Case Study on Global Guidance for a Risk-Based Contamination Control Strategy

Liz Brockson
Aseptic Processing and Sterility Assurance Lead
Global Sterility Assurance and Microbiology
04Dec2025

Better Health, Brighter Future

Overview

1. Fundamentals of Contamination Control
2. Considerations in the development of a contamination control strategy (CCS)
3. Quality Risk Management and CCS
4. CCS Development Case Study

Thank you to my colleagues **Joe Horvath**, Quality Risk Management Lead, and **Alberto Gonzalez**, **Hilary Chan**, and **Anna Campanella** from the Global Sterility Assurance and Microbiology team.

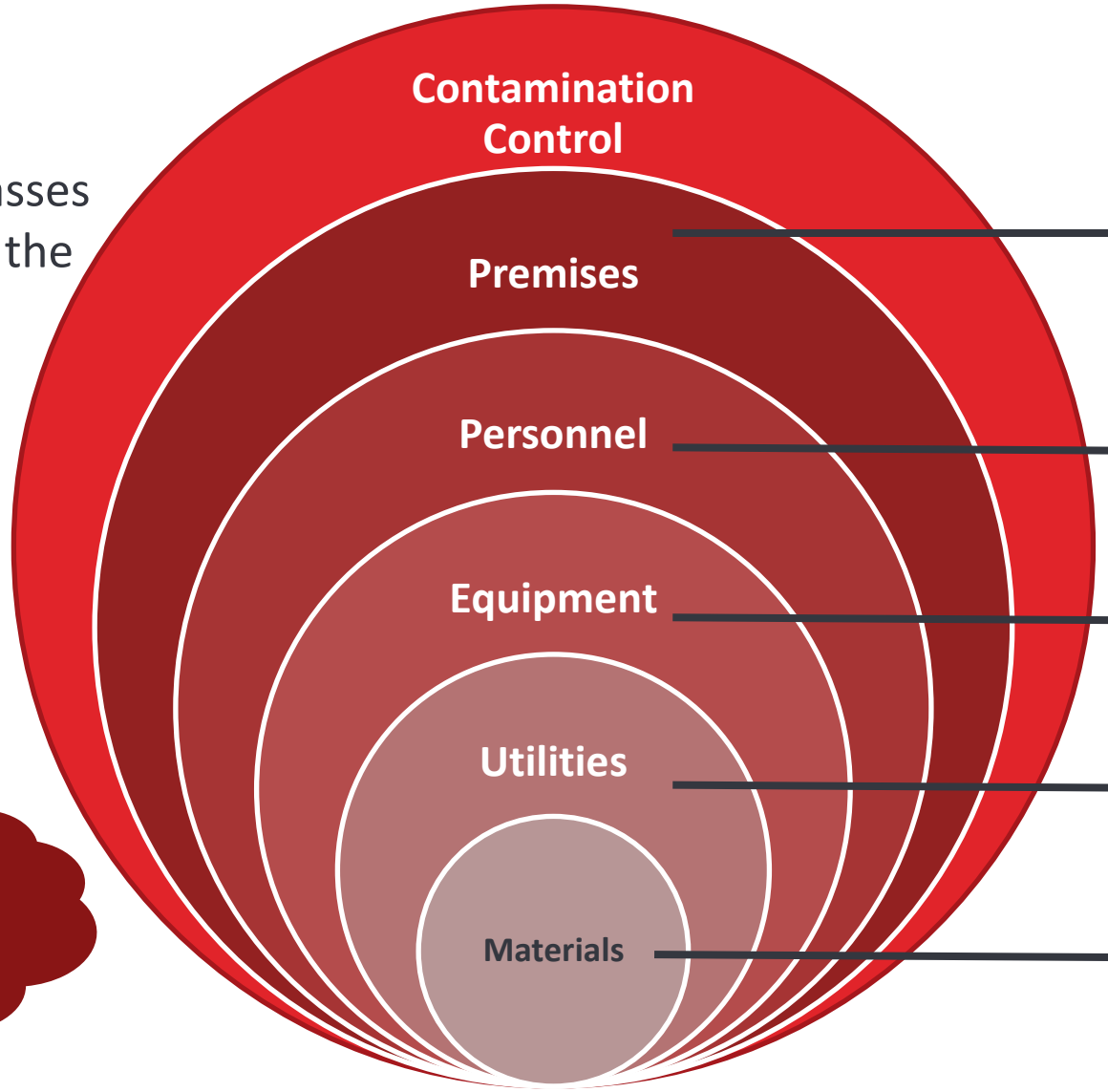



Fundamentals of Contamination Control

- Regulatory expectation (e.g., EU Annex 1):
  - Manufacture of **sterile products**
  - Principles of contamination control applied to support the manufacture of **products that are not intended to be sterile** (non-sterile products or low bioburden)
- Consider whether the control and reduction of microbial, particle and endotoxin/pyrogen contamination is important.
- See also:
  - USP <1115> “Bioburden Control of Nonsterile Drug Substances and Products”
  - PDA Technical Report 90 “Contamination Control Strategy Development”
  - EU Annex 2: Manufacture of Biological Medicinal Products for Human Use

Considerations in the Development of a Contamination Control Strategy

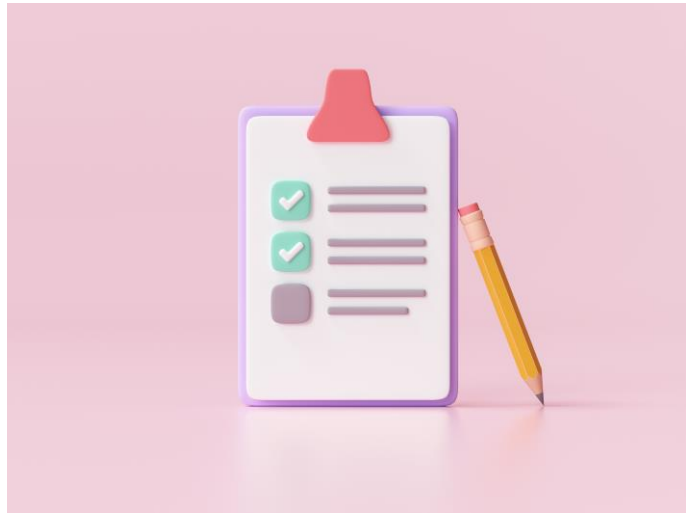
Holistic program that encompasses concepts within the context of the entire manufacturing process



Examples:

- Cleanrooms
  Airlocks
  HVAC system
- Gowning
  Cleanroom behavior
  Personnel flow
  Interventions
- Filling line
  Manufacturing equipment
  Supporting equipment
- Water
  Gases
- Raw materials
  Flow
  Transfer

Quality Risk Management and Contamination Control Strategy



Quality risk management (QRM) should be embedded in the contamination control strategy (CCS)

Certain controls/decisions should be based on a documented risk assessment

When making these risk-based decisions, certain risk factors should always be considered

Risk management activities and risk-based decision making should always follow “QRM principles” (i.e., ICH Q9)

Annex 1 QRM Challenge

Annex 1:

>100 references to risk and risk assessment

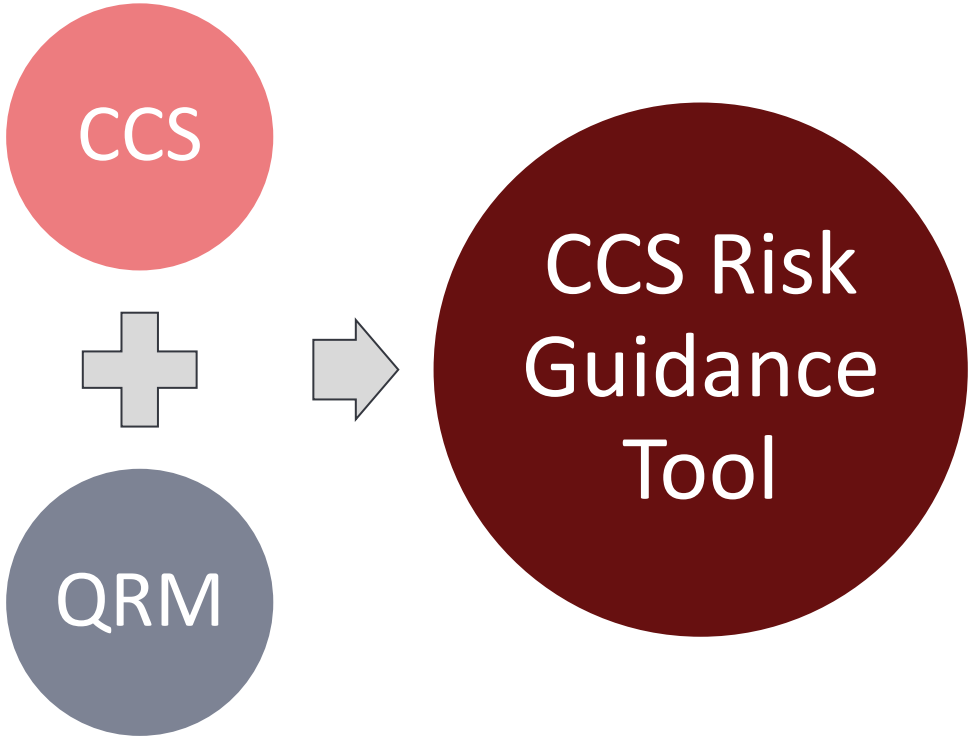
Use of **general language** -> what exactly is expected?

~40 **discrete requirements** for completion of risk assessment

(…) These methods should be ***demonstrated to effectively control the potential risk of contamination*** *of the grade A (…)*

A risk assessment should evaluate *the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones.*

Case Study: CCS/QRM Relationship



Case Study: Levels of Assessment Formality

Three levels of assessment formality are defined.

For each risk requirement, the Guidance Tool recommends:

- *Appropriate level of formality (ICH Q9: complexity, criticality, uncertainty)*
- *Suitable risk assessment methods/tools*

LEVEL 1: Risk-informed Technical Assessment:

A documented risk assessment that:

- Shows due consideration of relevant contamination risks
- Presents evidence demonstrating the adequacy of the current or proposed controls to minimize those risks.

Use of a structured risk assessment method not required.

e.g., Study report, Scientific rationale, etc.

LEVEL 2: Risk Factor Assessment:

A documented risk assessment that:

- Defines contamination risk factors (e.g., proximity of an activity to open product)
- Assigns risk scores based on these factors
- Specifies required controls based on risk score.

e.g., Risk Ranking and Filtering (RRF), Intervention Risk Evaluation Method (I-REM).

LEVEL 3: Detailed Risk Assessment:

A documented risk assessment that:

- Identifies specific contamination hazards (e.g., failure of a sterilizing filter)
- Estimates the degree of risk that each poses
- Evaluates each against acceptance threshold
- (Optionally) defines control points and associated limits critical to the prevention of contamination.

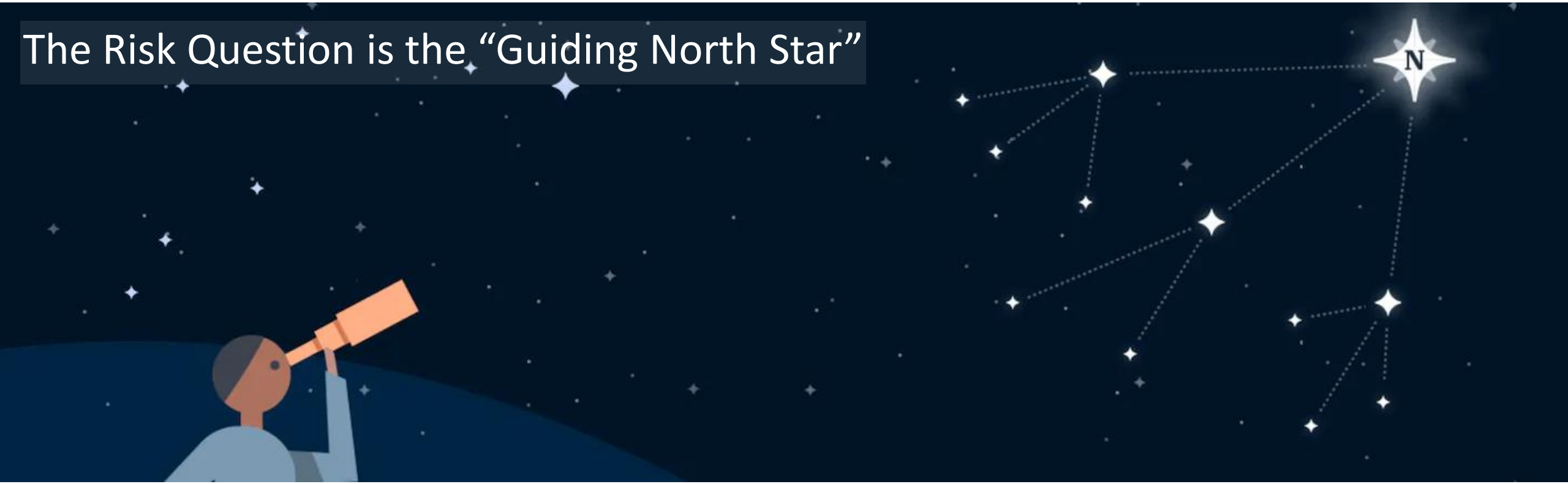
e.g., FMEA, HACCP, Risk Estimation Matrix (REM).

Is more formality always better?

Not necessarily!!

Do all the RAs need to be of the highest formality (FMEA, HACCP)?

Case Study: Risk Question



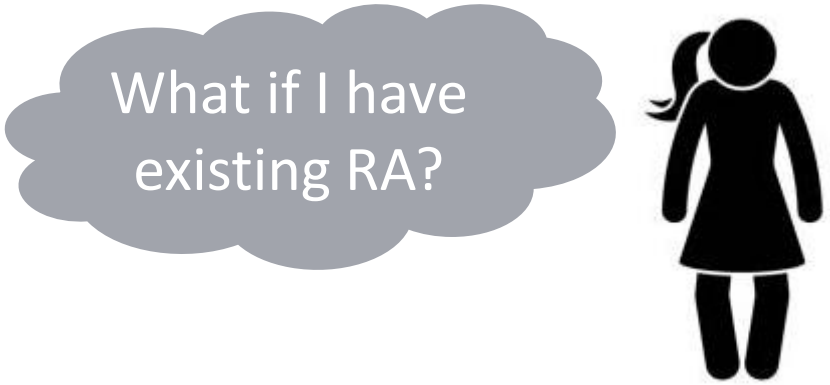
Example of Risk Question:

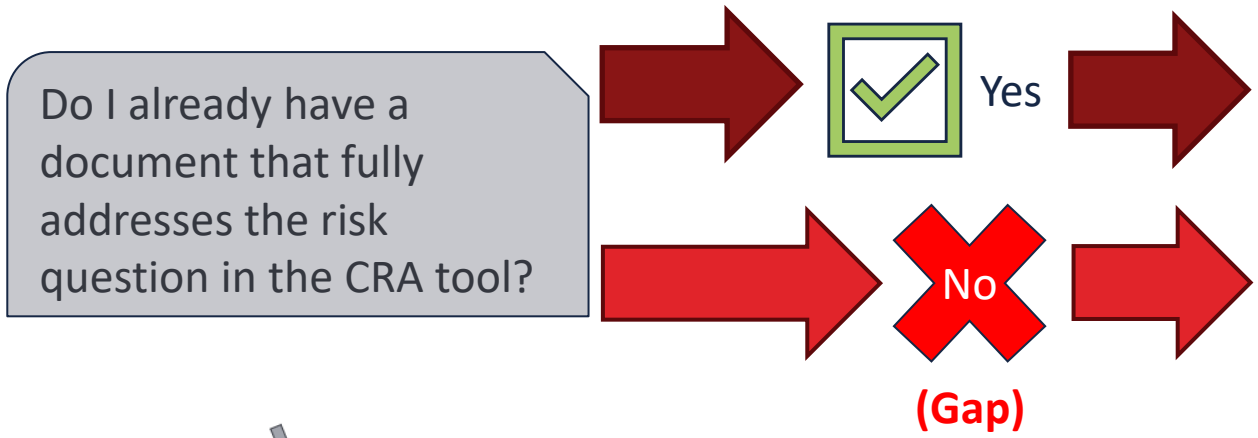
“What contamination risk is posed to the product by the transfer of items into Grade A via sealed packaging and/or rapid transfer ports and what controls are required to reduce the risk to an acceptable level?”

Case Study: Existing Risk Assessments

Example of Risk Question:

"What contamination risk is posed to the product by the transfer of items into Grade A via sealed packaging and/or rapid transfer ports and what controls are required to reduce the risk to an acceptable level?"





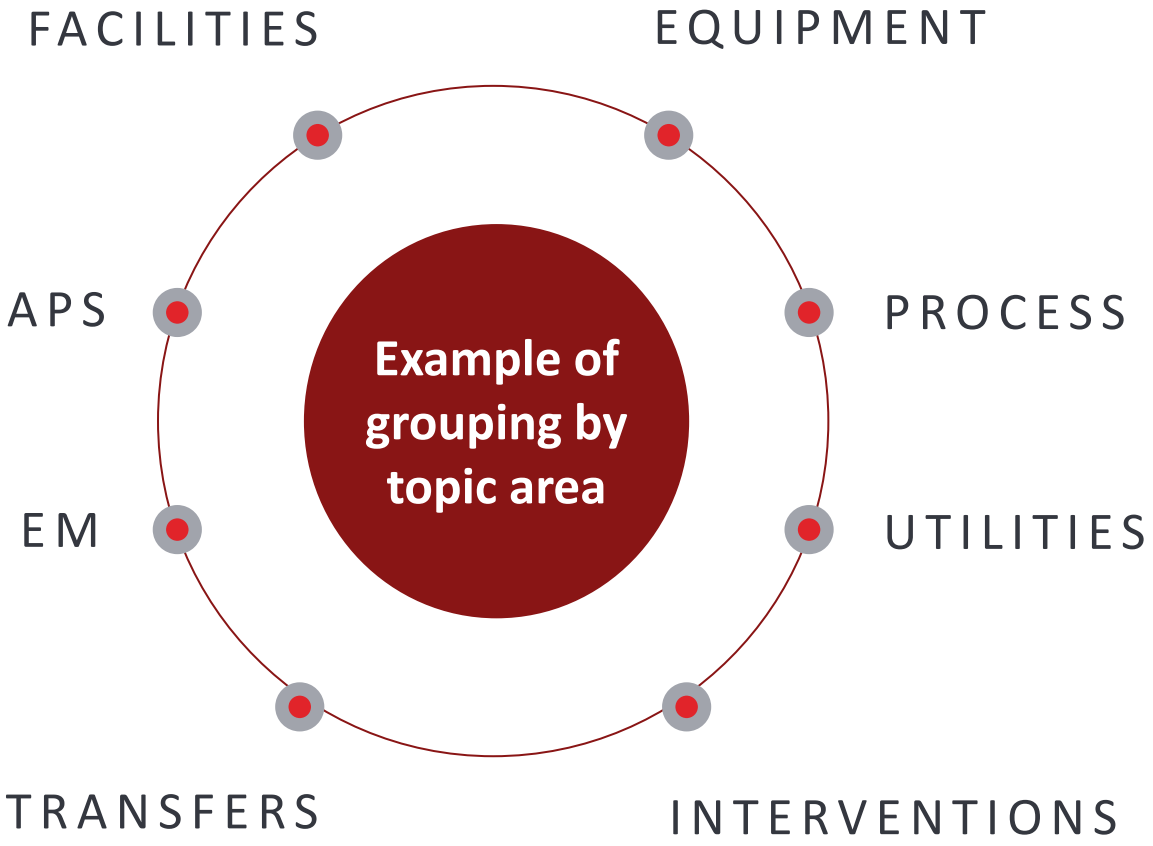
No action required

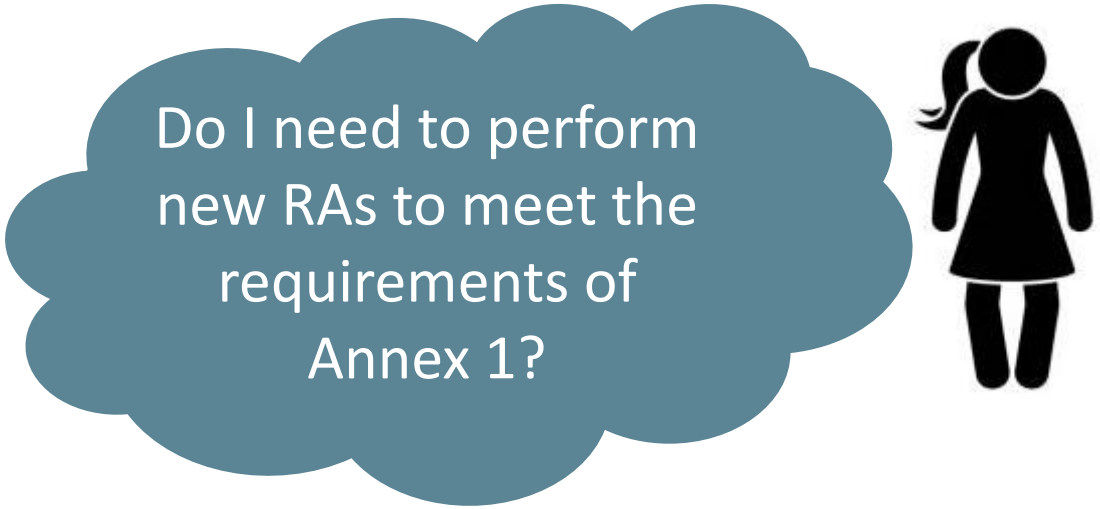
Address the risk question

- Completion of a **new** assessment, or
- Revision of an **existing** assessment

Risk-based, pragmatic approach

Case Study: Assessment Grouping





Risk questions can be grouped into new or existing assessments

Benefits of grouping

1. Fewer RAs
2. More efficient management of RAs

Case Study: Contamination Control Strategy

Pre-Annex 1 Approach	Annex 1 Issued and Effective	Continuous Improvement	Refined CCS

Global recognition of upcoming need for CCS

- Early drafts of Annex 1 updates
- Global guidance required for sites to implement / adapt locally
- Sites required to develop local CCS

Rollout of updated CCS guidance

- Global procedure and CCS template updated to reflect Annex 1 specifics
- CCS Risk Guidance Tool developed with Quality Risk Management team

Pilot Sites

Workshops

Industry Working Groups

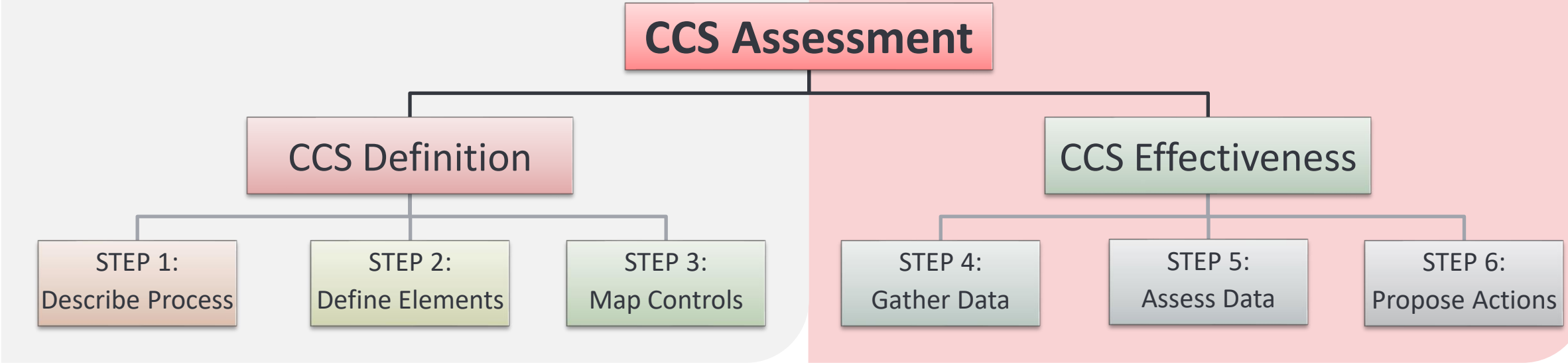
Compliant, practical approach

Annex 1 Guidance

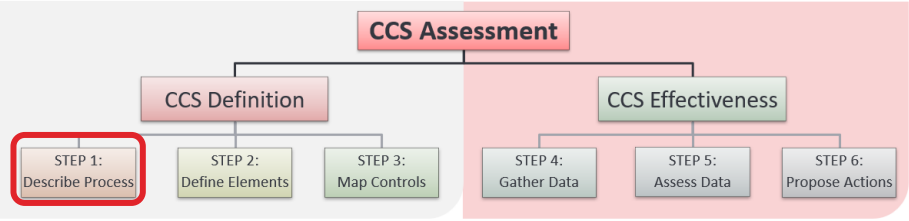
2.5 "(…) Elements to be considered within a CCS should include, but are not limited to, (…):

2.3 "A CCS should be implemented across the facility in order to:

- **Define** all critical control points, and
- Assess the **effectiveness** of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks to medicinal product quality and safety. (…)"

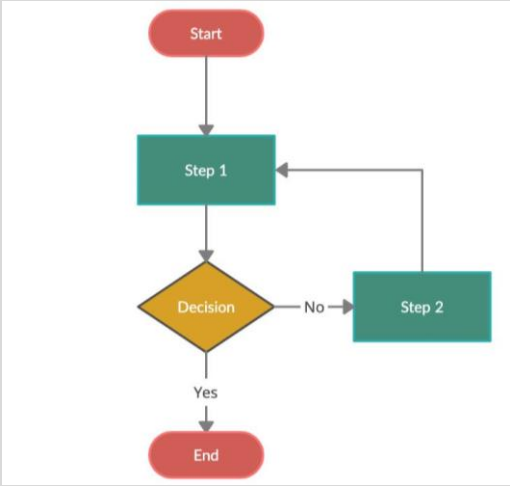


Case Study: Describe Process



MY PROCESS:

- _____
- _____

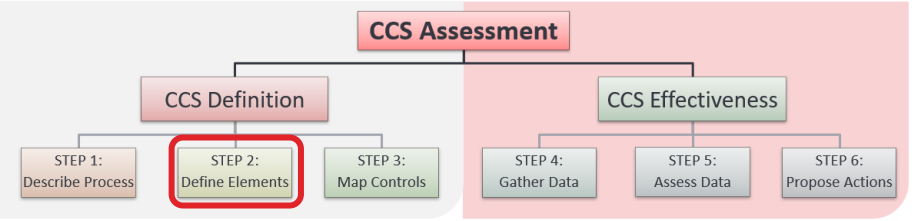


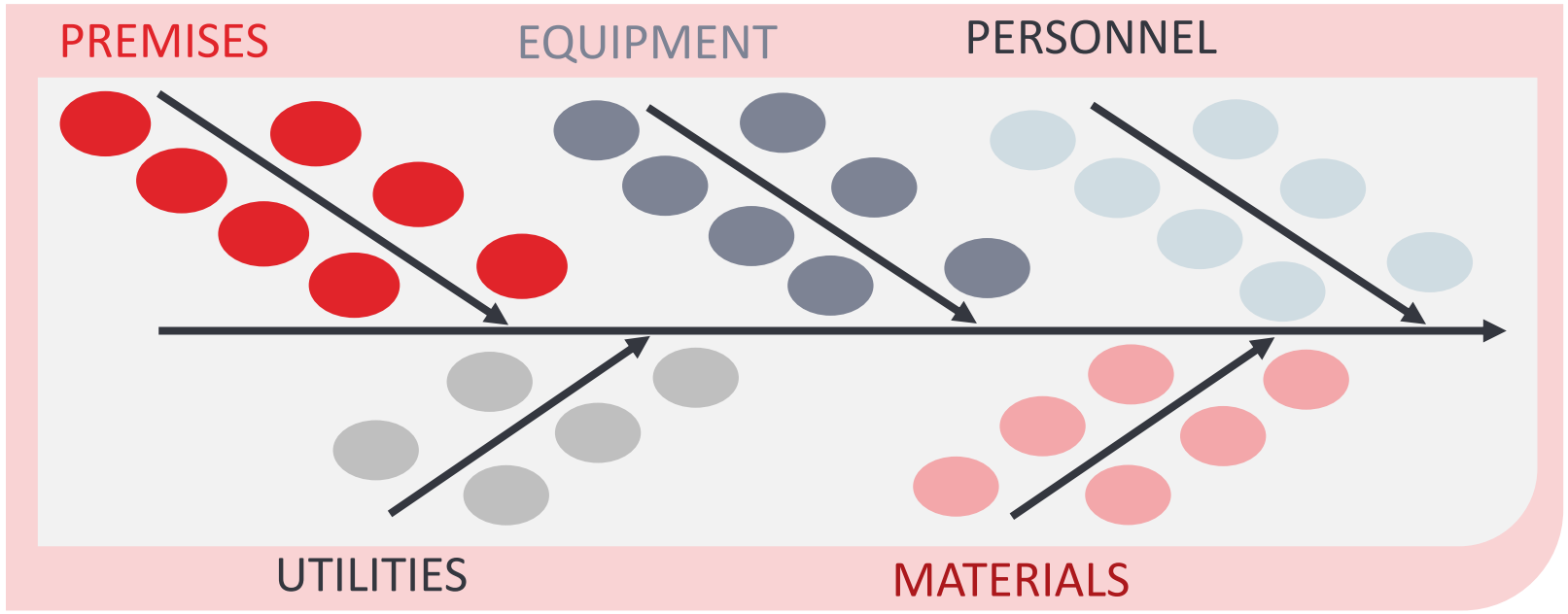
- _____

Short and sweet summary:

- High-level/generic description
- Leverage existing documentation

Case Study: Define Elements



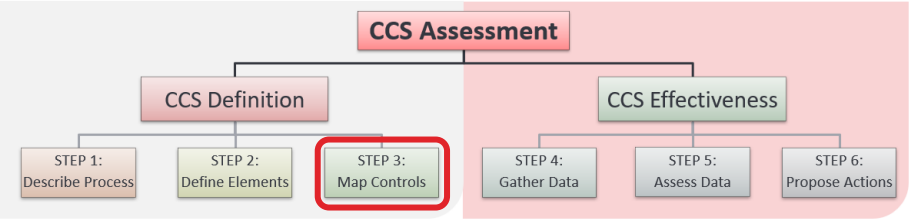


Global Template with 5 CCS Categories

…and 40+ CCS Elements

Sites can add/remove CCS Elements *depending on the process in scope*

Case Study: Map Controls



CCS Elements from step 2 (example):

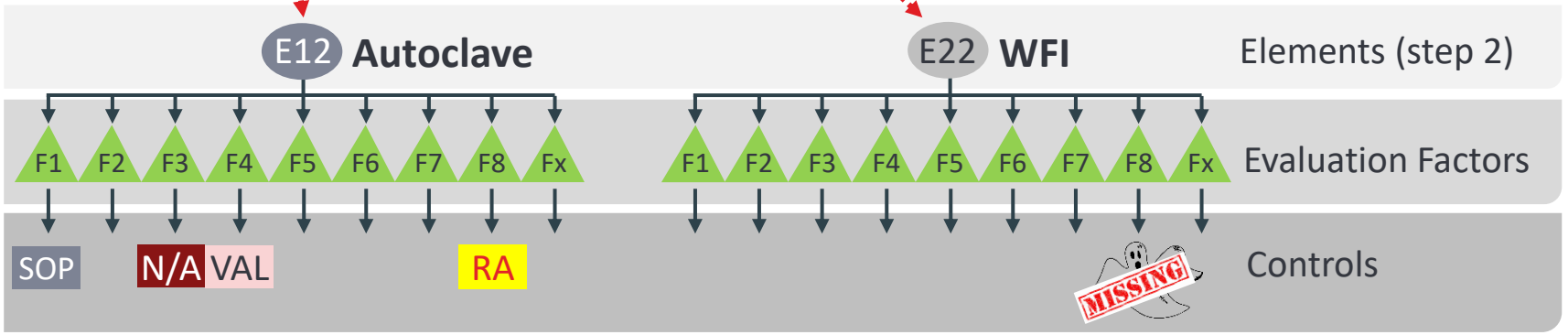
E1 E5 E9 E13 E17 E21 E25 E29
E2 E6 E10 E14 E18 E22 E26 E30
E3 E7 E11 E15 E19 E23 E27 E31
E4 E8 E12 E16 E20 E24 E28 E32

Compare each CCS Element against each Evaluation Factor

CCS trusts QMS
(We do not duplicate work)

EVALUATION FACTORS

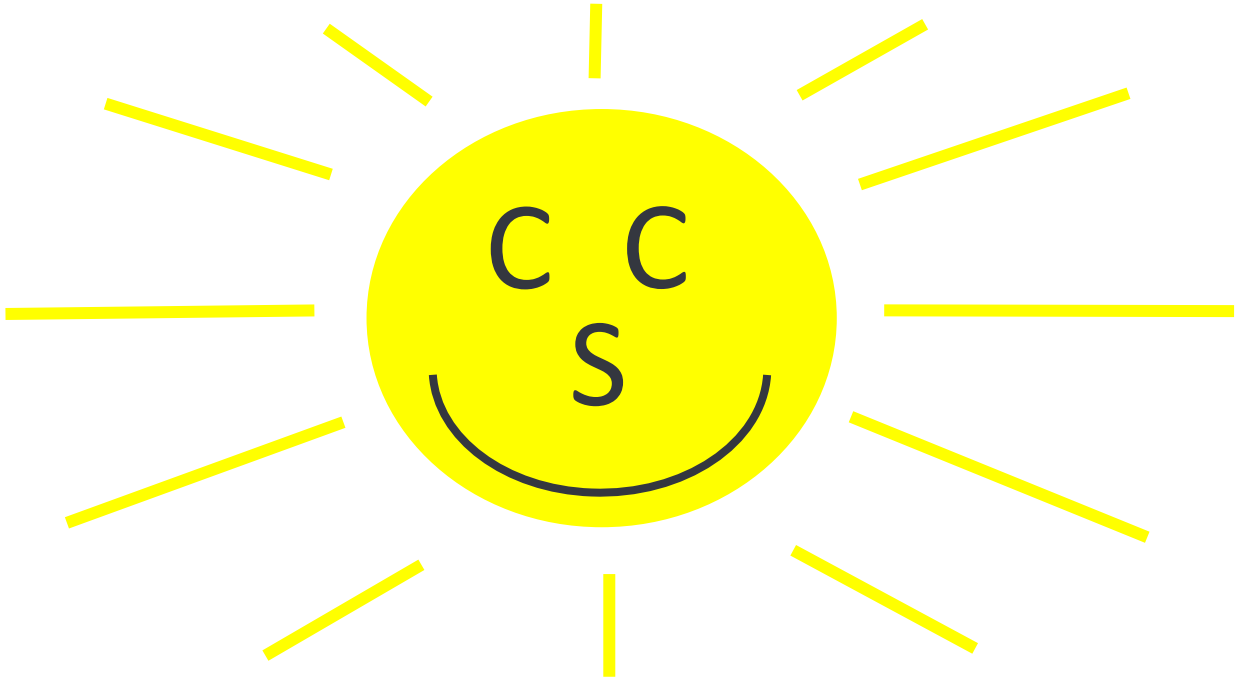
- F1 Design
- F2 Definition of Parameters
- F3 Execution
- F4 Cleaning & disinfection
- F5 Process validation
- F6 Validation of sterilization processes
- F7 Preventative maintenance
- F8 Monitoring systems
- Fx **Others**



TYPES OF CONTROLS

- SOP Procedure
- RA Risk Assessment
- VAL Validation/Qual Report
- N/A Not Applicable
- MISSING Missing control

OUR CCS TRUSTS OUR QUALITY MANAGEMENT SYSTEMS (QMS)



Document Management

Deviations & CAPAs

Change Controls

Audits

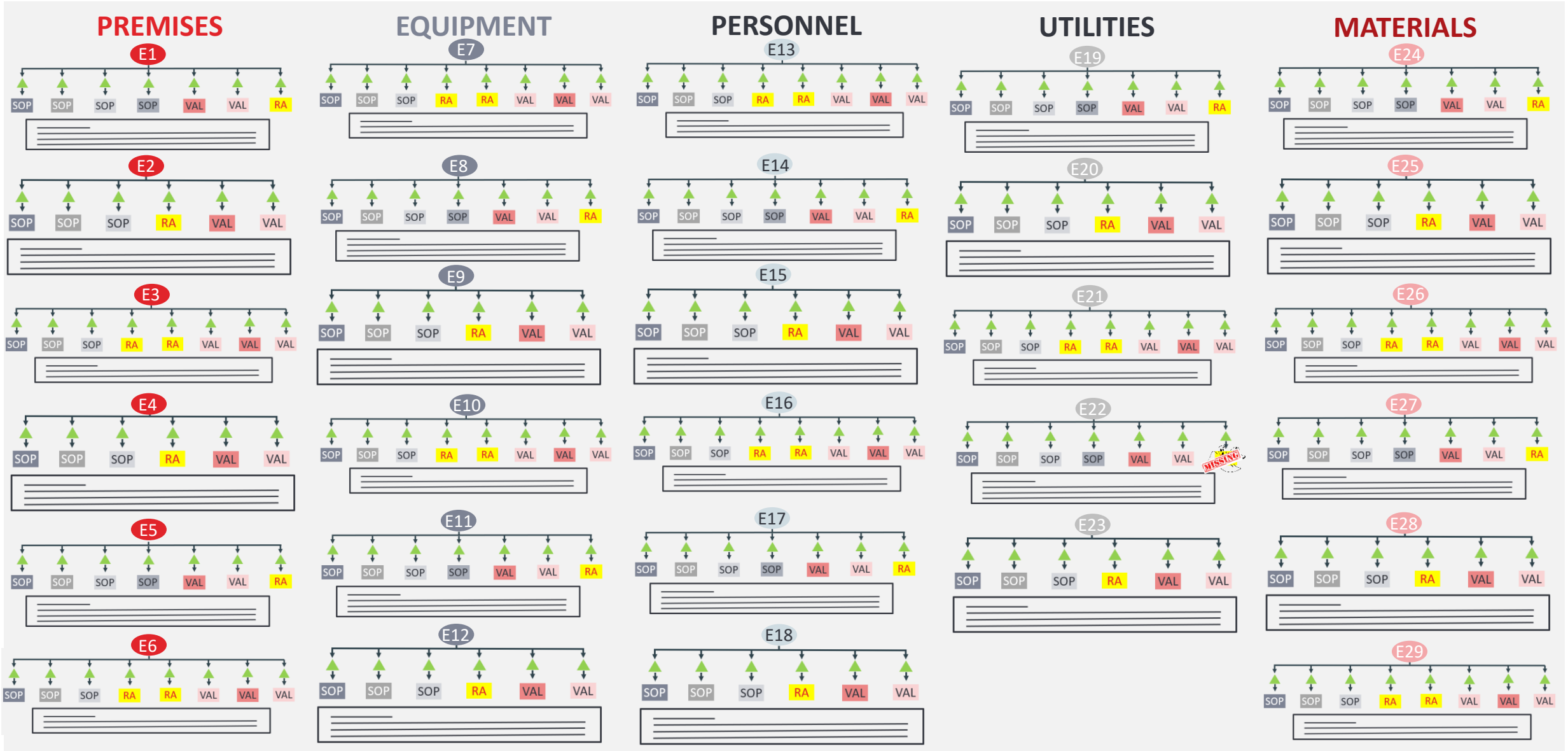
Risk Assessments

Validations & Qualifications

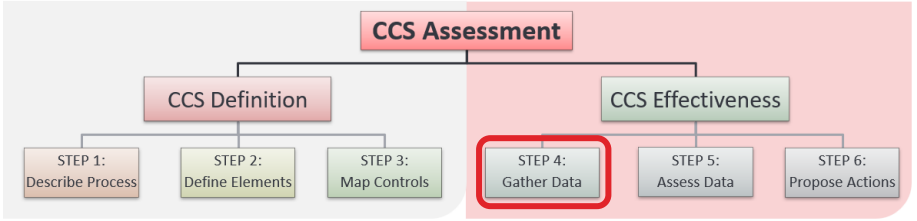
Maintenance

Training

Case Study: Example of CCS Definition



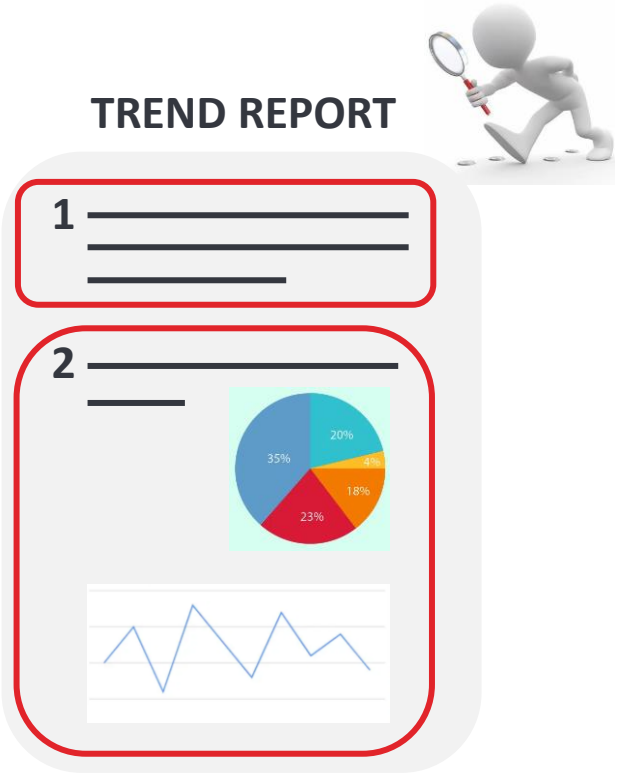
Case Study: Gather Data



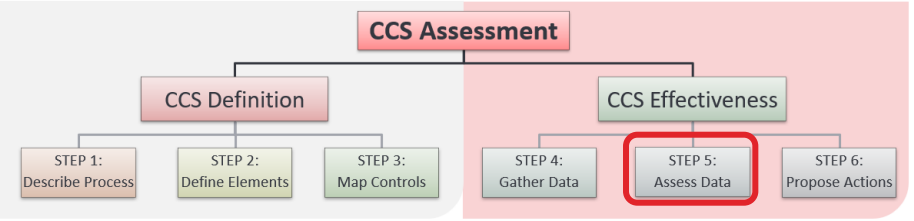
Examples of Data Sources

- Annual Product Quality Review
- Micro Trend Reports
- Outcomes from management review (e.g., Quality Council)
- Observations (internal audits, external inspections)

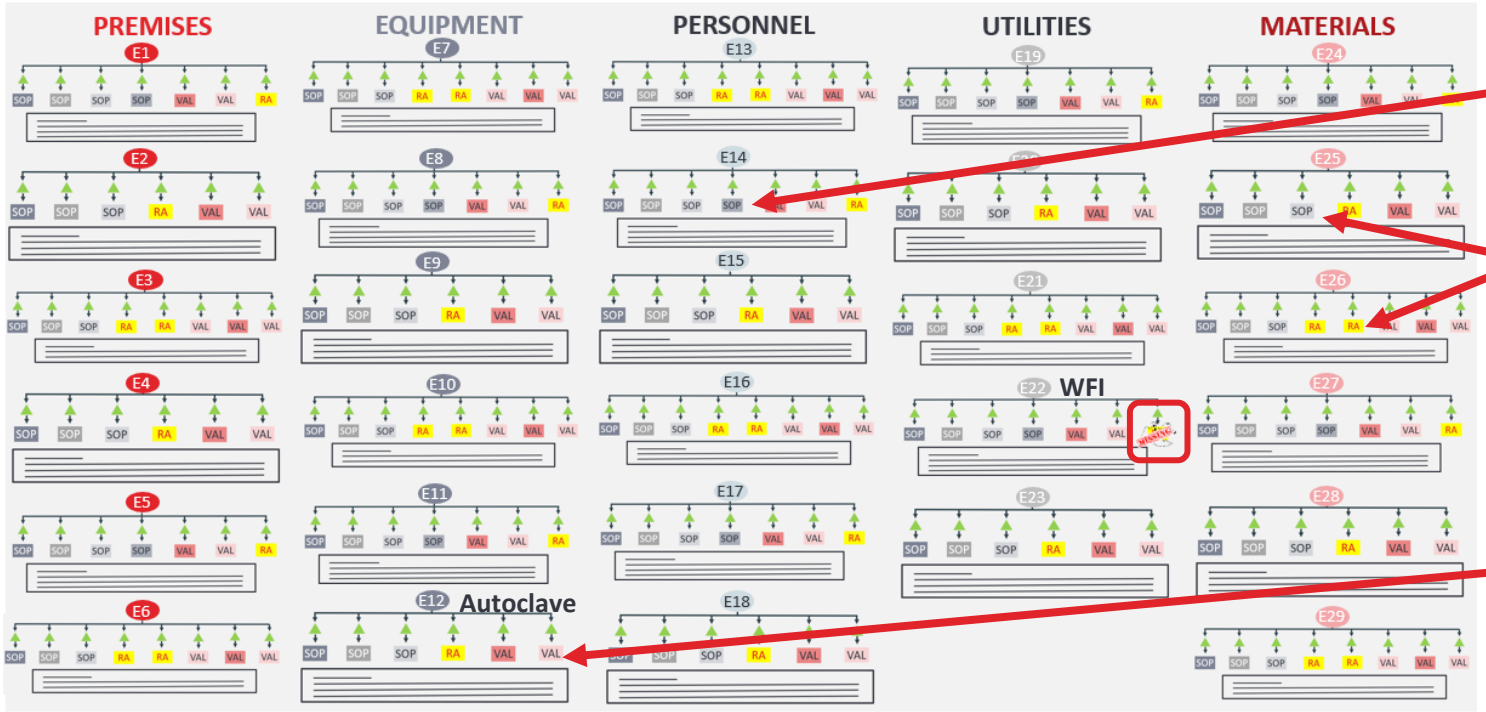
- Not required to generate new data
- Gather local data **relevant to contamination control**



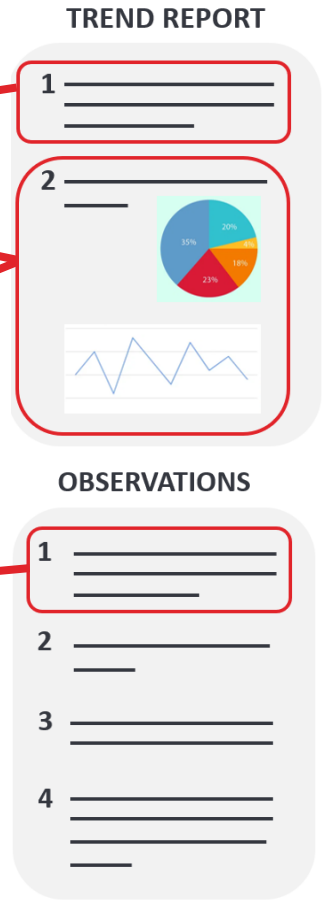
Case Study: Assess Data



From step 3:



From step 4:



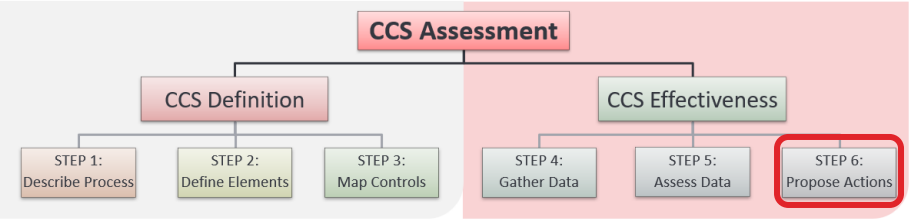
Truly HOLISTIC Method

Are the set of controls for the CCS Element effective?

- Yes
- Yes, but some controls need to be improved
- No

In step 5, all data collected in step 4 which may impact contamination control must be traced back to the control(s) that have been ineffective at preventing and/or detecting contamination

Case Study: Propose Actions

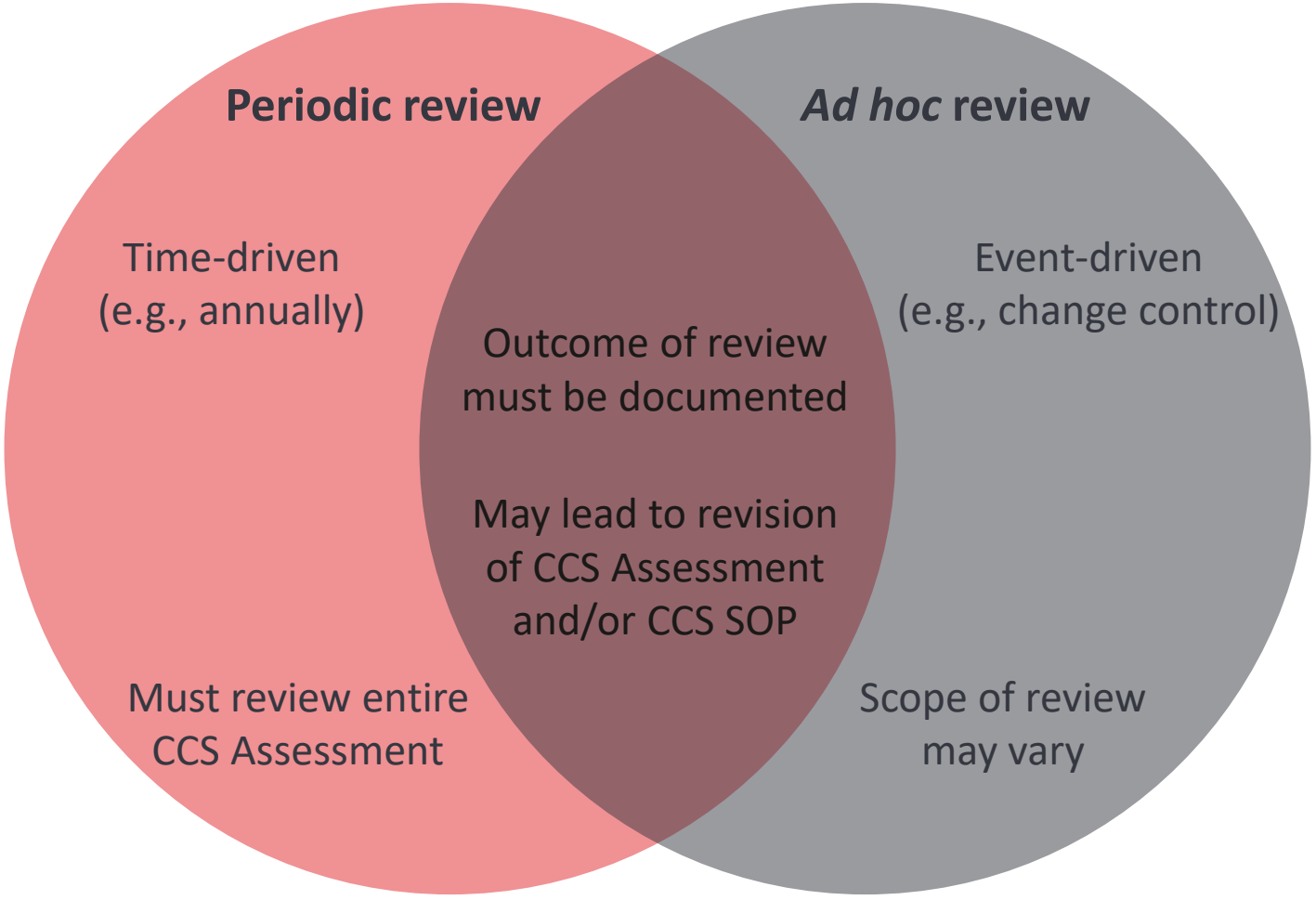


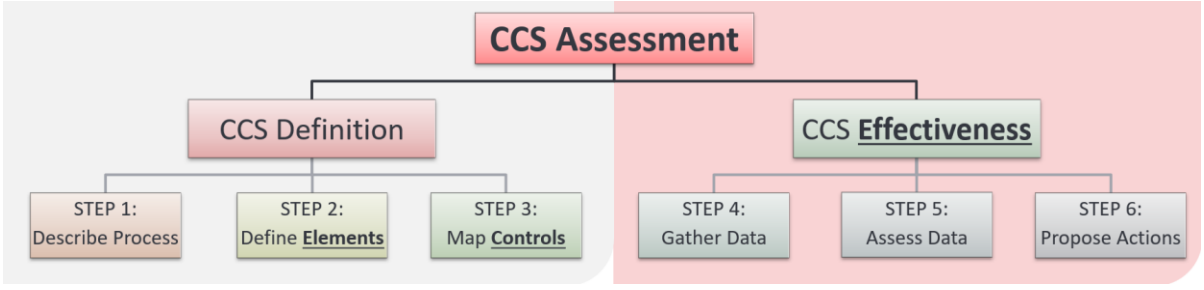
Are the set of controls for the CCS Element effective?	Actions
Yes	N/A
Yes, but some controls need to be improved	Define a CONTINUOUS IMPROVEMENT plan
No	Define a MITIGATION plan

Examples of Actions

1. Capital investments
2. CAPAs
3. Change Controls

Case Study: CCS Lifecycle

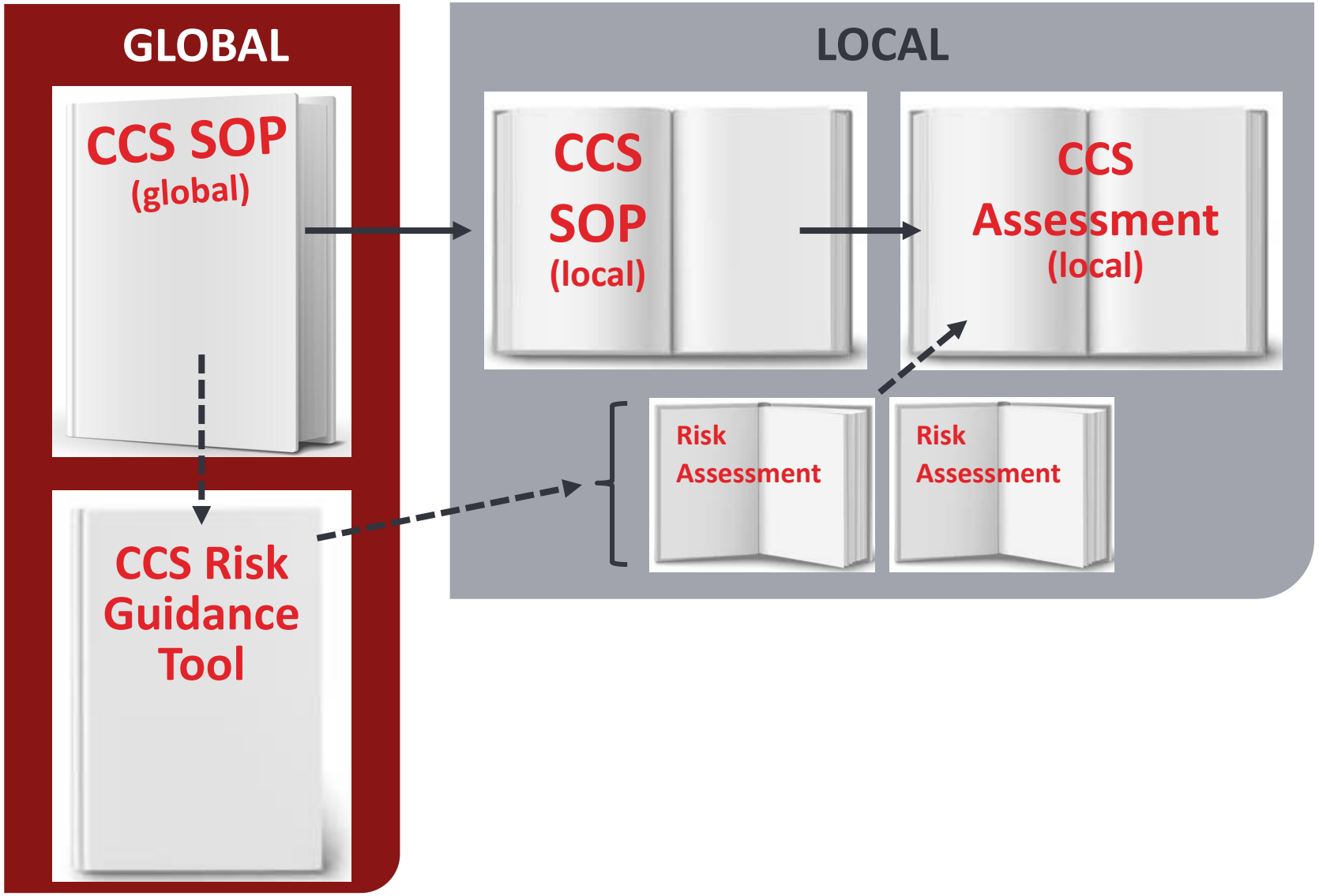




Case Study: Post-Annex 1 Contamination Risk Assessment

Company Requirements

- Ensuring safety of our patients
- Internal Right First Time (RFT) initiative aligned with company goals
- Meet regulatory expectations and adopt a *proactive mindset* towards *contamination prevention* across all Takeda manufacturing facilities



Keep in Mind

Financial Aspects

- OpEx or CapEx funds may be required to address gaps
- E.g., new equipment, new gowning

Management Involvement

- Site level management of impacted functions
  - Quality
  - Quality Control / Microbiology
  - Engineering
  - Finance
  - Manufacturing / Operations
  - Etc.
- Global support if applicable and necessary

Ultimately, our patients benefit

CCS Risk Guidance Tool

01 Helps sites decide whether their existing risk assessments are adequate

02 Helps address risk assessment requirements from Annex 1:

1. Risk question
2. Levels of formality
3. Grouping
4. Best practices
5. Available resources

CCS Assessment

01 Define the controls that prevent and detect contamination; assess the effectiveness of these controls.

02 Provides an action plan for continuous improvement and mitigation or remediation where required.

Overall

- Enhanced Quality and Compliance through a **Right First Time** mindset
- Ensuring continued **market supply** through reductions in manufacturing downtime
- Sharing **best practices** across the company through global **Community of Practice**
- **Culturing** contamination awareness / prevention **mindsets and behaviors**

Beaker

Thank you for your attention

Questions?

Better Health, Brighter Future