WHITE PAPER

Contamination Control Strategy

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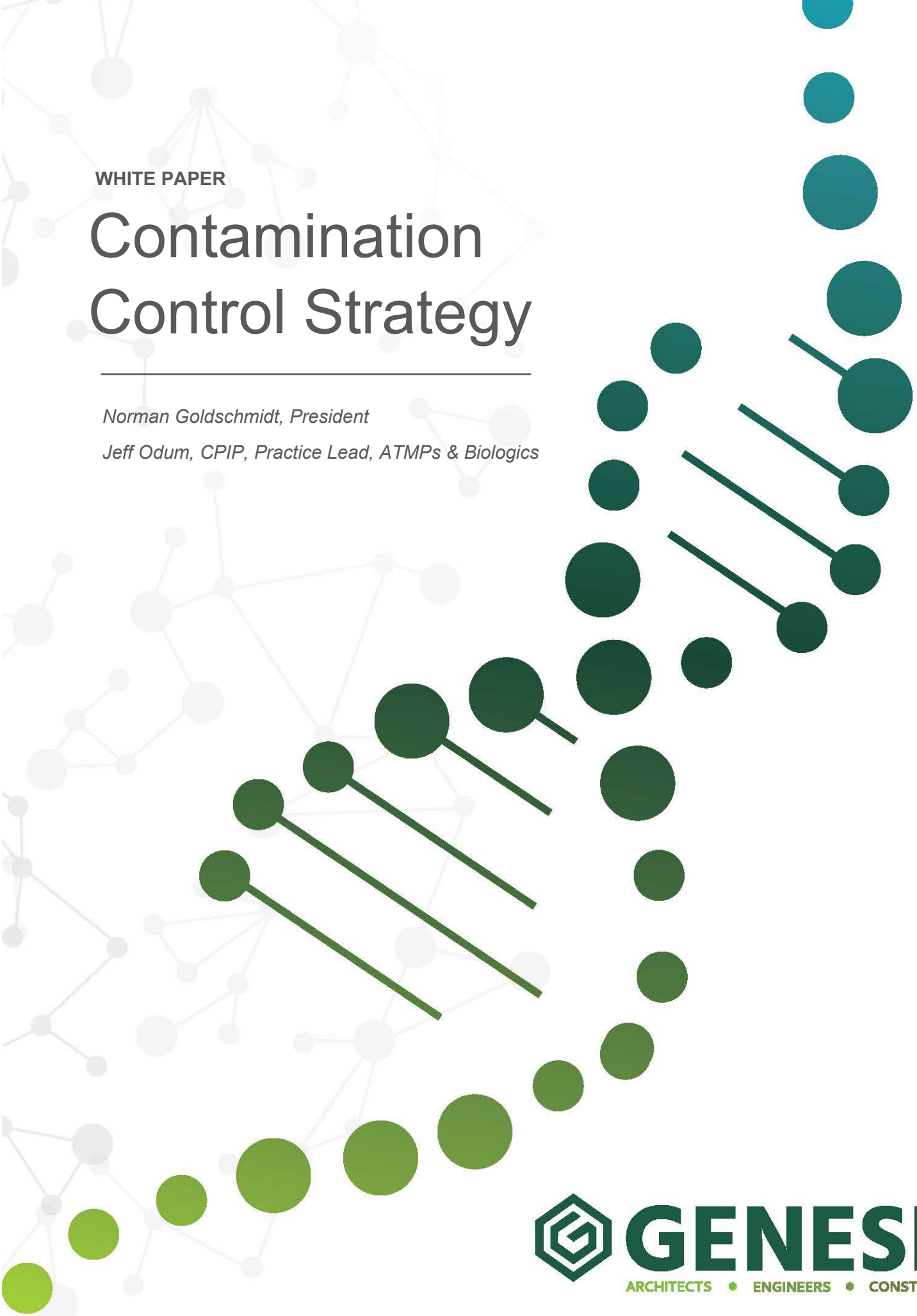

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Contamination Control Strategy

OVERVIEW

A Contamination Control Strategy (CCS) as identified within the EudraLex, Vol. 4 Annex 1, is a document or family of documents that unites, evaluates, and records the adequacy of the many tools used to assure the purity and quality of products.

While there are many factors that contribute to product strength, identity, safety, purity, and quality, CCS is intended to focus specifically on extrinsic contaminants, specifically: particulate, microorganisms, and endotoxin/pyrogen. The CCS shows not only the mechanisms used to control contamination, but also how they work together; how their efficacy is monitored or checked; and how they are managed as a group, rather than individually.

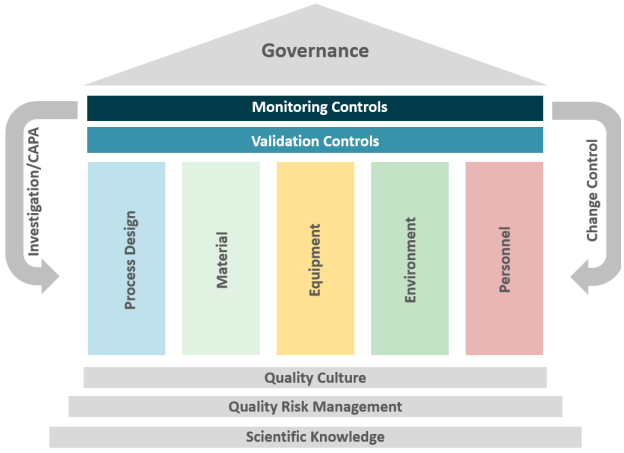

Figure 1

REGULATORY BASIS

The definition of a CCS, its requirements and the uses appear approximately 50 times in the latest (2022) approved version of Annex 1. Some of the most descriptive citations appear early in the document:

"1 SCOPE The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g., biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used for the manufacture of all sterile products, applying the principles of Quality Risk Management (QRM) to ensure that microbial, particulate, and endotoxin/pyrogen contamination is prevented in the final product.

QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, they should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.

The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden intermediates, but where the control and reduction of microbial, particulate, and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated."

The Scope of Annex 1 makes it clear that this document, while focused on sterile products, is also applicable to other drugs and therapies. It is particularly applicable to products which are bioburden-controlled and those which are produced within classified cleanrooms.

"2.3 A Contamination Control Strategy (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. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are approporiately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood."

This citation explains that the CCS is not intended to replace existing controls, but rather to serve as a basis for evaluating the adequacy, robustness, and interaction of existing controls. It also suggests that a CCS is a living document and, like all risk assessment, needs to be revisited periodically to assure that it stays relevant and that processes continually improve. Lastly, it suggests the need for new risk tools to assess interaction between systems.

"2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g., pyrogen, endotoxin) as well as particulate matter (e.g., glass and other visible and sub-visible particles).

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

i. *Design of both the plant and processes*
ii. *Premises and equipment*
iii. *Personnel*
iv. *Utilities*
v. *Raw material controls – including in-process controls*
vi. *Product containers and closures*
vii. *Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and critical service providers*
viii. *Management of outsourced activities and availability/transfer of critical information between parties, e.g., contract sterilization services*
ix. *Process risk management*
x. *Process validation*
xi. *Validation of sterilization processes*
xii. *Preventative maintenance – maintaining equipment, utilities, and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination*
xiii. *Cleaning and disinfection*
xiv. *Monitoring systems – including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination*
xv. *Prevention mechnanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools*
xvi. *Continuous improvement based on information derived from the above"*

This citation gives an idea of the expected scale and scope of the CCS. The intention is clearly to provide an analysis that spans all contamination controls and strategies. It includes monitoring and continuous improvement within the CCS umbrella. It also gives a hint at some of the tools which might be used in developing a CCS as it alludes to "critical control points," a term taken from Hazard Analysis and Critical Control Points (HACCP) risk analysis.

"2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review, resulting in updates within the pharmaceutical quality system, as appropriate. Changes to the systems in place should be

assessed for any impact on the CCS before and after implementation."

This citation suggests that CCS should be part of the change control process. It also includes pre- and post- change to better understand the impacts of change.

"2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within the facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test."

Here, the authors of Annex 1 reinforce that quality cannot be tested in or rely solely on terminal sterilizion, it must be managed throughout processing, which is what CCS is intended to help do.

"3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's Pharmaceutical Quality System (PQS) should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate, and endotoxin/pyrogen contamination is minimized in sterile products. In addtion to the PQS requirements detailed in Chapter 1 of the GMP guidelines (Part I – Basic Requirements for Medicinal Products), the PQS for sterile product manufacture should also ensure that:

iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable), and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk."

This section of Annex 1 makes it clear that the development of a CCS is intended to be a risk-based process. It also suggests the need to document properly, including the rationale for accepting residual risk.

"Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipients and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."

This definition reinforces the scope and scale of CCS. It also highlights that monitoring is part of the CCS.

DEVELOPING A CCS PROCESS

Contamination control hinges on three main criteria for success; prevention, remediation, and monitoring/continuous improvement (CI).

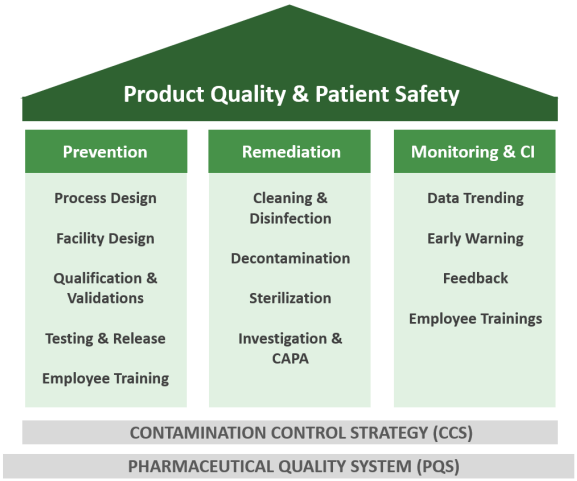

Figure 2

First, a sound prevention strategy should apply to all possible sources of risk and variability in the manufacturing process, including variables associated with human error (personnel), machines (technology/equipment), materials (components/supplies), methods

(process/procedures), and the manufacturing facility (cleanroom/environment).

All of these must be managed with an understanding of the interdependency or overall effect of all prevention steps taken together. For each CCS effort, there are three primary elements of aseptic practice focus: personnel, technology, and materials. These are reflected in the elements of the fishbone diagrams which are developed as part of the CCS.

Remediation is the identified reaction to contamination events due to non-existent or non-robust preventive steps. It includes evaluating or investigating the source of contamination and taking the specific actions (i.e., CAPAs) required to maintain or return the process to a state of control.

Critical control point parameters should be identified and monitored to a level that allows for the evaluation of the effectiveness of the controls. Some critical parameters, such as differential pressure and total particulates in cleanrooms, may require monitoring on a continuous basis. Critical controls should be established, and systems should be qualified to detect contamination events.

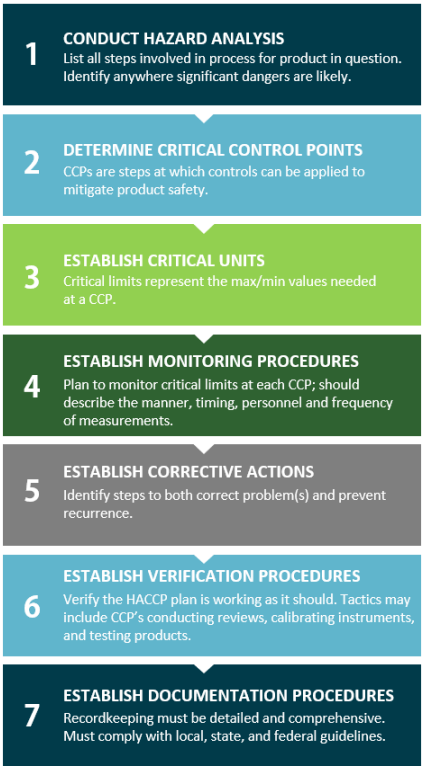

Figure 3

THE GENESIS CCS PROCESS: OVERVIEW

The Genesis process for creating the CCS utilizes risk tools, formatted in a HACCP-style process, to identify risks (or hazards); analyze control; identify control points for monitoring or qualification; and assess the current plans for these points – identifying gaps, if any. *See Figure 3.*

Identification of Control Points and Limits

Our risk assessment will identify critical control points and limits for monitoring or validation to assure or verify the functioning of the desired controls.

Identification of Monitoring Plan

We perform a gap analysis of the current monitoring and qualification plans against the risk assessment to ensure that plans are robust and reliable.

Identification of CAPAs

We capture any additional mitigations identified in the risk assessment as a list of CAPAs for introduction into the site CAPA management system.

Identification of Verification Procedures

We verify that monitoring analysis, CAPA implementation/tracking, and periodic qualification plans are in place to ensure that the HACCP plan is, again, robust and reliable.

Documentation

We issue a final report documenting the entire CCS including the philosophy, process, results, actions, and long-term management plan.

THE GENESIS CCS PROCESS: DETAIL

Risk (Hazard) Identification

We use Ishikawa (fishbone) diagrams, or Preliminary Hazard Analysis (PHA)-style brainstorming, as well as our library of prior risk assessments to identify the potential sources of contamination and current controls. *See Figure 4.*

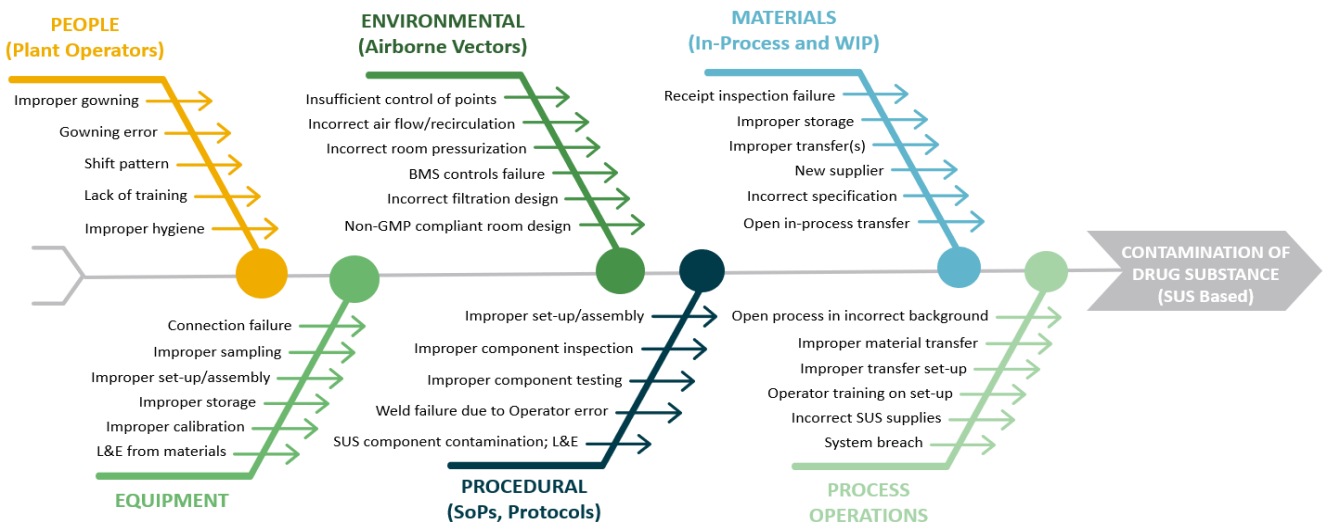

Figure 4

Risk (Hazard) Analysis

We score the effectiveness of controls at managing the risks identified using the Failure Mode, Effects, and Criticality Analysis (FMECA) style scoring.

S The **SEVERITY** of the consequence of failure

O The probability of **OCCURANCE** of failure

D The probability of **NON-DETECTION** of the failure

$$RPN = S \times O \times D$$

Figure 5

Layers of Protection Analysis (LOPA)

To fulfil the need of evaluating the interaction of controls, we examine the effectiveness of the remaining controls when one or more controls have failed, via LOPA, within our risk assessment. The controls may either prevent contamination or mitigate the impact of contamination on the process or product.

Figure 6

CONCLUSION

Developing a CCS can be a daunting task. All operating facilities have many disparate contamination controls, without a good roadmap, it can be hard to find the way from your current state to an integrated contamination control strategy. The good news is that you can build an approach from existing tools and knowledge. The final product can be useful in numerous ways and give better insight into how you maintain a state of control.

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