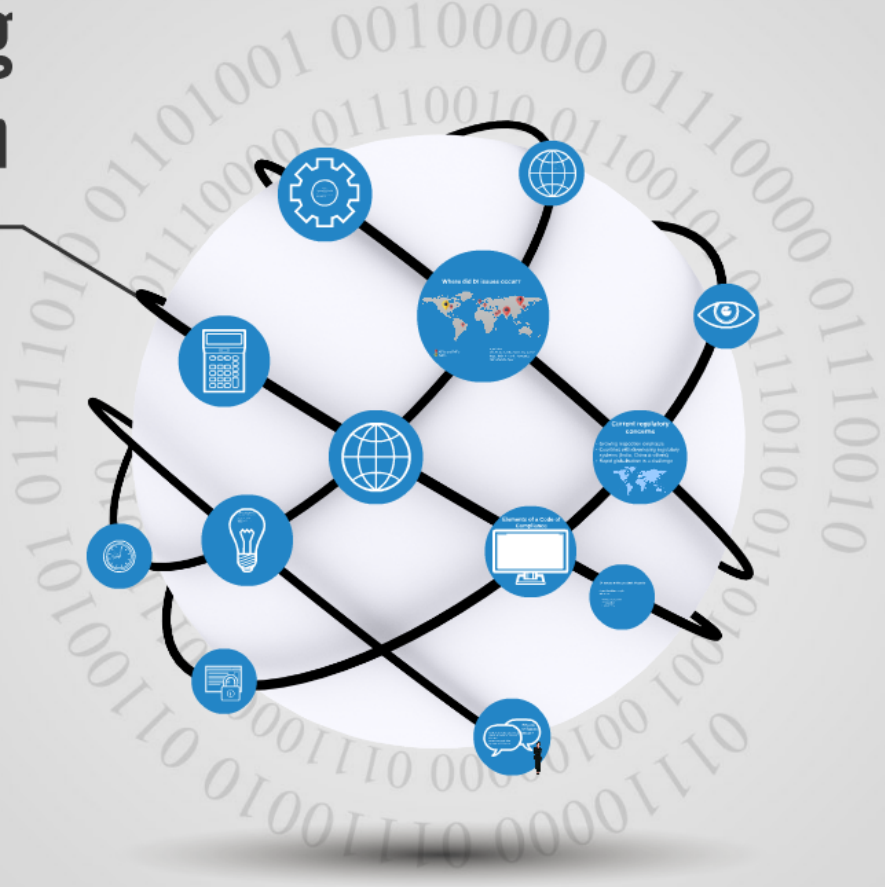
DI-A Study of Thinking and Regulatory Action



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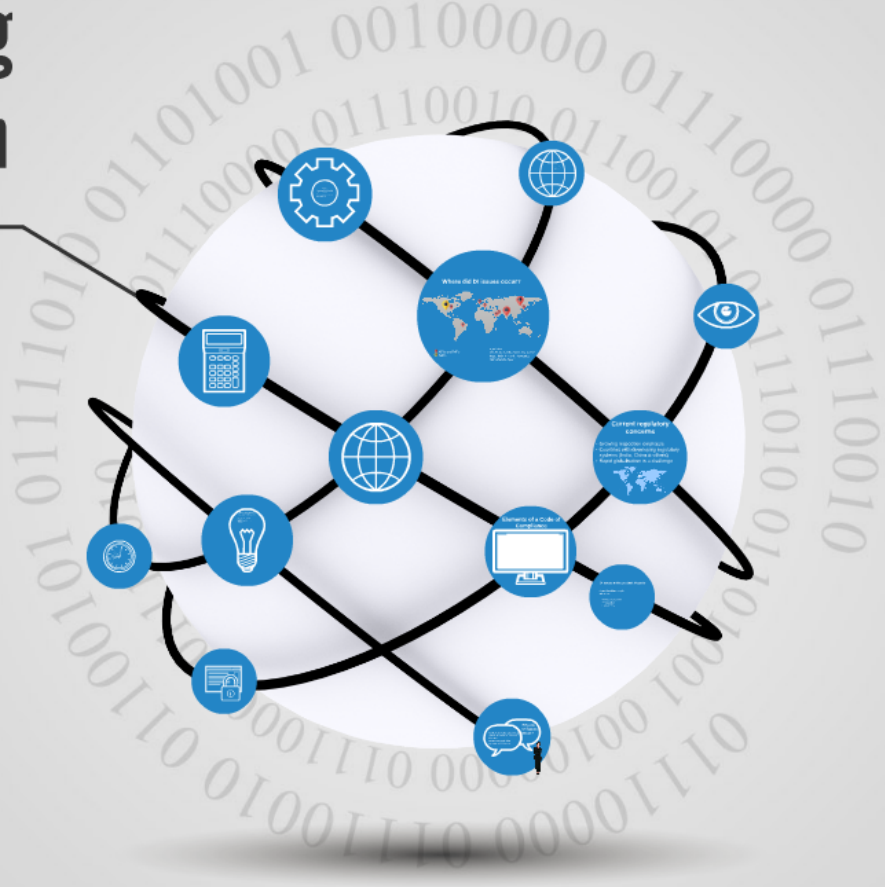
DI-A Study of Thinking and Regulatory Action



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Agenda:

- PDA Case Study titled: "**Data Integrity - A Study of Current Regulatory Thinking & Action**", *PDA J Pharm Sci and Tech 2015 69 762-770*

  Also:

- PDA Points to Consider: "**Elements of a Code of Conduct for Data Integrity**"

What is Data Integrity?

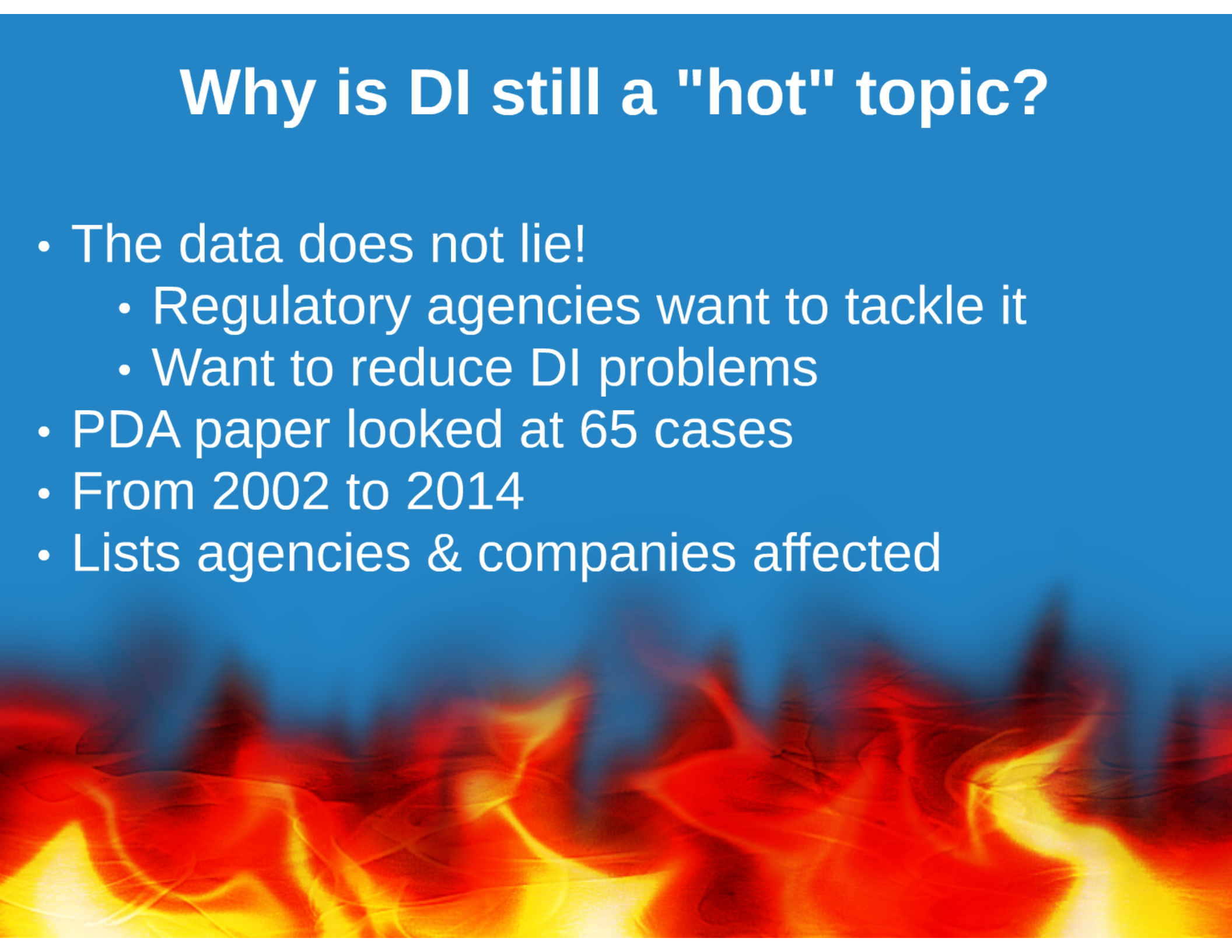
"*Data Integrity is the degree to which a collection of* ***GxP data*** *is* ***managed*** *through* ***effective organisational***, ***human*** *and* ***technical mechanisms*** *to ensure GxP* ***data reliability***"

Why is DI important?

- Agencies need to protect public health
- Need to be confident in manufacturers
- Medicines must be fit for use
- They heavily rely on data to do this
- Gaps in data...less/no confidence

Why is DI still a "hot" topic?

- The data does not lie!
  - Regulatory agencies want to tackle it
  - Want to reduce DI problems
- PDA paper looked at 65 cases
- From 2002 to 2014
- Lists agencies & companies affected



Reason for the PDA paper

- Authors looked at available data to understand:
  - The regulatory thinking
  - Actions on breaches of DI
- It covered:
  - Non-clinical
  - Clinical
  - Manufacturing
  - Laboratory
- Paper and e-records

The human aspects

- The paper also discusses the human aspects as potential sources of DI problems
- These problems are the most difficult to fix
  - Motive
  - Opportunity
  - Means
- Paper has recommendations to avoid/fix these
- PDA "code of conduct"

DI issues in the product lifecycle

Paper identifies 3 high risk areas:

- Clinical research
- Production
- Laboratory

Data from clinical trial is the fundamental basis for the product

Data from production assures compliance with the marketing authorisation

Data from the laboratory is critical to assure product quality

Why do DI issues occur?

- No internal checks & balances
- Lack of expertise to discover DI issues
- No verification of data
- Systems not fit for use

How to deal with DI issues?

- When DI issues are found, revising an SOP and re-training is not enough.
- The MHRA will look for a review of the effectiveness of governance systems, including outsourced activities.

The integrity of data is therefore influenced by:

- Organisational factors
- Technical factors
- Human/operational factors

Organisational Factors

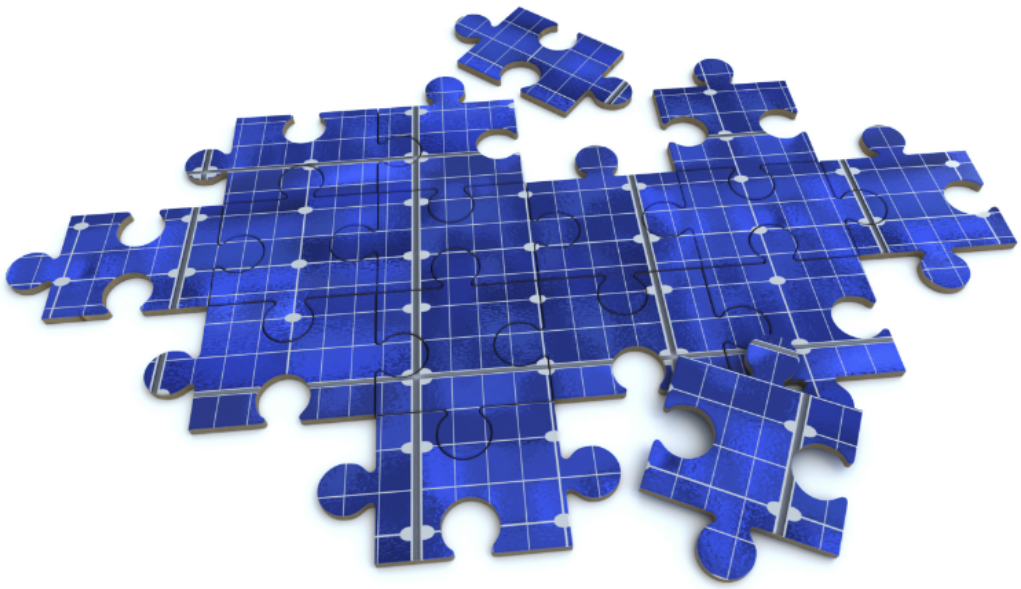
- Oversight by Management
- Training/Education
    - DI & Ethics
- Self-inspection/auditing
- Good Documentation Practices
- Quality Risk Management
- Computerised Systems

Human Factors

- Motive, Opportunity, Means
- Enforcing procedures and methods
- Removing distractions
- Less manual activities
- Tools/aides to prevent data handling errors

Technical Controls

- The design of systems
- Fit for intended use
- Data creation
- Data authentication
- Protection of data
- Retaining data



Where did DI issues occur?

APIs and MPs
IMPs

Agencies:
US, France, UK, Germany, Czech Rep., Italy, Finland, Romania, Netherlands, Spain

Root Causes of DI problems

- Computer systems not secure
- Inadequate procedures
- Driven by goals/metrics
- Supply/demand
- Poor training/GDP
- Resource issues
- No management/supervision

Some examples of DI Problems:

- Fabricating data
- Discarding data
- Recording wrong data
- Back/forward dating
- Unreliable data

Some examples of DI Problems:

- Copying data
- Not saving data
- Data manipulation
- Unjustified repeats
- Approval without review

Current regulatory concerns

- Growing inspection emphasis
- Countries with developing regulatory systems (India, China & others)
- Rapid globalisation is a challenge

The US

- The US obtains the following from overseas:
  - 40% of drug products
  - Over 50% of medical devices
  - 80% of APIs
- Released Draft Guidance on **DI & Compliance with GDMP**
- Cooperation with CFDA
- Workshops in India
- US FDA involvement with industry:
  - PDA
  - ISPE

Europe

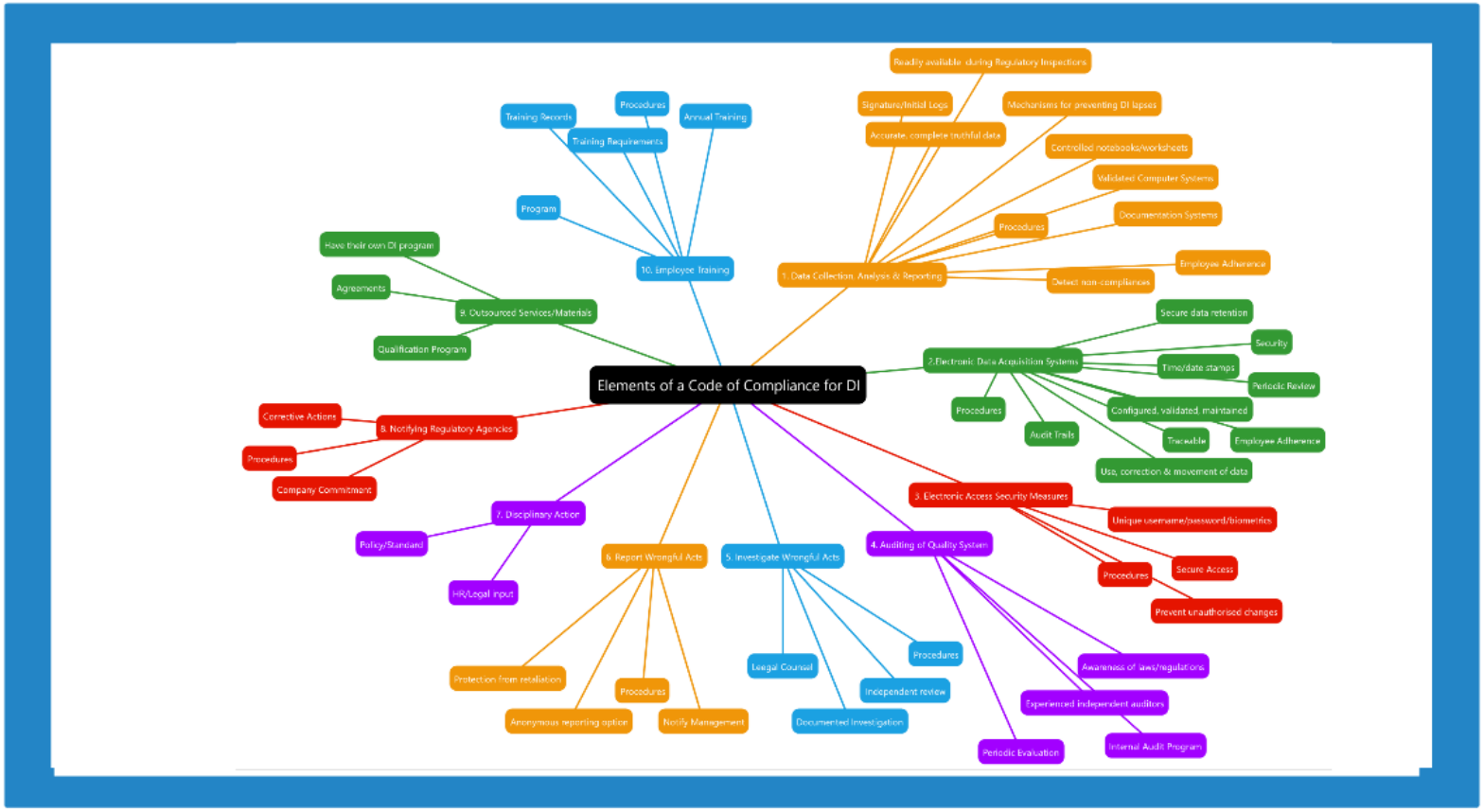
- Growing concerns for the increasing amount of APIs sourced outside the EU
- Substandard materials entering the supply chain
- EU GMP Annex 11 in 2011
- MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015
- Increase in foreign oversight
- PIC/S seminar in Manchester

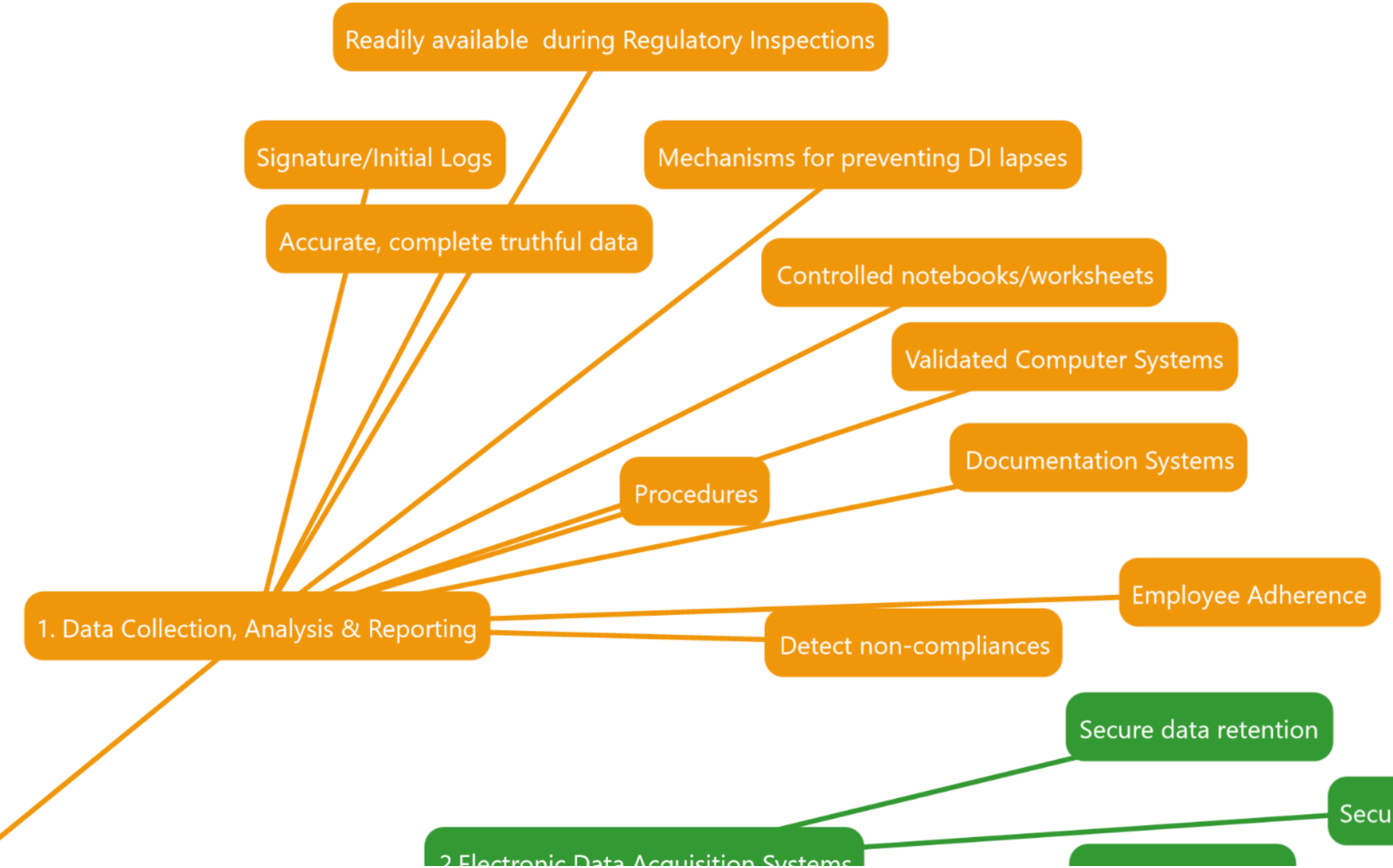
PDA release "Elements of a Code of Conduct for Data Integrity in the Pharmaceutical Industry"

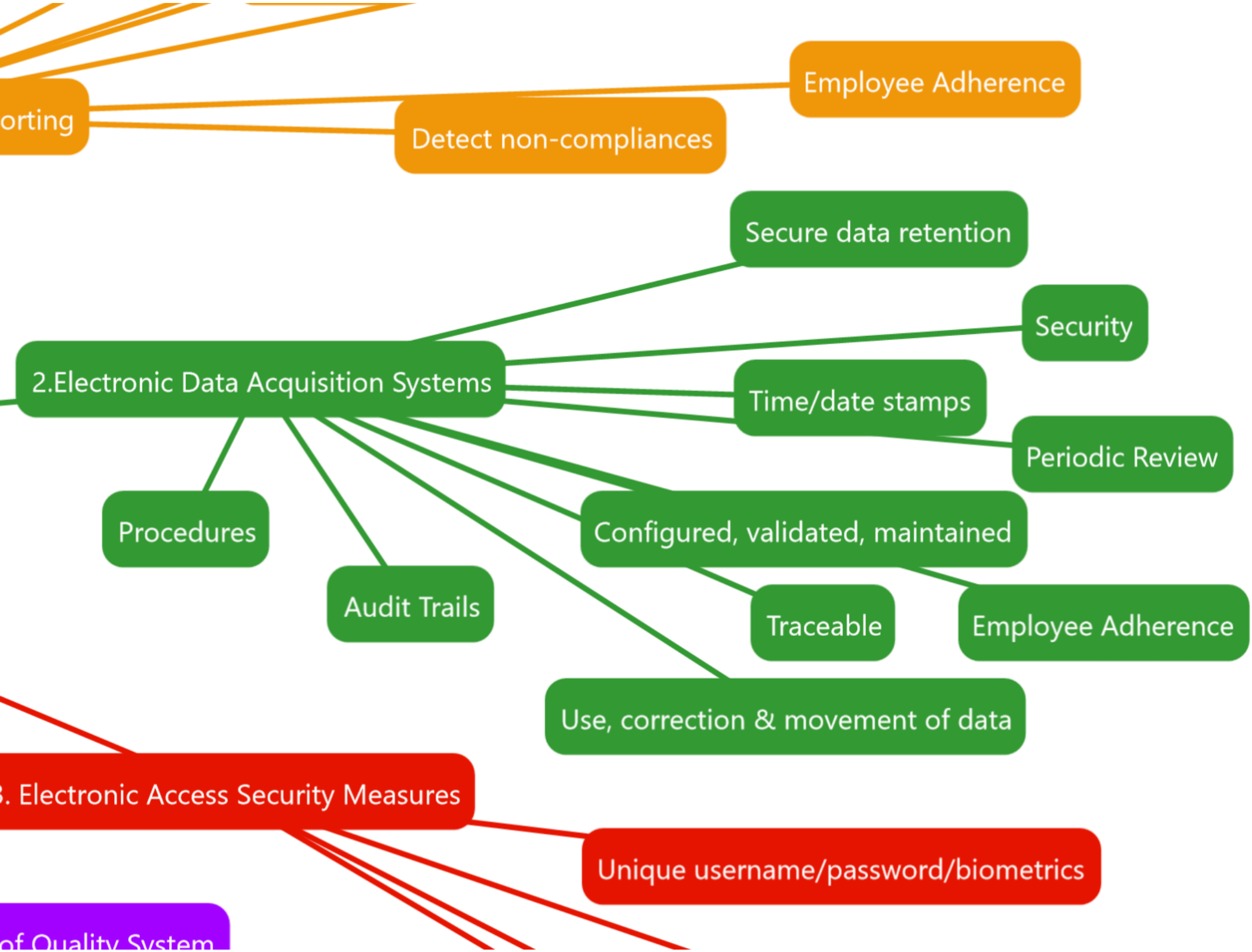
- Elements should be **in the PQS** already
- Code could highlight & reinforce aspects of "**quality and trust**" for data
- Emphasizes the importance of **truth**, **trust in compliance** and **ethics**
- Has the following statement:

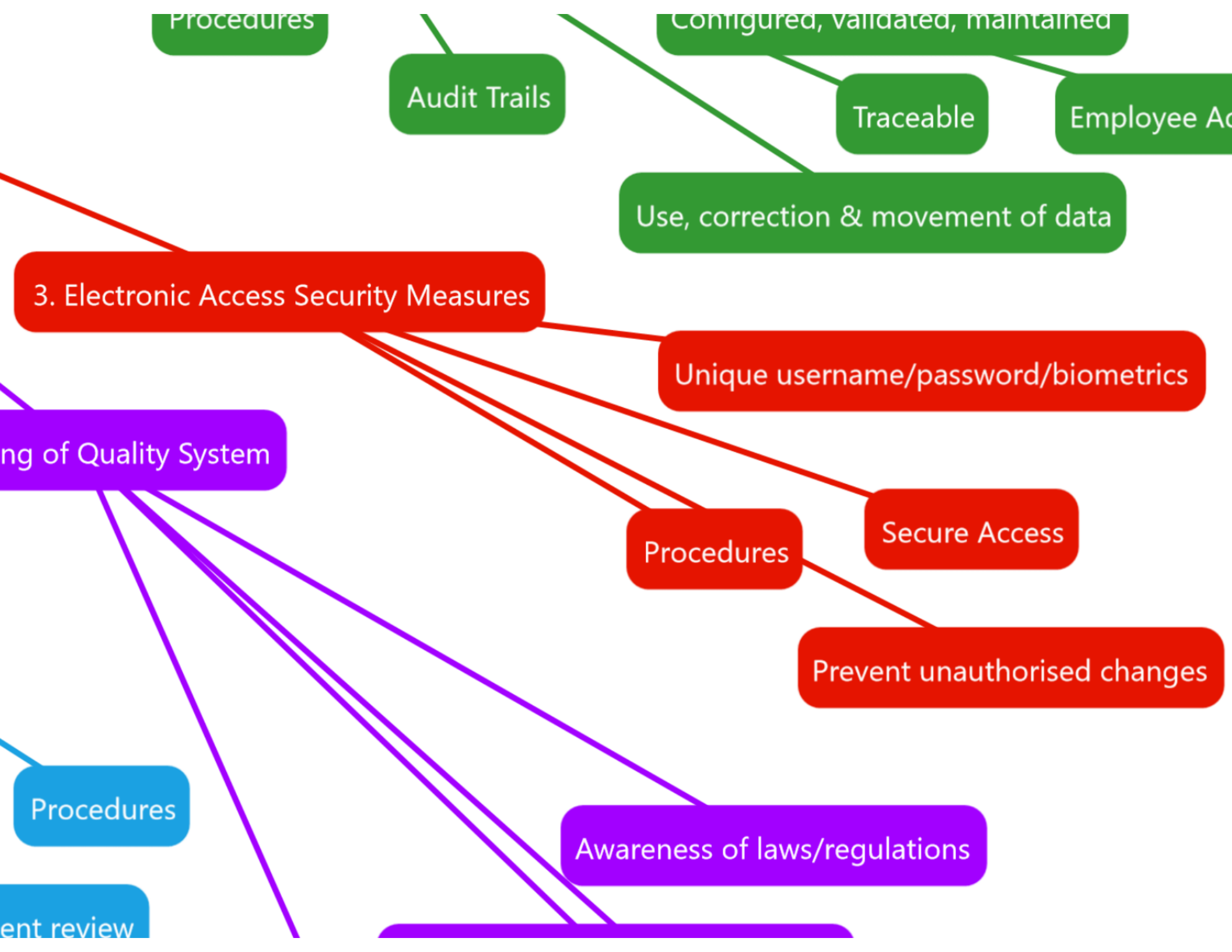
"Every employee has a duty to engage in conduct to ensure that all stakeholders can trust employee decisions that are based on data and information that are accurate, truthful and complete"

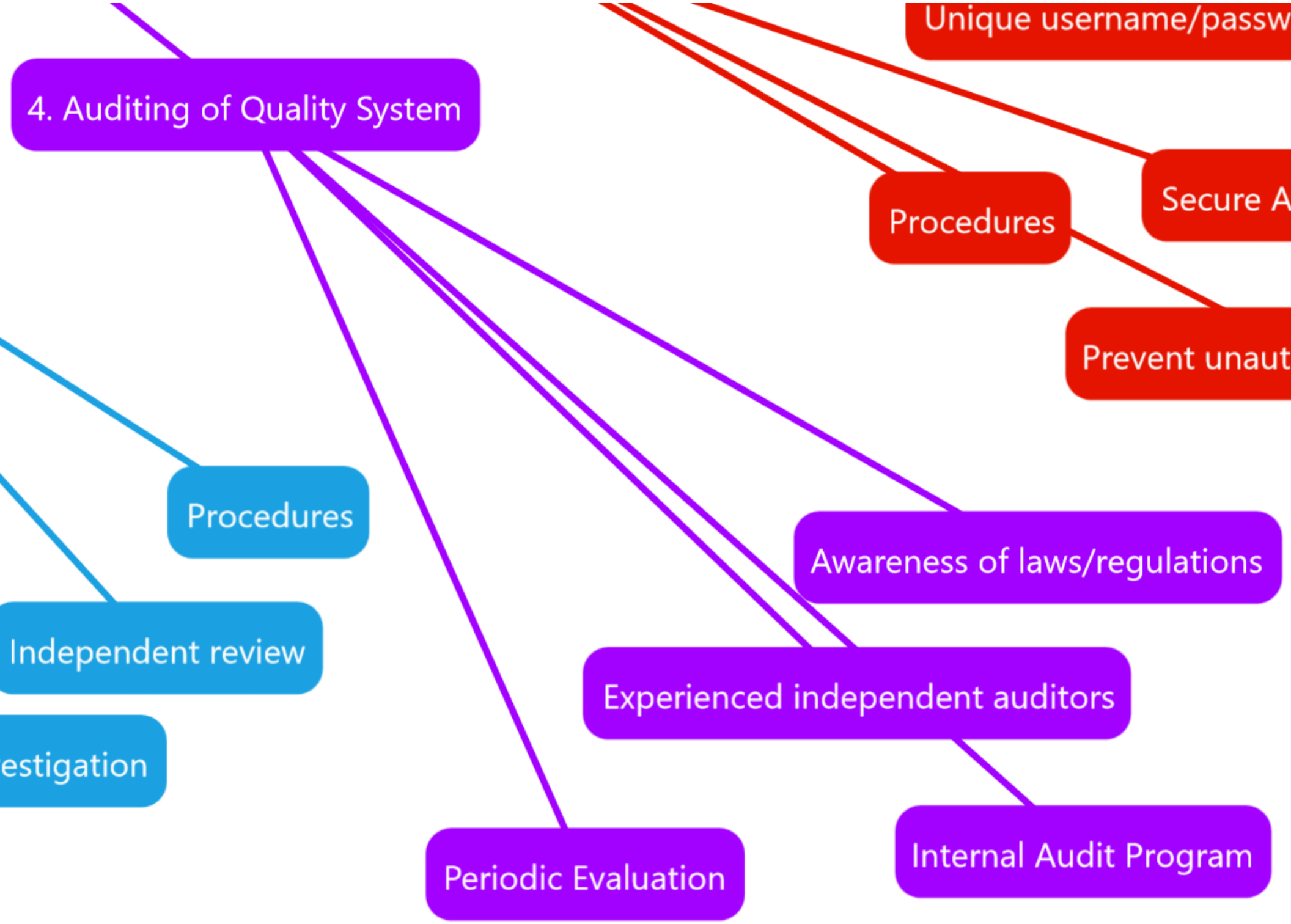
Elements of a Code of Compliance

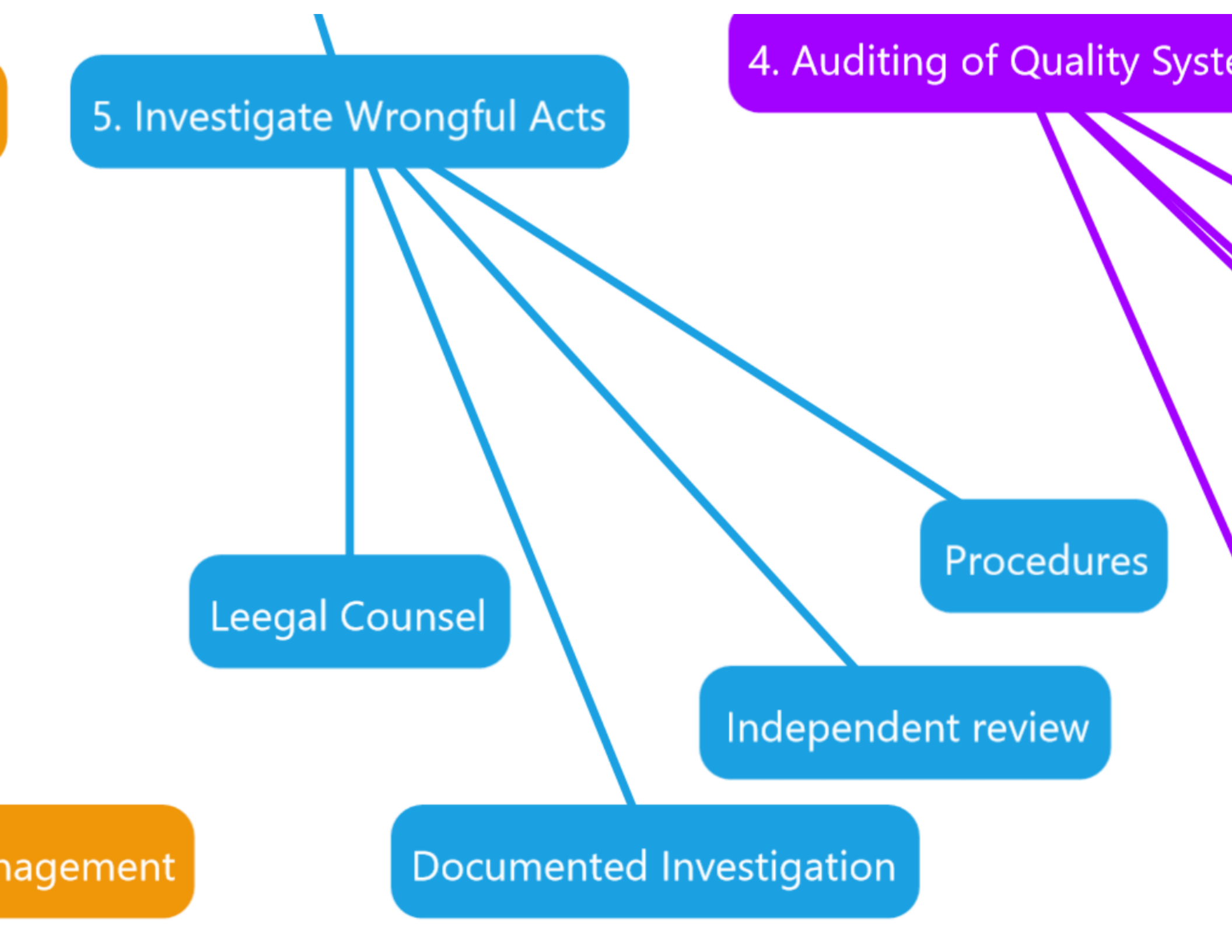


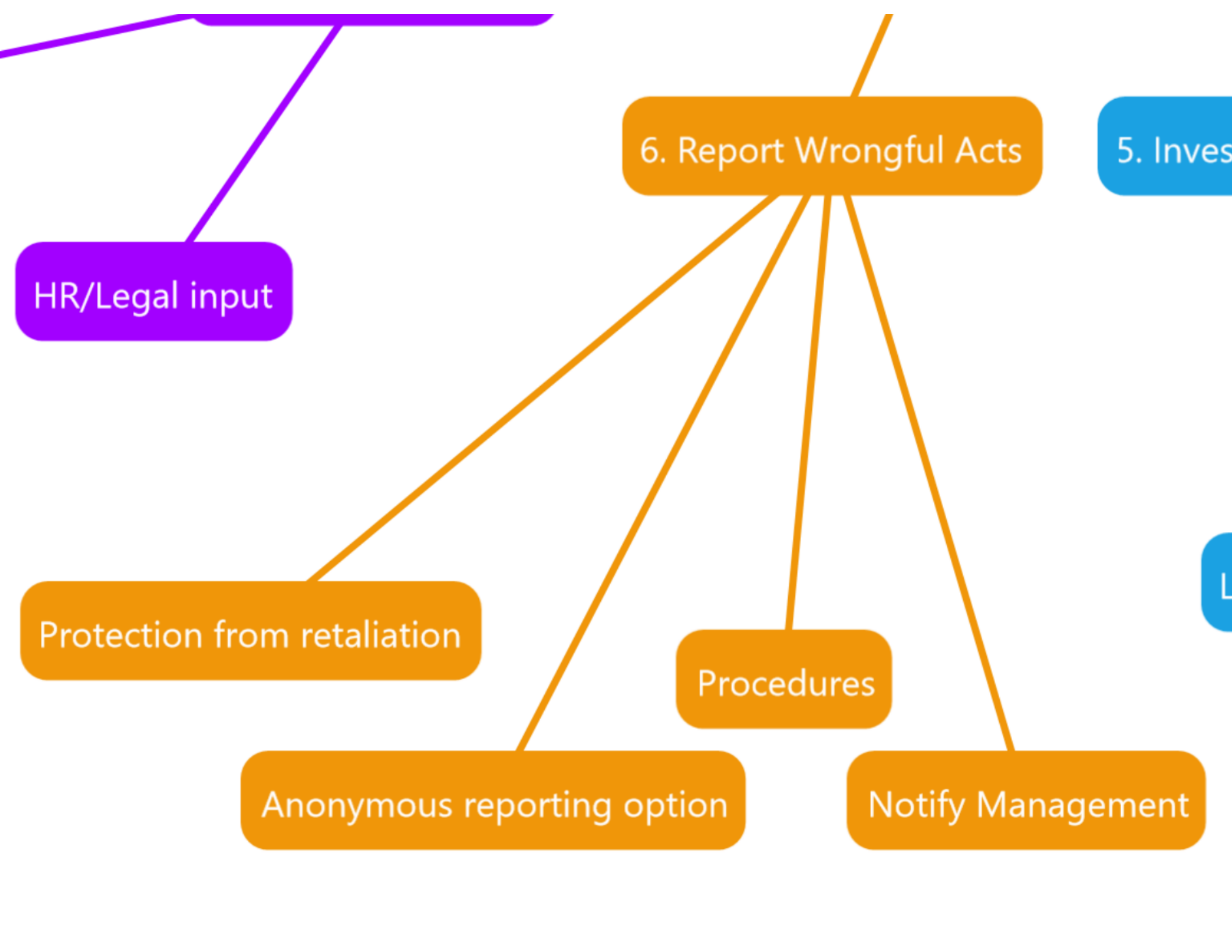

Readily available during Regulatory Inspections
Signature/Initial Logs
Mechanisms for preventing DI lapses
Accurate, complete truthful data
Controlled notebooks/worksheets
Validated Computer Systems
Documentation Systems
Procedures
Employee Adherence
1. Data Collection, Analysis & Reporting
Detect non-compliances
Secure data retention
Secu
2 Electronic Data Acquisition Systems

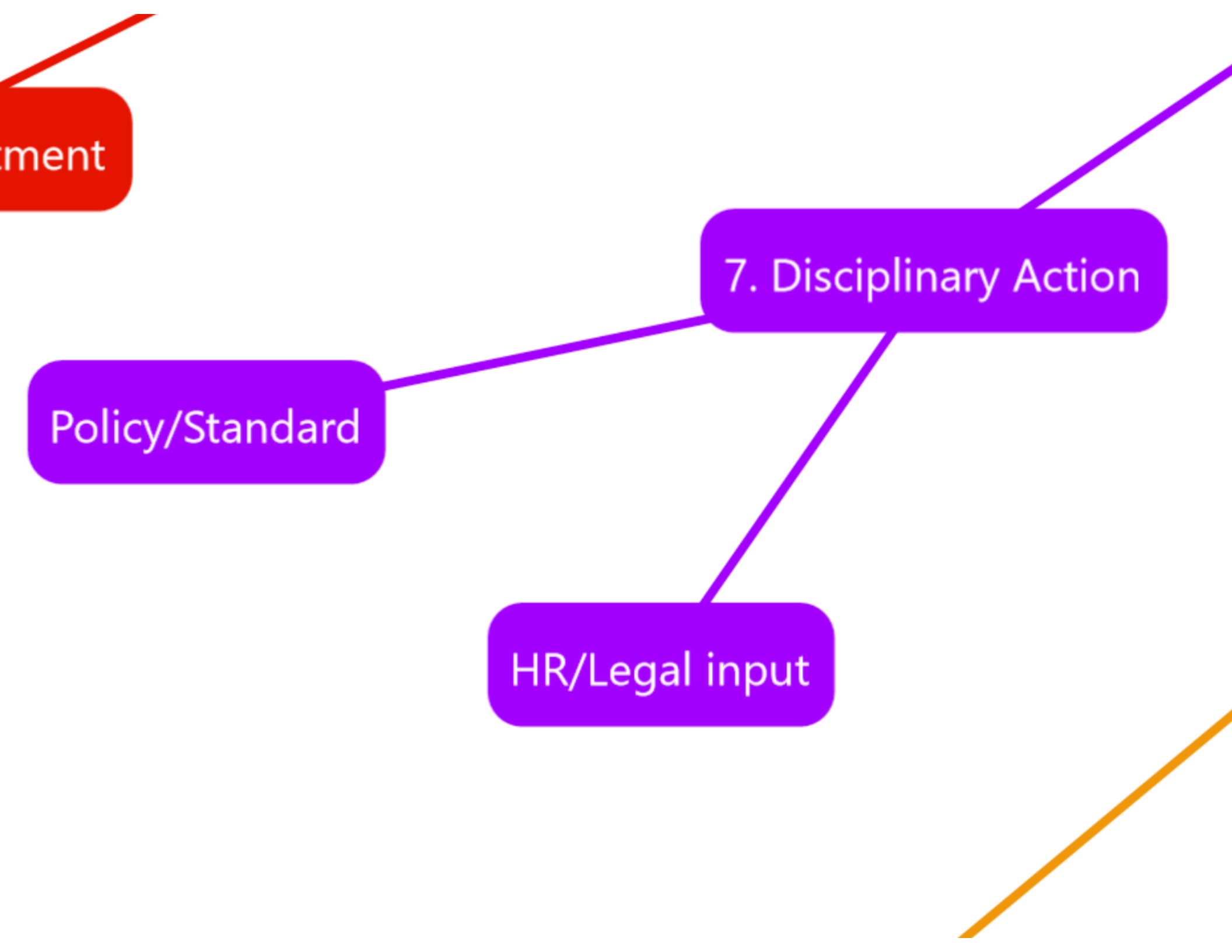

orting
Employee Adherence
Detect non-compliances
Secure data retention
Security
2.Electronic Data Acquisition Systems
Time/date stamps
Periodic Review
Procedures
Configured, validated, maintained
Audit Trails
Traceable
Employee Adherence
Use, correction & movement of data
. Electronic Access Security Measures
Unique username/password/biometrics
of Quality System


Procedures
Audit Trails
Configured, validated, maintained
Traceable
Employee Ac
Use, correction & movement of data
3. Electronic Access Security Measures
Unique username/password/biometrics
ng of Quality System
Secure Access
Procedures
Prevent unauthorised changes
Procedures
Awareness of laws/regulations
ent review

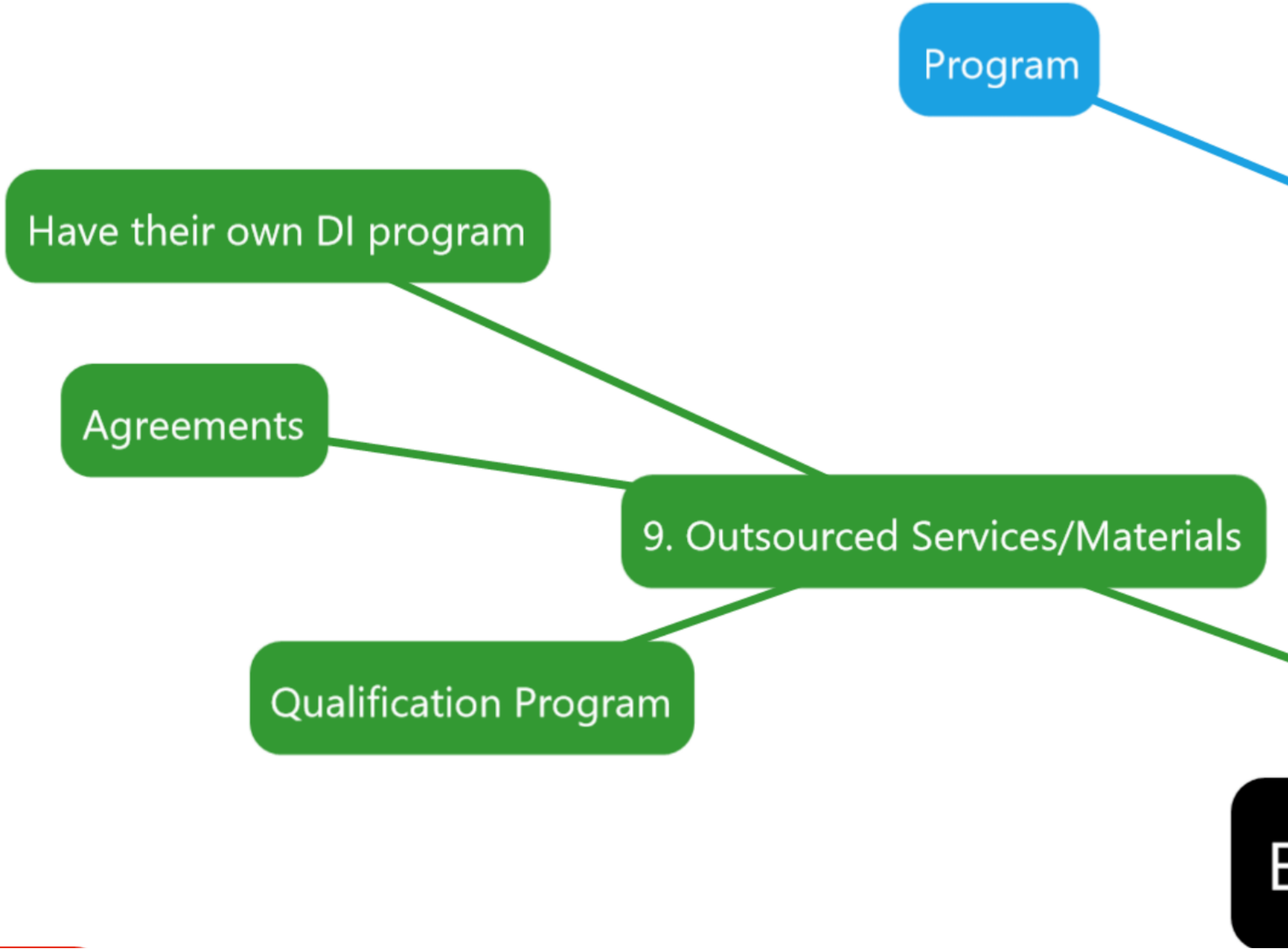

4. Auditing of Quality System
Unique username/passw
Procedures
Secure A
Prevent unaut
Procedures
Awareness of laws/regulations
Independent review
Experienced independent auditors
estigation
Internal Audit Program
Periodic Evaluation

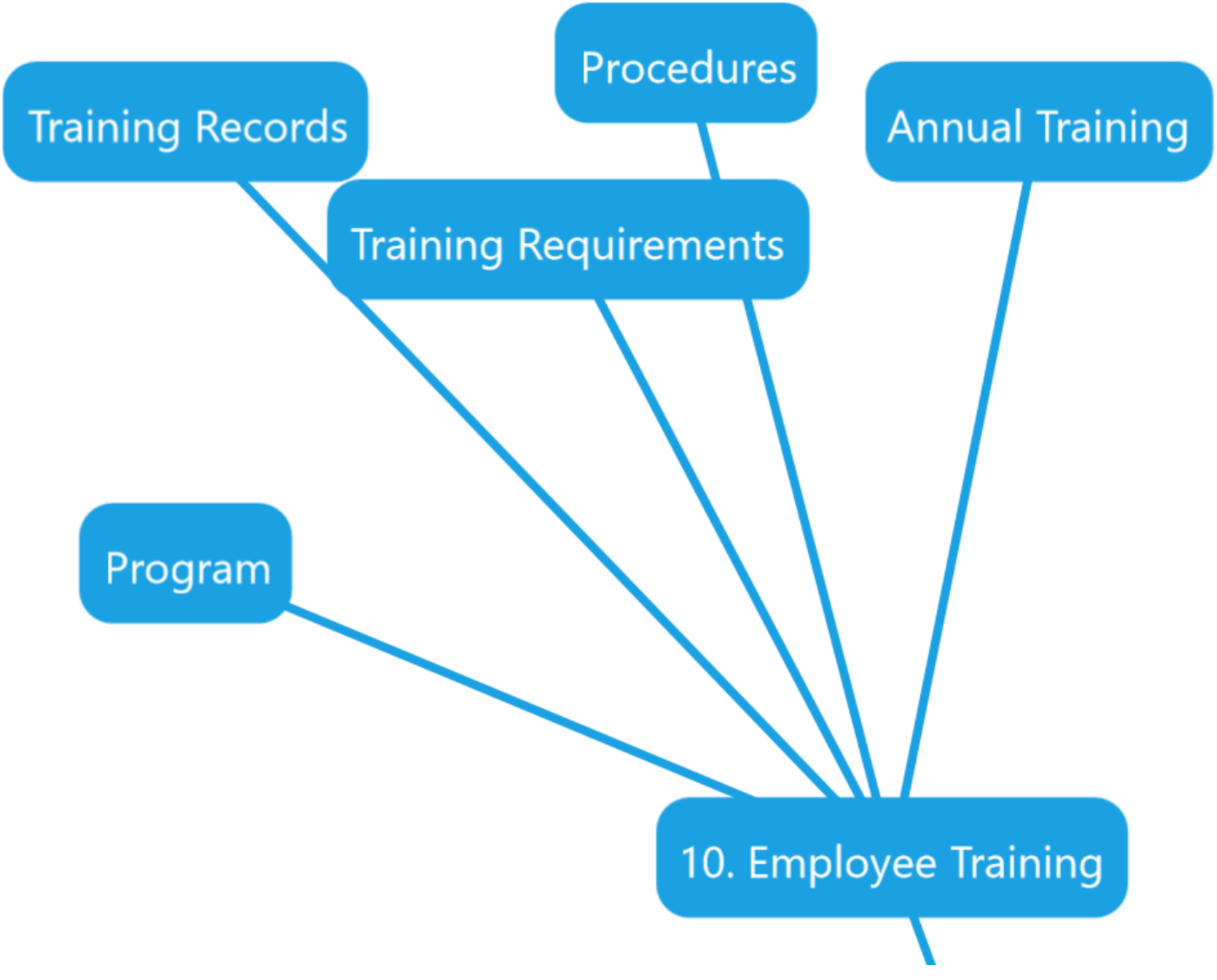

4. Auditing of Quality Syste
5. Investigate Wrongful Acts
Procedures
Leegal Counsel
Independent review
Documented Investigation
nagement


HR/Legal input
6. Report Wrongful Acts
5. Inves
Protection from retaliation
Procedures
Anonymous reporting option
Notify Management


tment
7. Disciplinary Action
Policy/Standard
HR/Legal input


Qualification Program
Corrective Actions
8. Notifying Regulatory Agencies
Procedures
Company Commitment
7. Disc
Policy/Standard


Program
Have their own DI program
Agreements
9. Outsourced Services/Materials
Qualification Program


Procedures
Training Records
Annual Training
Training Requirements
Program
10. Employee Training

The future?

- It will take time to fix DI issues
- Regulatory agencies will continue to look at DI
- Plan for remediation
- Effective QS
    - Detect, control, communicate, prevent
- Have an ethics program

PharmOut
Regulatory Knowledge, Practically Applied

Thank you for your time. Questions?

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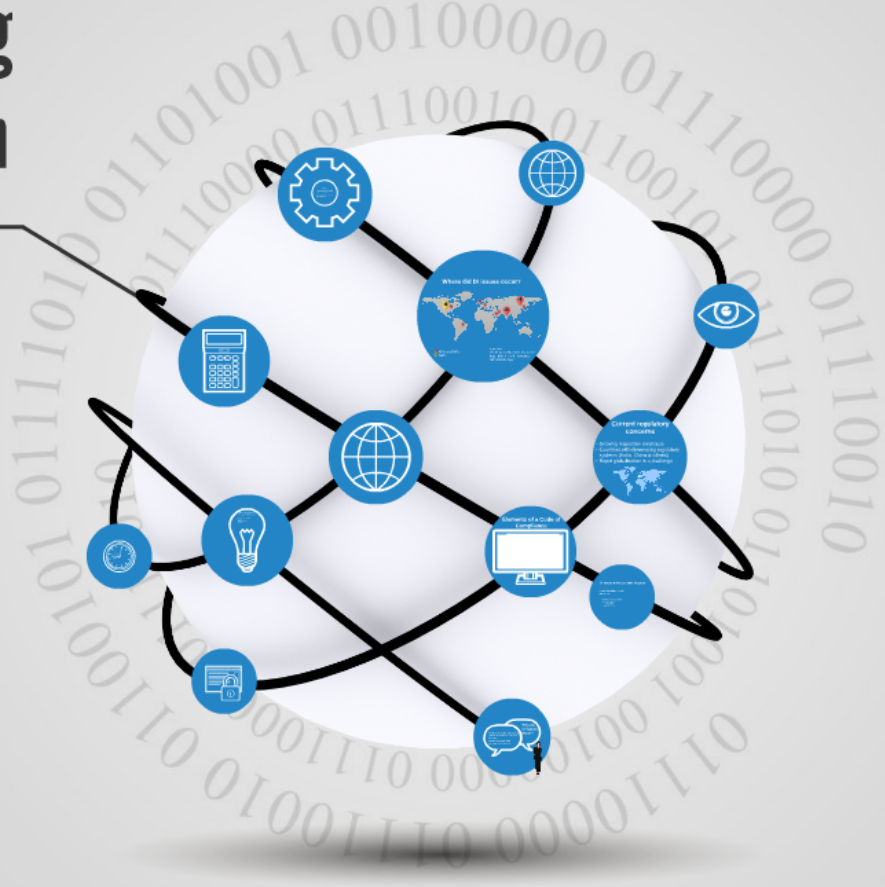

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- MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015
- US FDA Guidance for Industry, Data Integrity & Compliance with CGMP, Draft Guidance, April 2016