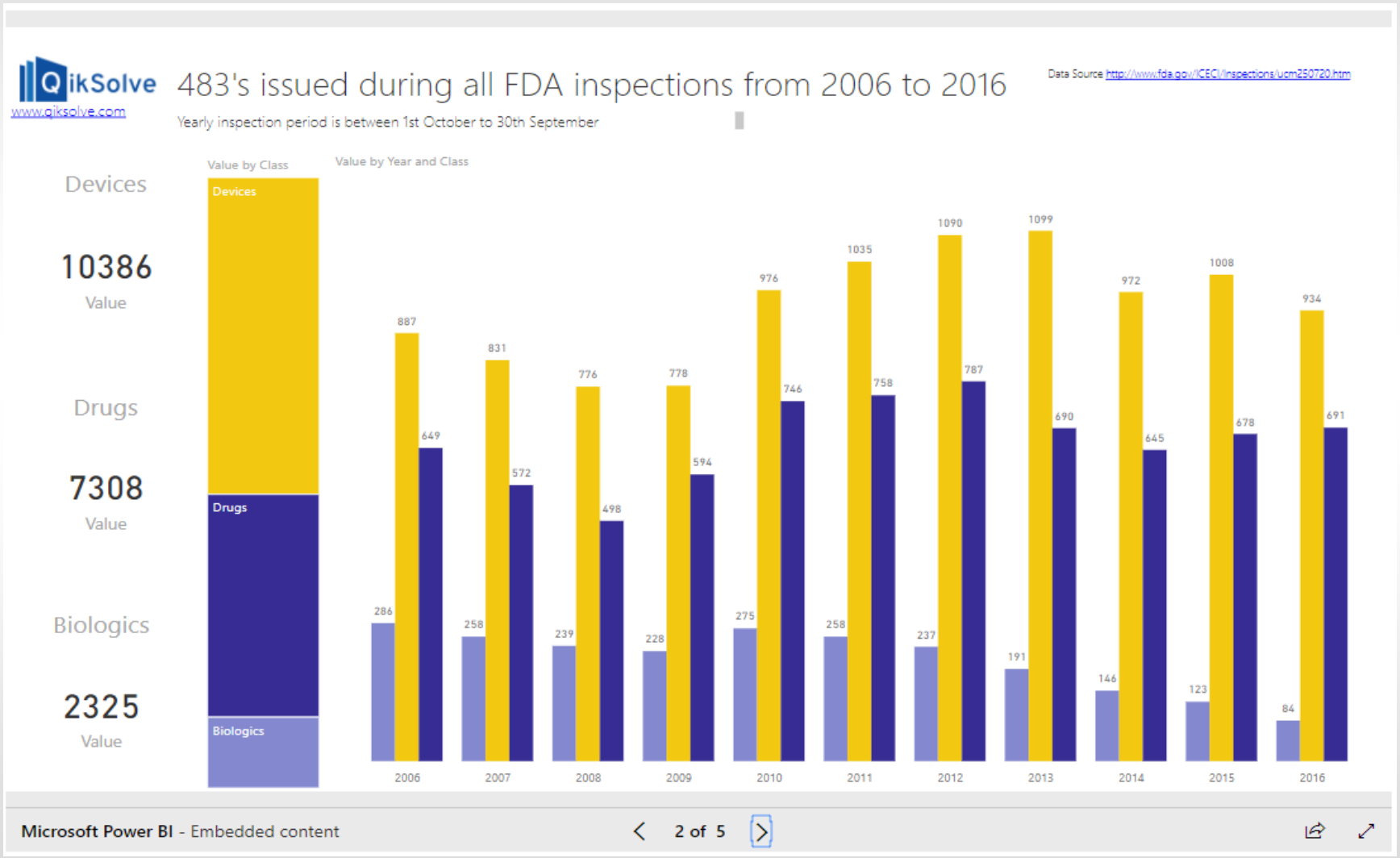

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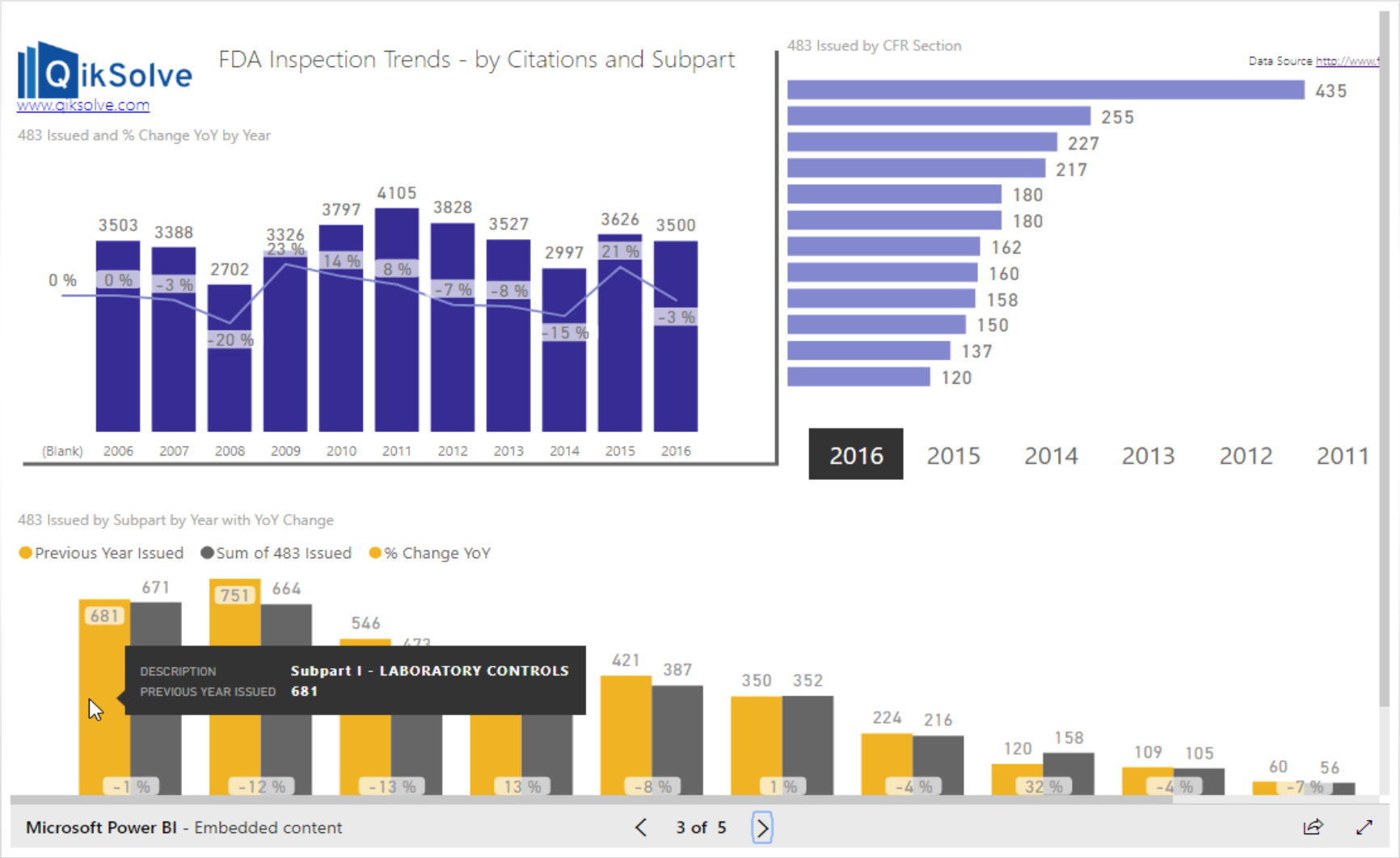

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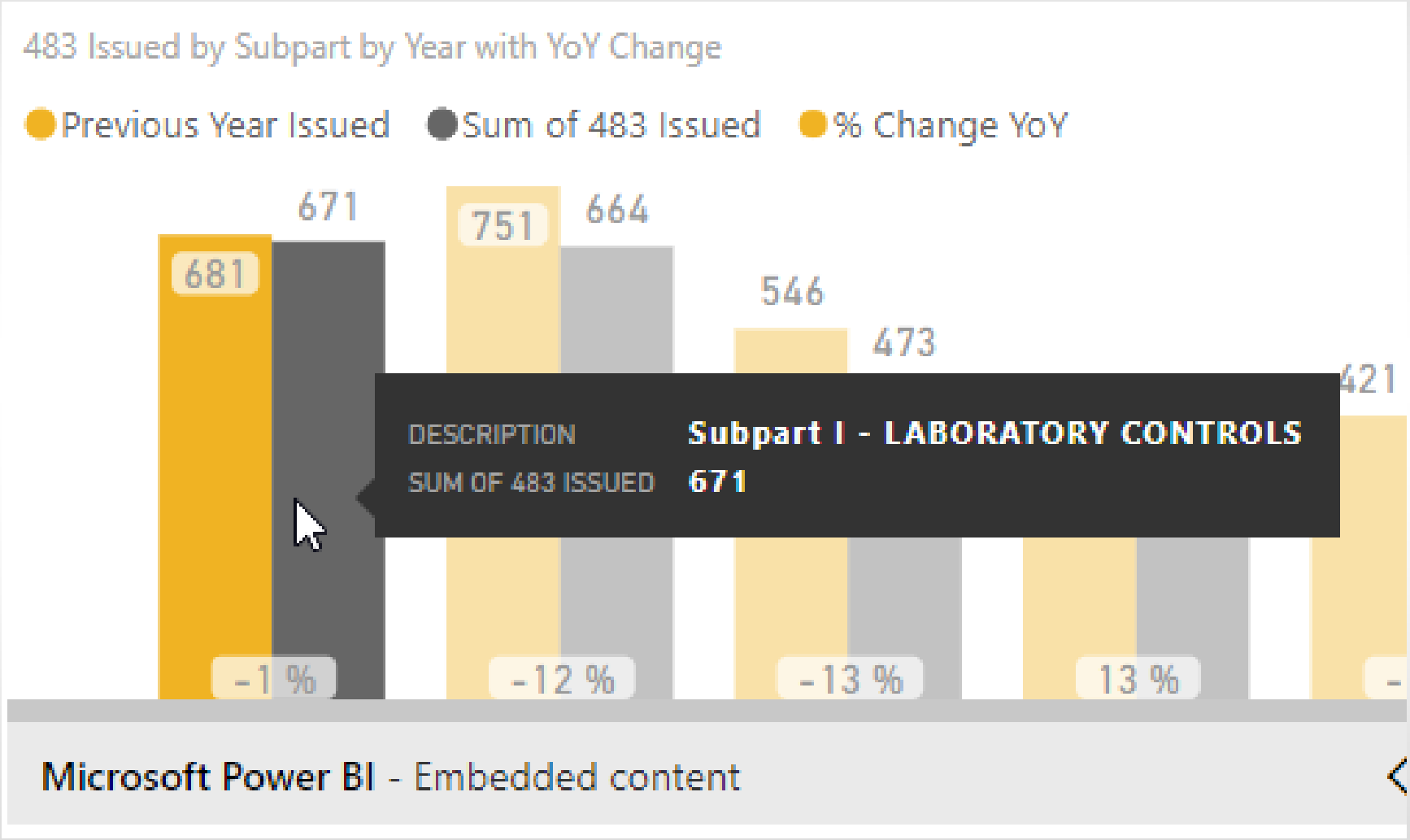

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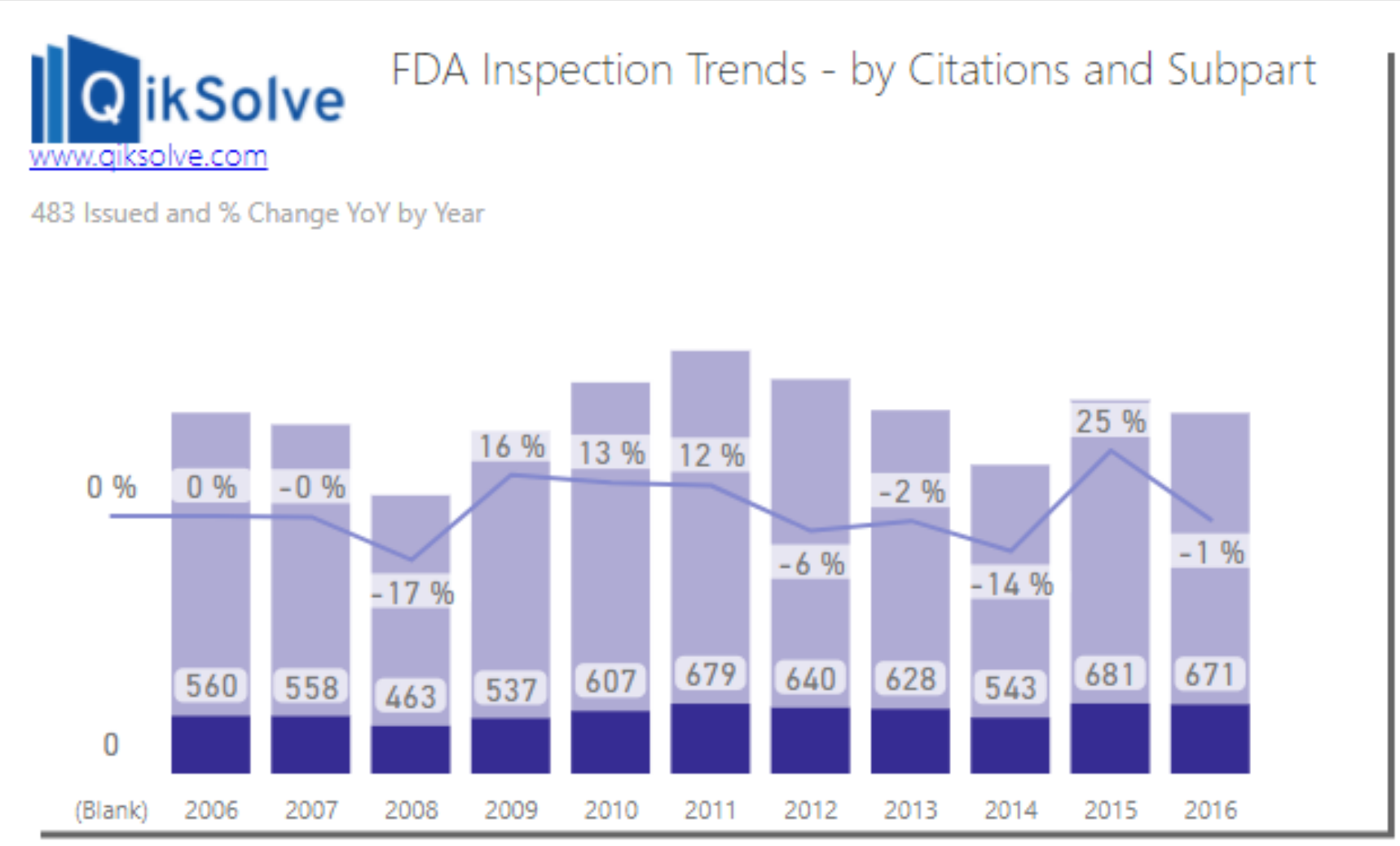

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Introduction - FDA Trends in QC Lab Deficiencies

What does the data tell us?

- Ongoing and continued focus
- Repeated issues

What have we learnt?

- How to move forward
  - Through innovation and collaboration
  - Best practice
  - Developing regulatory guidelines

- However it's hard to look back, or is it?

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Case Study: What happened and why?

1. Accuracy, sensitivity, specificity and reproducibility of test methods has **not been established and documented**.
2. **Appropriate controls are not exercised over computers or related systems** to assure that changes in master production and control records or other records are instituted only by authorised persons.
3. Verification of the suitability of testing methods is deficient in that they are **not performed under actual conditions of use**.
4. **Laboratory controls do not include** a determination of conformance to written descriptions of sampling procedures for drug products.
5. The calibration of instruments, apparatus, gauges and recording devices is **not done at suitable intervals**.

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Case Study: What happened and why?

Observation 1 – 21 CFR 211.165 (e)

- Subpart I – Laboratory Controls

Observation 2 – 21 CFR 211.68 (b)

- Subpart D – Equipment

Observation 3 – 21 CFR 211.194 (a)(2)

- Subpart J – Records and Reports

Observation 4 – 21 CFR 211.160 (b)(3)

- Subpart I – Laboratory Controls

Observation 5 – 21 CFR 211.160 (b)(4)

- Subpart I – Laboratory Controls

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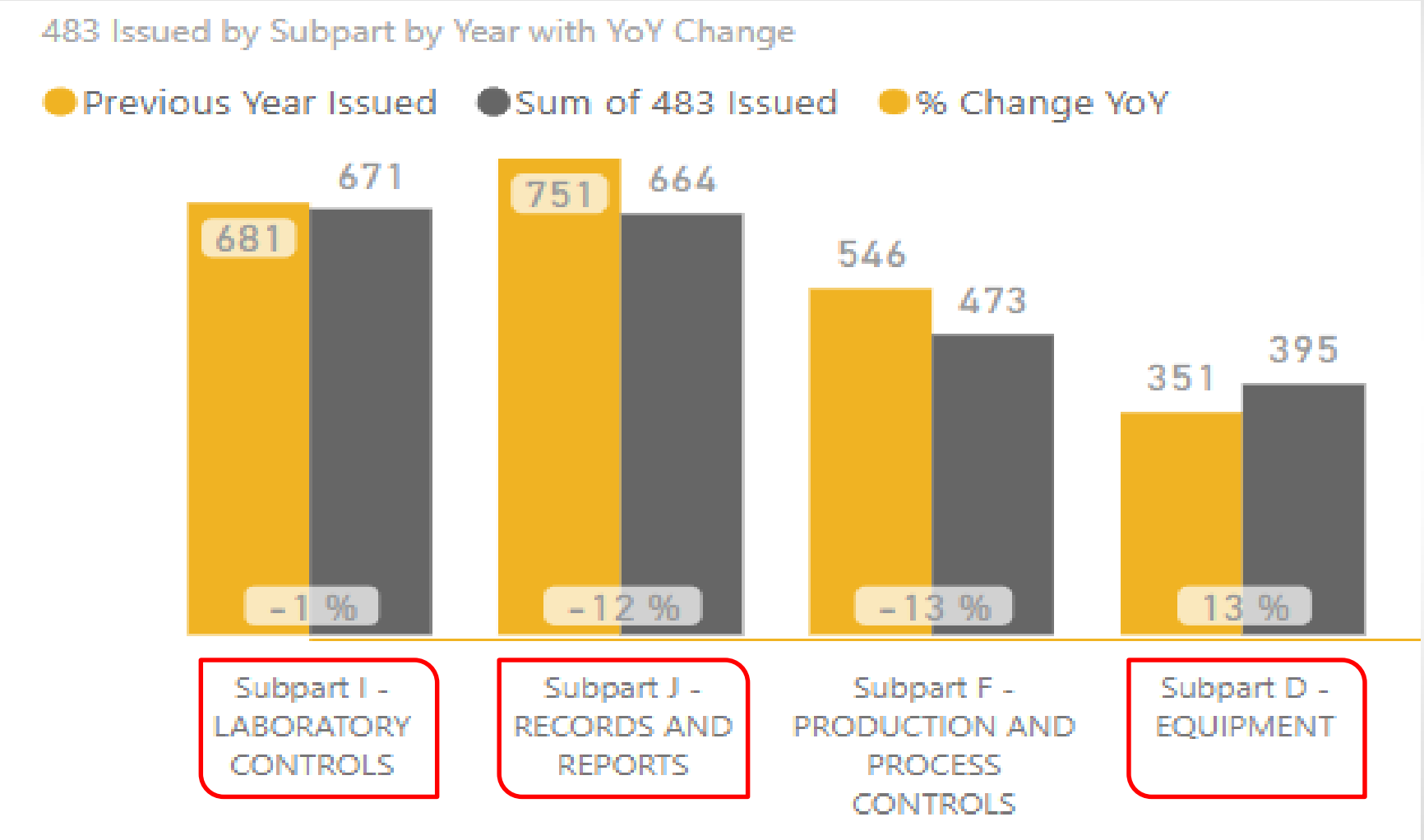
Case Study: What happened and why?



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Case Study: What happened and why?

Observation 1 – 21 CFR 211.165 (e)

- "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2)."

Observation 2 – 21 CFR 211.68 (b)

- Subpart D – Equipment

Observation 3 – 21 CFR 211.194 (a)(2)

- "A statement of each method used in the testing of the sample."…" The suitability of all testing methods used shall be verified under actual conditions of use."

Observation 4 – 21 CFR 211.160 (b)(3)

- "Determination of conformance to written descriptions…"

Observation 5 – 21 CFR 211.160 (b)(4)

- "The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program…"

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Case Study: What happened and why?

2. Subpart D – Equipment - 21 CFR 211.68 (b) – Automatic, mechanical and electronic equipment

- Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

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Case Study: What happened and why?

2. Subpart D – Equipment - 21 CFR 211.68 (b) – Automatic, mechanical and electronic equipment

- "Appropriate controls shall be exercised over computer or related systems… by authorized personnel.",
- "…verification shall be based on the complexity and reliability of the computer or related system.",
- "A backup file of data entered into the computer or related system shall be maintained except where certain data, … are eliminated by computerization or other automated processes."

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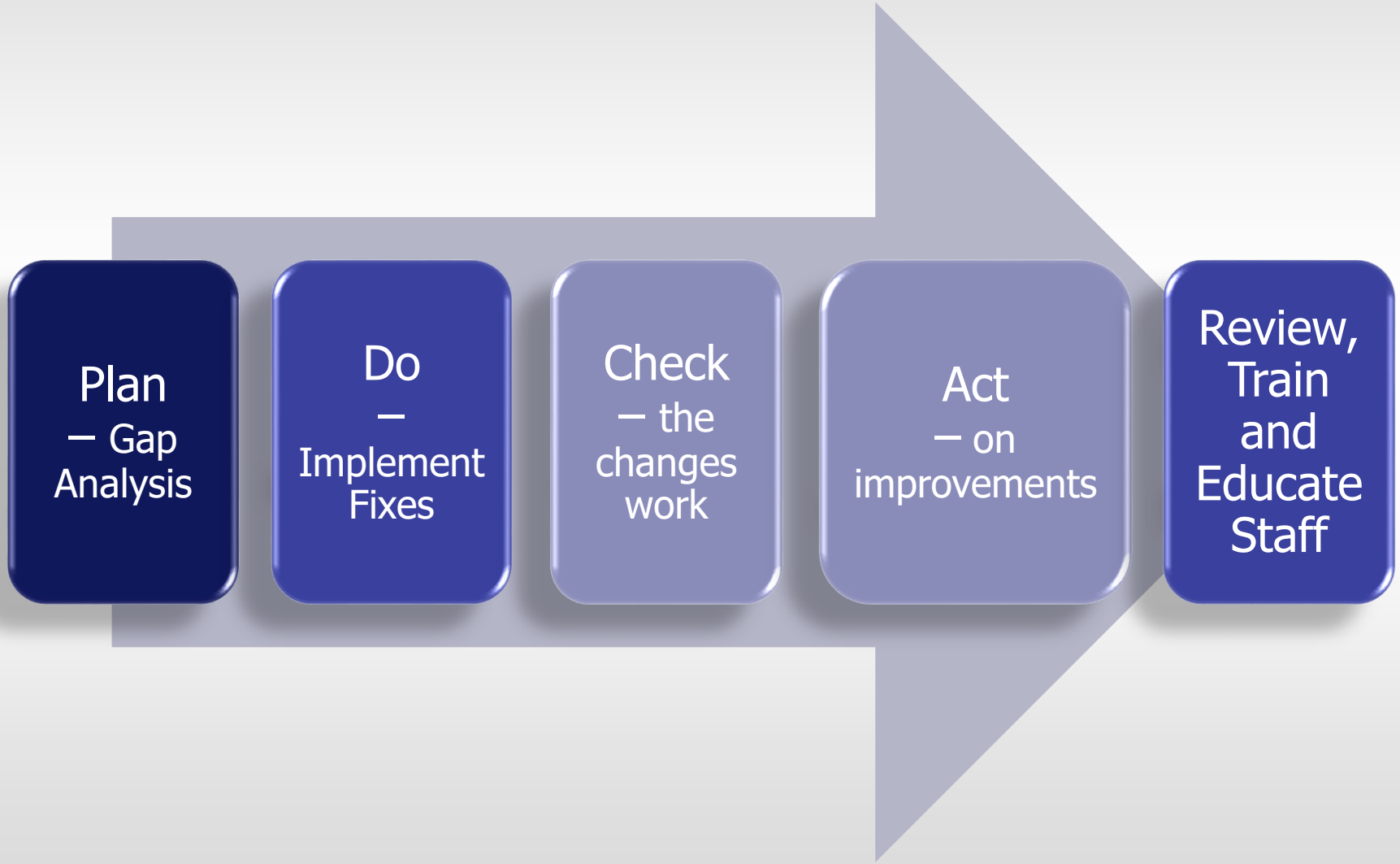
Remediation strategy



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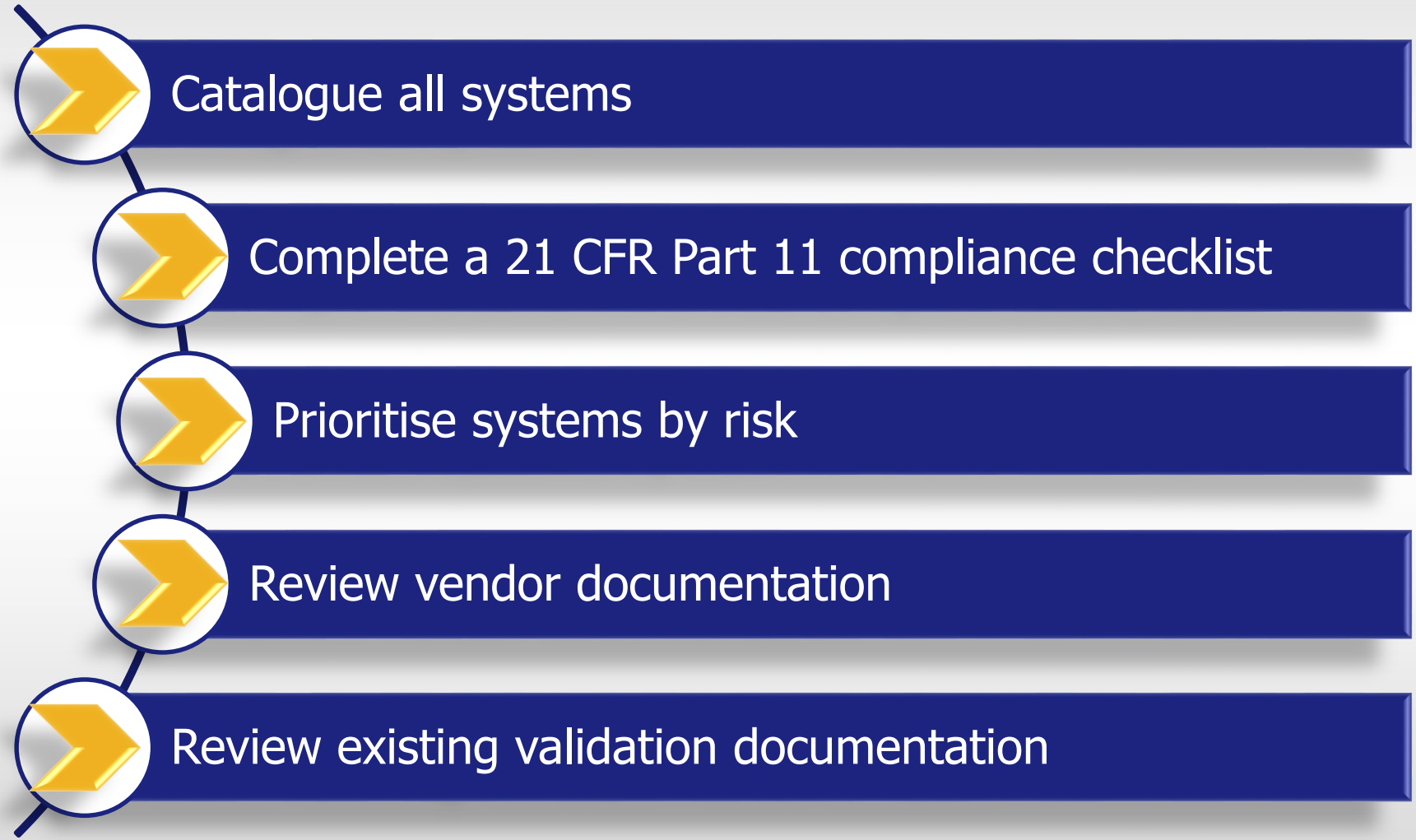
Plan – Gap Analysis



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Plan – Gap Analysis

No.	Requirement
1	Is this system used for product distributed to the United States? (§ 11.1)
2	Are these records specifically required under and cGxP / QSR regulation? (§ 11.1 – 11.70)
3	Do these records show or relate to product safety, product quality or effectiveness? (§ 11.1 – 11.70)
4	Is the system used to automate laboratory or clinical regulated (cGLP/cGCP/QSR) processes? (§ 11.1 – 11.70)
5	Does the system generate, use, transmit and/or store electronic records? (§ 11.1 – 11.70)
6	Is the system used to generate records, reports or results requiring a signature? (§ 11.70)
7	Does the system require the use of electronic signatures? (§ 11.100, 11.200)
8	Are system functions or processes controlled using passwords or codes? (§ 11.300)
9	Have you answered "Don't know" to ANY of Questions 2 - 8?

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Do – Implement Fixes

- Implement access groups and password policies
- Update software versions and patches
- **Confirm the network connectivity**
- Implement back-up schedules
- Lock analytical methods
- Review audit trail active status and scope

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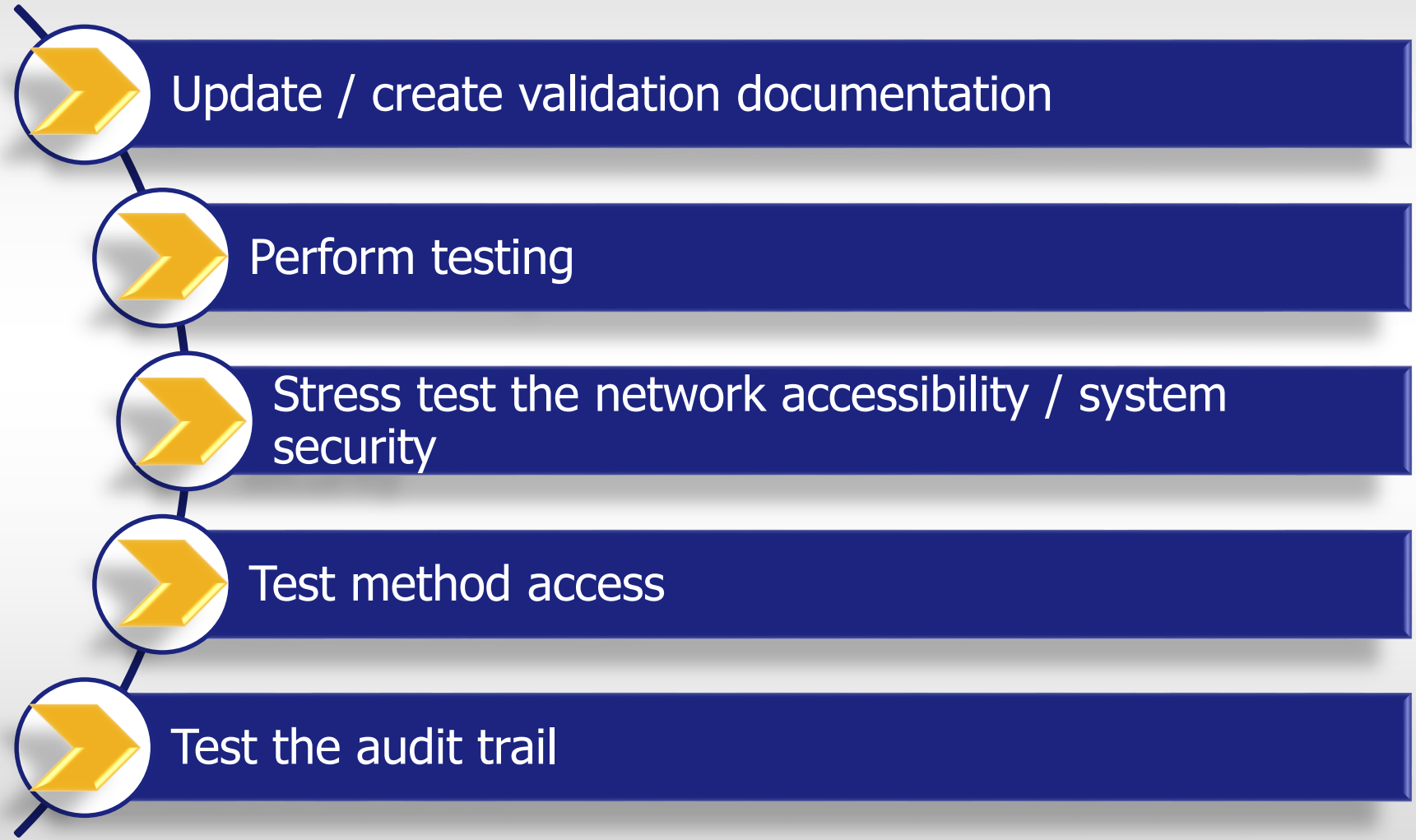
Check – the changes work



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Act – on improvements

Update servers

Increase server capacity

Update SOPs with additional controls (if necessary)

Ensure independent IT support (internal / external)

Implement a periodic review of systems

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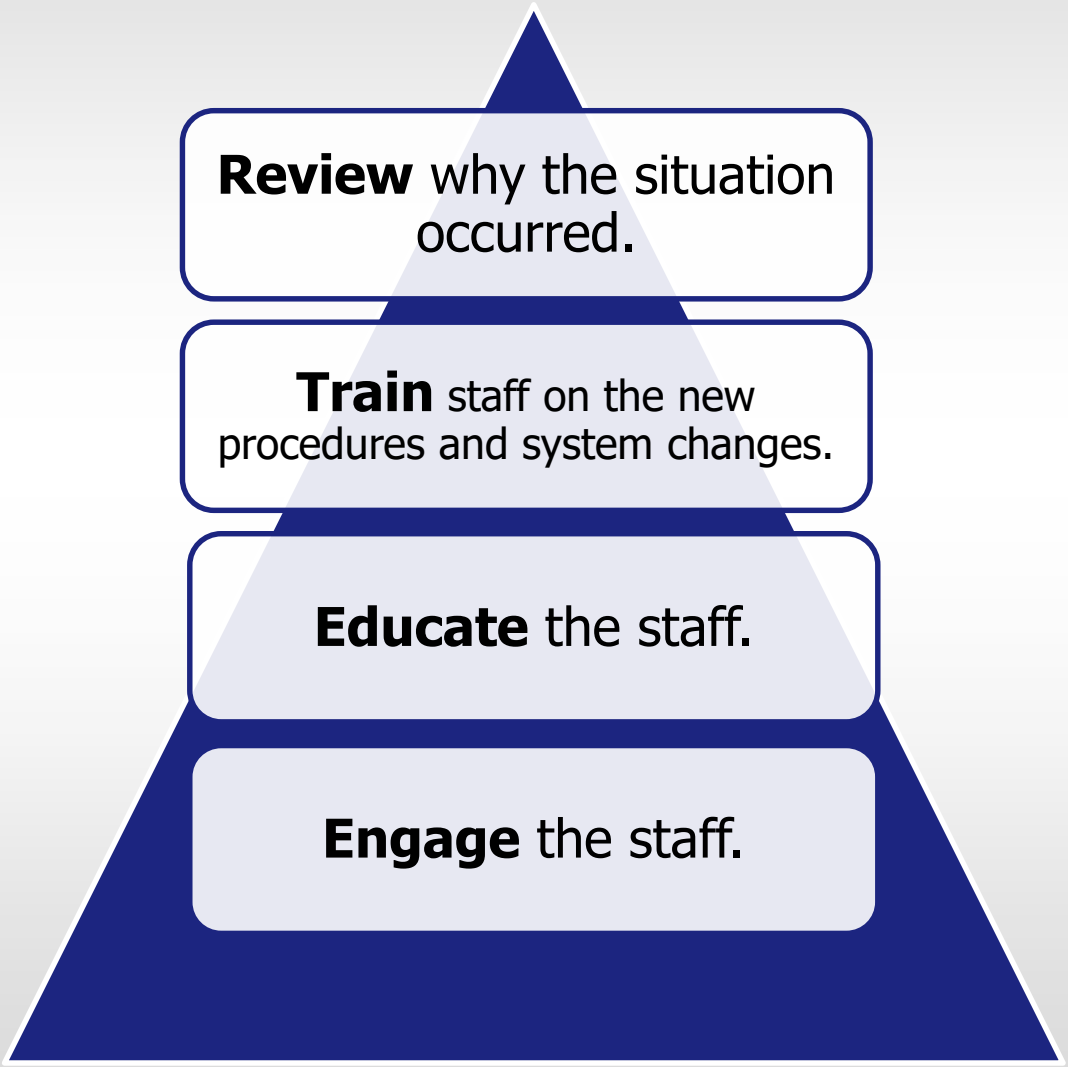
Moving forward…



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Next regulatory inspection

- Manage expectations of the next regulatory inspection through systematic application of…
  - 21 CFR Part 11, 211
  - FDA Guidelines on Validation
  - PIC/S PE009 Annex 11, 15, 20
  - GAMP 5
  - ISPE

- Demonstrate control over your systems
- Show awareness of system inadequacies
- Document risk mitigation strategies

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Recap?

- Take affirmative action
- Identify what you don't know
- Document strategies & mitigations
- Manage the expectations

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PharmOut
Regulatory Knowledge, Practically Applied.

Thank you for your attention.

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Consultant

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