

A Comprehensive Annex 1 Compliance Approach using Site Protocol Audits

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Introduction

A **protocol audit** for **Annex 1** compliance was performed by site internal auditors across sites.

The approach leveraged learnings from previously performed **protocol audits**.

Protocol audits upskill all involved in regulatory expectations, audit techniques, and technical knowledge – resulting in a step-change to inspection readiness.

Both site and global CAPA can be taken to address site-specific and global finding trends.

Annex 1 Audit Protocol Item

Site and global SMEs provide input to optimize content

Sub-Topic	Sterile Fill	Vaccines	Biologics	Potential Risk (Problem Statement)
Aseptic Behaviors	Y	Y	Y	Aseptic behaviors are incorrectly executed. Personnel Environmental Monitoring samples are not taken as required. Related deficiencies are observed in risk assessments, processes & documentation.

Are gaps repeats from audits or inspections?
Does the design meet regulatory expectations?
What is the "So-What"? Challenge potential impact across systems.

Protocol instructions

Applies to Isolators, RABS, BSC (open processes), Laminar flow hoods.
Observe each aseptic process for 6 to 8 hours, from set-up to post-processing.

- Review procedures for aseptic behaviors and personnel monitoring.
- Operator aseptic behaviors are maintained over the extended period of time.
NOTE: Issues often appear after elapsed time; stand back and observe.
 - Operators maintain proper gowning, first air principles, and sanitize hands at required intervals/spray IPA away from settle plates.
 - Operators perform Personnel Monitoring (PM) when exiting from Grades A/B and following a critical intervention.
 - The following are aligned for PM: Contamination Control Strategy, Quality Risk Assessment, procedures, and observed execution.
 - Operator performs cleaning/sanitization per procedure and documentation is contemporaneous.

Foundation

Previous protocol audit topics (e.g.)

Full Protocol (2X/year)

Mini-protocol* (2X/year)

Microbial Controls	Quality Risk Mgt
Lab Controls	Deviation Mgt
Data Integrity	Validation
Facilities & Utilities	Supplier Mgt

*Abbreviated version of a full Protocol

Protocol Features

To maximize risk detection & upskilling:

- Extended shop-floor observation periods (3-8 hours)
- Challenge **design** of process and **execution** to regulations
- Consistent depth of challenge across sites
- Instructions model 'pulling the thread' to identify gaps across systems

Auditor Support:

- Training given by SMEs
- Weekly auditor Office Hours forum - collaborative learning:
 - Audit technique and technical knowledge

Impact

Effectively identifies risks, within / across sites, with focus on CAPA:

- Individual sites report audit results to global/site Sr. Leaders:
Leaders provide sponsorship:
 - Collaborative risk identification
 - Consistent approach for CAPA
- Network-wide finding trends reported to Quality Councils:
 - Allows global CAPA to be taken based on cross-site trends

Acquired auditing skills, technical knowledge, and increased site collaboration to address risks independently:
learnings applied to subsequent site audits

Annex 1 Protocol Risks

To challenge risks:

Auditors use protocol instructions & training:

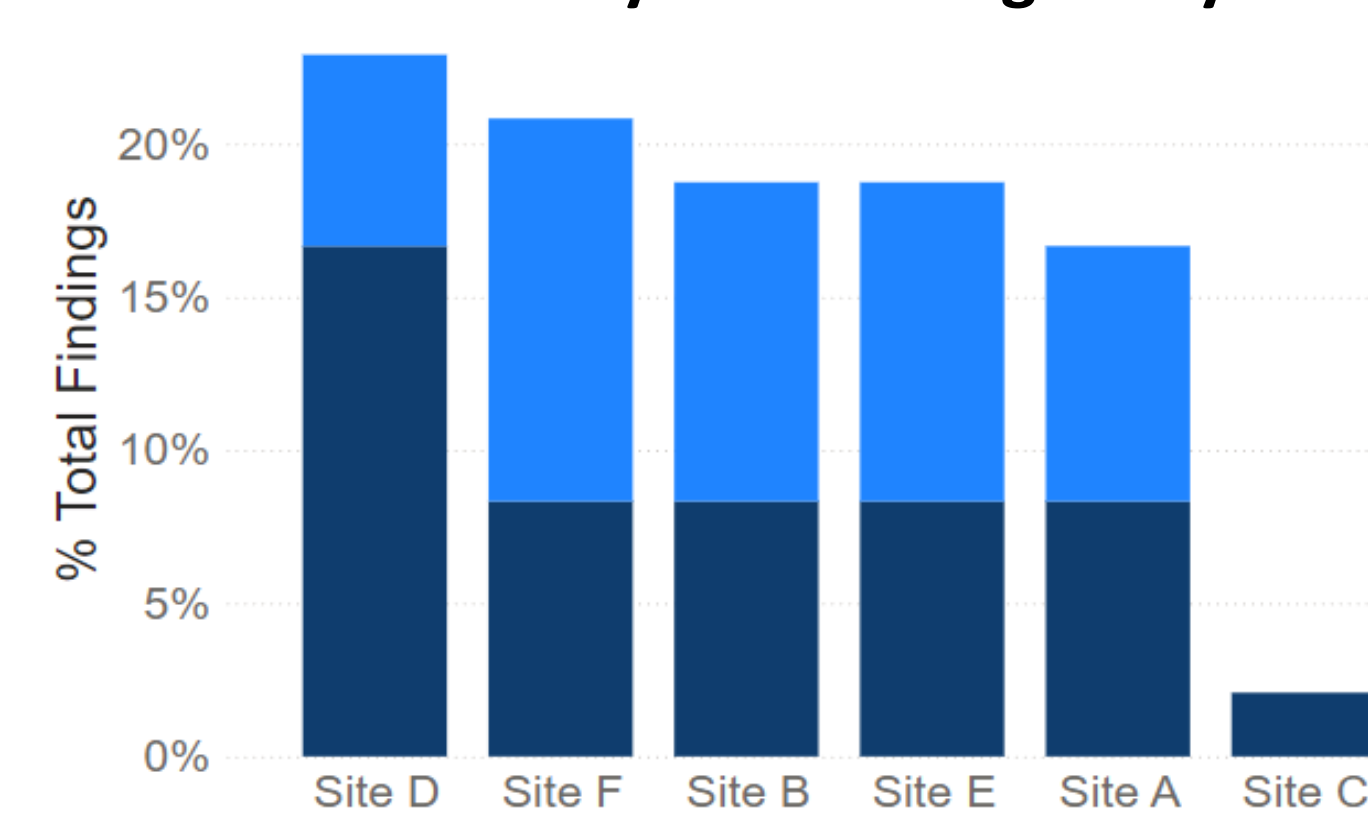
CAPA effectiveness
Personnel gowning
Aseptic behaviors
Aseptic interventions
Air visualization studies
Parts sterilization
Operator disqualification
Contamination control strategy
Personnel monitoring
Personnel/material movement
Cleanroom requalification
Non-viable particle counters
Pre-use & post-sterilization integrity test

Trending* to Inform Global Actions

* The data presented below is for illustrative purposes only and does not reflect real-world data.

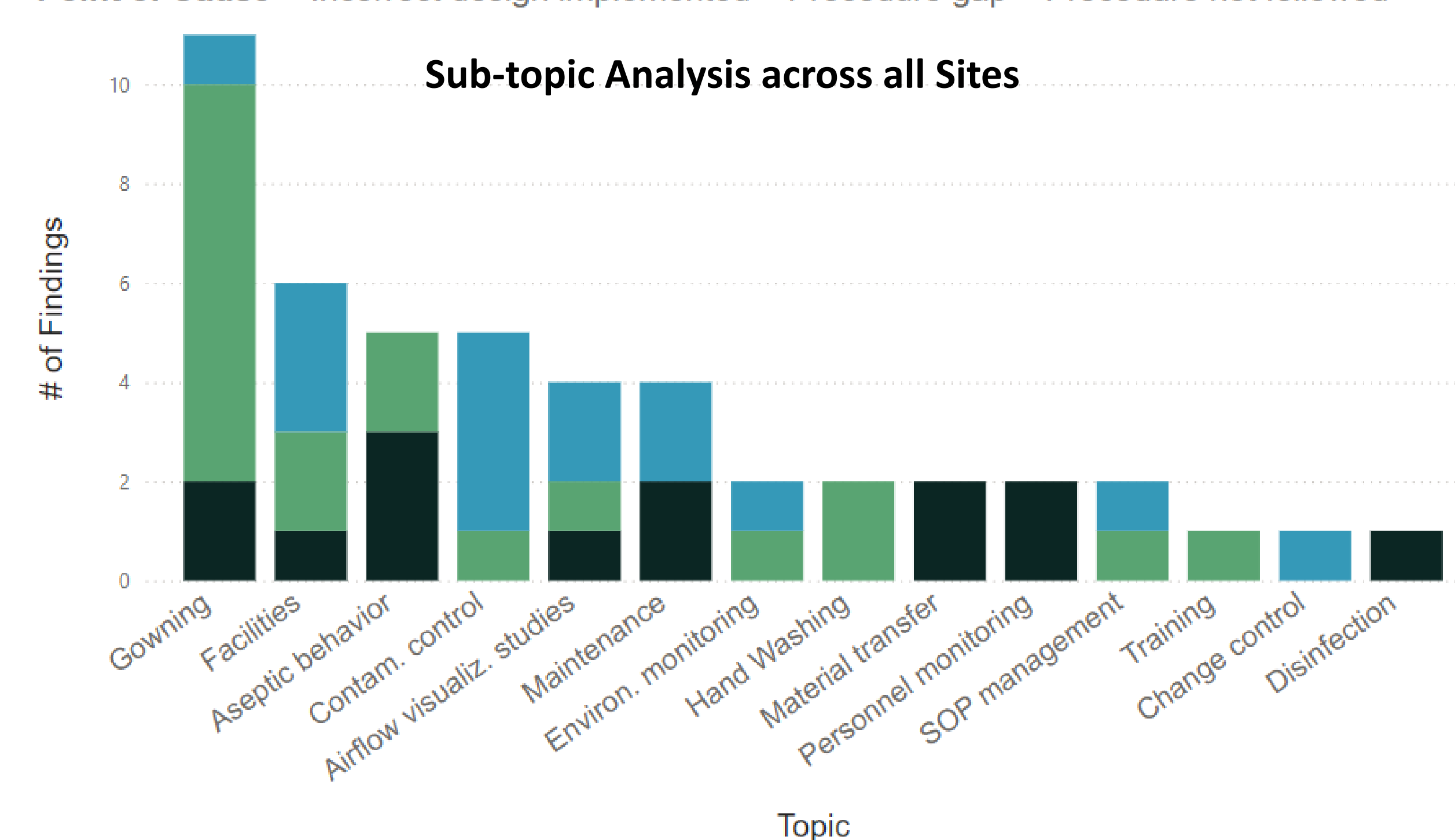
Example Trend Analysis: Identify Actions to mitigate identified risks

Site-by-Site Finding Analysis



Top 4 sub-topics	Repeat finding? (from previous audits/inspections)
Gowning	Yes (1 finding)
Facilities	No
Aseptic behavior	Yes (2 findings)
Contamination Control	No

Point of Cause



Acknowledgement