PART II — THE CONTAMINATION CONTROL STRATEGY

CHAPTER 5

The Contamination Control Strategy: Framework and Development

LEARNING OBJECTIVES

After reading this chapter, you will be able to:

1. Explain what a Contamination Control Strategy (CCS) is and why EU GMP Annex 1 (2022) requires it.
2. Identify and describe the 16 CCS elements listed in EU GMP Annex 1 (2022) §2.5 (i–xvi) and explain what each means in practice.
3. Describe the recommended structure and document architecture for a CCS, including when to use a single document versus a tiered approach.
4. Walk through the step-by-step CCS development process from team assembly to lifecycle review.
5. Assess existing controls against each of the 16 CCS elements and apply risk assessment principles to CCS development, connecting to ICH Q9(R1) and the tools detailed in Chapter 6.
6. Identify common mistakes in CCS development and explain how to avoid them.
7. Explain how to operationalize a CCS as a living document with defined review triggers.
8. Prepare for regulatory inspection questions about your CCS and understand how inspectors assess CCS effectiveness.

A contamination control strategy is the living framework that connects every control in your facility into a single, coherent system.

5.1 Introduction: Why the CCS Changes Everything

If you have worked in sterile pharmaceutical manufacturing for more than a few years, you already know what contamination control involves. You monitor your cleanrooms, you validate your sterilization processes, you train your operators, you qualify your equipment, and you investigate deviations when things go wrong. You have been doing these things—probably well—for years. So why does EU GMP Annex 1 (2022) now require you to have a formal, documented Contamination Control Strategy?

The answer is integration. Before Annex 1 (2022), most pharmaceutical sites managed contamination control as a collection of separate programs. Environmental monitoring lived in the microbiology department. HVAC qualification lived in engineering. Gowning programs lived in production. Cleaning validation lived in quality assurance. Each program had its own SOPs, its own

data, its own review cycles—and, critically, its own blind spots. What was often missing was a single document that connected all of these programs, explained how they work together, identified the gaps between them, and demonstrated that the combined effect of all your controls is sufficient to protect your product and your patients.

The Contamination Control Strategy (CCS) is that document. It is one of the most significant new explicit requirements introduced by the 2022 revision of EU GMP Annex 1, and it represents a fundamental shift in how regulators expect you to think about contamination control. The CCS is not another SOP. It is not a validation master plan. It is not a summary of your environmental monitoring program. It is the overarching, risk-based framework that describes all of your contamination controls, explains why each one exists, demonstrates how they interact, and provides evidence that the system as a whole is effective.

This chapter walks you through the CCS from the ground up. You will learn what the regulation actually requires, how to structure a CCS document, how to develop one step by step, what each of the 16 CCS elements means in your facility, how to manage the CCS over its lifecycle, and how to prepare for the inspection questions that will inevitably come. If you are building a CCS from scratch, this chapter gives you the roadmap. If your site already has one, this chapter will help you evaluate whether it is doing what it should. Either way, the CCS is *your* strategy—and understanding it thoroughly is essential to your work.

> **IN PLAIN TERMS — Contamination Control Strategy (CCS)**
> A Contamination Control Strategy is a single, documented plan that connects every element of your facility's contamination prevention system—from building design and HVAC to gowning procedures and environmental monitoring—into one integrated, risk-based framework. Think of it as the master blueprint that shows how all your contamination controls work together, where the gaps are, and how you know the system is effective. EU GMP Annex 1 (2022) requires every sterile manufacturing site to have one.

5.2 The Regulatory Mandate: What Annex 1 Actually Requires

The CCS requirement is established in the opening paragraphs of EU GMP Annex 1 (2022) [Ref. 1], which signals how central the concept is to the entire regulation. Let us walk through the key paragraphs in plain English.

5.2.1 The Core CCS Paragraphs (§2.2–2.7)

Section 2.2 establishes the philosophical foundation. It states that processes, equipment, facilities, and manufacturing activities should be managed in accordance with Quality Risk Management (QRM) principles. Importantly, it establishes a hierarchy: first, design your facility and equipment correctly; second, implement well-designed procedures; third, apply monitoring systems to verify

that the design and procedures are working. The final sentence of §2.2 is one of the most important in the entire Annex: *"Monitoring or testing alone does not give assurance of sterility."* This is the regulatory foundation for the prevention-over-detection mindset discussed in Chapter 3.

Section 2.3 introduces the CCS itself. A CCS should be implemented across the facility to define all critical control points and assess the effectiveness of all controls—design, procedural, technical, and organizational—and monitoring measures employed to manage risks to product quality and safety. The CCS should establish robust assurance of contamination prevention. Critically, Annex 1 states that the CCS should be *actively reviewed* and, where appropriate, updated, and that its effectiveness should form part of the periodic management review. This paragraph establishes three clear expectations: a CCS should be implemented, it should be actively reviewed and updated, and its effectiveness should form part of the periodic management review. In GMP practice, "should" denotes an expectation that is to be followed unless a risk-based justification supports an alternative approach.

Section 2.4 addresses the interrelated nature of contamination controls. It states that contamination control steps are typically assessed, controlled, and monitored individually, but *their collective effectiveness should be considered together.* This is the integration requirement—you cannot evaluate your environmental monitoring program in isolation from your gowning program, your HVAC system, or your cleaning procedures. The CCS must consider the system as a whole.

Section 2.5 lists 16 elements that should be considered within the CCS. These are the building blocks of your strategy, and Section 5.5 of this chapter discusses each one in practical detail.

Section 2.6 states that the CCS should consider all aspects of contamination control with ongoing and periodic review, resulting in updates within the pharmaceutical quality system as appropriate. Critically, it requires that changes to existing systems be assessed for their impact on the CCS both before and after implementation. This creates a bidirectional relationship between your CCS and your change control process.

Section 2.7 reinforces the prevention principle: the manufacture of sterile products requires a systematic approach to the design and implementation of contamination controls. The assurance of sterility *cannot rely on any final process or finished product test.* Your CCS is the documented expression of that systematic approach.

5.2.2 How Other Regulatory Bodies Address the CCS

While EU GMP Annex 1 (2022) provides the most explicit CCS requirement, the concept is not unique to European regulation. The U.S. FDA does not use the term "Contamination Control Strategy" in its current regulations, but the principles are embedded throughout 21 CFR Parts 210 and 211 and the 2004 FDA Guidance for Industry on Aseptic Processing. The FDA expects you to have a comprehensive system of controls—facility design, personnel qualification, environmental monitoring, sterilization validation, and investigation procedures—that together assure the sterility

of your product. An FDA inspector may not ask to see a document called "CCS," but they will assess whether your contamination controls are integrated, scientifically justified, and effective. If they are not, the finding will be the same regardless of the regulatory terminology.

PIC/S, which comprises 57 Participating Authorities (as of 2026), has aligned its expectations with EU GMP Annex 1. Sites inspected by PIC/S member authorities should expect the CCS concept to be part of the inspection framework. The World Health Organization (WHO) Technical Report Series also references contamination control principles consistent with the CCS approach, though the specific documentation expectations vary by member state.

Table 5.1 maps each of the 16 CCS elements from Annex 1 §2.5 to the chapters in this book where you will find detailed guidance on implementing each one.

Table 5.1 — The 16 CCS elements listed in EU GMP Annex 1 (2022) §2.5 (i–xvi), with cross-references to chapters in this book. Note: §2.5 states elements "should include (but are not limited to)" these 16 items, so additional site-specific topics may also be relevant.

Annex 1 §2.5 Element	Description	Book Chapter(s)
(i) Plant and process design	Facility layout, process flow, associated documentation	Ch. 7, 17
(ii) Premises and equipment	Cleanroom design, equipment qualification	Ch. 7, 8
(iii) Personnel	Gowning, training, health monitoring, behavior	Ch. 19, 20
(iv) Utilities	Water, HVAC, compressed gases	Ch. 7, 28
(v) Raw material controls	In-process controls, incoming materials	Ch. 3, 5
(vi) Product containers and closures	Container integrity, closure validation	Ch. 15, 16
(vii) Vendor approval	Supplier qualification, SUS, sterilization services	Ch. 5, 32
(viii) Outsourced activities	CMO oversight, information transfer between parties	Ch. 5, 32
(ix) Process risk management	Risk assessment, risk-based decisions	Ch. 6
(x) Process validation	Ongoing process verification, lifecycle approach	Ch. 16, 31
(xi) Sterilization process validation	Validation of sterilization methods	Ch. 9–15
(xii) Preventive maintenance	Equipment, utilities, and premises maintenance	Ch. 5, 31
(xiii) Cleaning and disinfection	Cleaning validation, disinfectant efficacy	Ch. 27
(xiv) Monitoring systems	Environmental monitoring, water monitoring, utilities	Ch. 21, 28
(xv) Prevention mechanisms	Trend analysis, investigation, root cause, CAPA	Ch. 23, 29
(xvi) Continuous improvement	Improvement based on information from all above	Ch. 5, 34

5.3 The Structure of a CCS Document

Annex 1 does not prescribe a specific format for the CCS. There is no mandatory template, no required number of pages, and no single correct way to organize the document. What the regulation does require is that your CCS is documented, that it covers all the elements listed in §2.5, that it is risk-based, and that it is actively maintained. How you achieve that is up to you—but the structure you choose matters, because it determines whether your CCS is a usable operational tool or a compliance artifact that gathers dust on a shelf.

In practice, two main approaches have emerged across the industry.

5.3.1 The Single-Document CCS

A single-document CCS is exactly what it sounds like: one controlled document that contains your entire contamination control strategy. It describes your site, your processes, your contamination risks, the controls you have in place for each of the 16 Annex 1 elements, how you monitor effectiveness, and how you manage the document over its lifecycle. This approach works well for smaller sites, single-product facilities, or organizations where the manufacturing scope is relatively straightforward. The advantage is clarity—everything is in one place, and an inspector can read the document from start to finish and understand your entire contamination control approach.

The disadvantage is size. For a large, multi-product site with complex manufacturing operations, a single-document CCS can easily exceed 100 pages. At that length, the document becomes difficult to maintain, slow to update, and less likely to be read by the people who actually need to use it.

5.3.2 The Tiered (Master Index) CCS

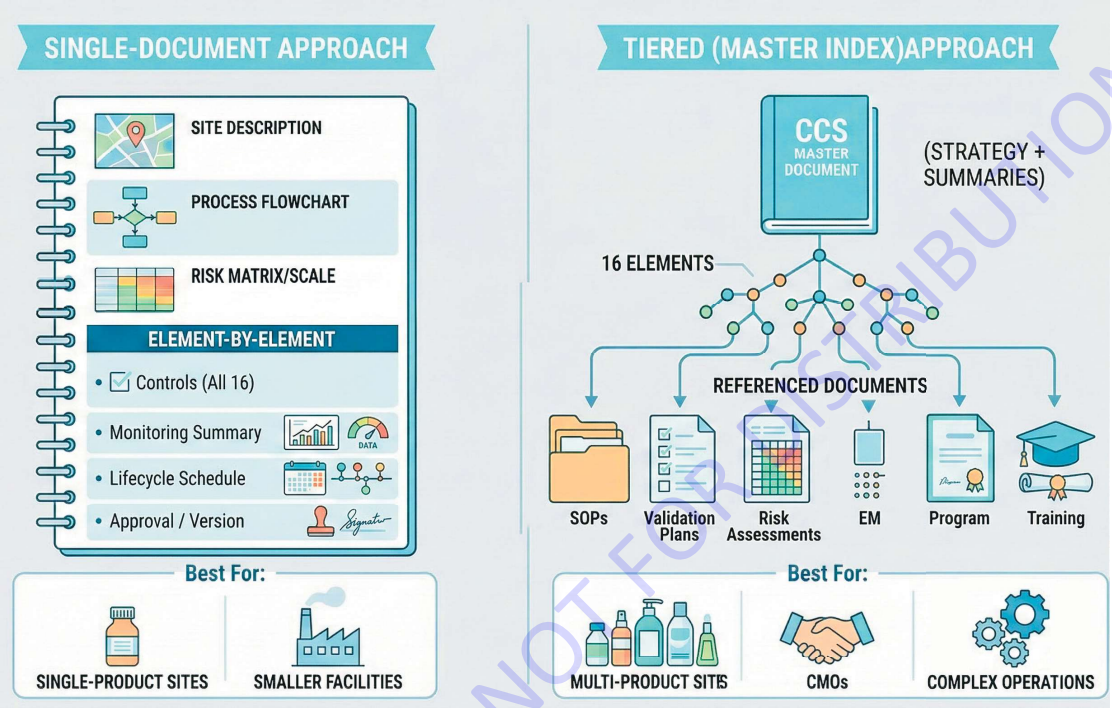
A tiered CCS uses a master document—sometimes called a CCS master index or CCS overview—that provides the strategic framework and references existing controlled documents (SOPs, validation protocols, monitoring programs, risk assessments) for the operational detail. The master document describes your contamination control philosophy, identifies each of the 16 Annex 1 elements, summarizes the controls and monitoring strategies for each, and provides document references for the detailed procedures. The supporting documents already exist in your quality management system—the CCS master document connects them into a coherent strategy.

This approach works well for larger sites, multi-product facilities, and contract manufacturing organizations (CMOs) where different products may have different contamination risk profiles. The master index stays manageable in length (typically 30–60 pages), while the detailed procedures remain in the controlled documents where your operators and technicians already use them.

Whichever approach you choose, one principle is non-negotiable: your CCS must describe controls, not merely list document numbers. A CCS that says “Gowning is addressed in SOP-GOW-001” without describing what the gowning controls are, why they are appropriate for your facility, and how you know they are effective is just a document index. Inspectors have made this distinction

clearly in recent years, and a CCS that reads like a table of contents will not satisfy the Annex 1 requirement.

FIGURE 5.1 — Two Approaches to CCS Document Architecture.



The single-document approach combines all content in one controlled document. The tiered approach uses a master document that references existing controlled documents for operational detail. Either is acceptable provided the CCS describes controls.

5.4 Developing a CCS: The Step-by-Step Process

Building a CCS can feel overwhelming, especially if your site has never had one. The key is to approach it systematically. The following ten-step process provides a practical framework you can adapt to your organization.

Step 1: Assemble the Multidisciplinary Team

The CCS cannot be written by a single department. Annex 1 §2.3 requires that the CCS be implemented across the facility and actively reviewed as part of periodic management review. In practice, developing and maintaining an effective CCS is best done with cross-functional expertise—microbiology, quality assurance, production, engineering (HVAC and utilities), validation, and regulatory affairs at a minimum. For facilities using contract sterilization services or outsourced testing, include supply chain or vendor management representatives as well. If your site

manufactures biological products, include a subject matter expert in biological safety. The team lead should have sufficient authority to drive decisions and allocate resources.

Step 2: Define the Scope

Before you write anything, define what your CCS covers. Is it site-wide or specific to a particular manufacturing area? Does it cover all products or only sterile products? Does it include support areas such as warehousing, weighing, and component preparation? For most sterile manufacturing sites, the CCS should be site-wide, covering all areas that contribute to or could affect the sterility assurance of finished products. Document the scope clearly at the beginning of your CCS.

Step 3: Map Contamination Sources and Routes

Using the framework from Chapter 3, identify all potential contamination sources and routes relevant to your facility and processes. This includes microbial, particulate, endotoxin, and chemical contamination. Map these to specific areas, equipment, utilities, materials, and personnel activities. This step builds the risk landscape that your CCS will address.

Step 4: Identify Critical Control Points

For each contamination source and route, identify the points in your process where contamination risk is highest and where a control failure could directly affect product quality or patient safety. These are your critical control points. Examples include the aseptic filling zone, the point where a sterilized container exits the depyrogenation tunnel, the connection point for a sterile filter, and the moment a stopper is placed on a vial.

> **IN PLAIN TERMS — Critical Control Point**
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> A critical control point is a step, location, or moment in your manufacturing process where failure of a contamination control could allow a contaminant—microorganism, particle, or endotoxin—to reach or affect the drug product. Identifying your critical control points is the first step toward knowing where your controls matter most.

Step 5: Assess Existing Controls Against Each CCS Element

Walk through each of the 16 CCS elements listed in Annex 1 §2.5 and document the controls you currently have in place. For each element, describe the control, the rationale for the control, the acceptance criteria, and the monitoring or verification method. This is the core of your CCS—it transforms your separate programs into a single, integrated strategy.

Step 6: Perform Gap Analysis

Compare your existing controls against the Annex 1 requirements and against your own risk assessment. Where are the gaps? Where do you have controls that are undocumented? Where do you have risks that are unmitigated? Where is your monitoring insufficient to detect a control

failure? Document every gap, no matter how small. A thorough gap analysis now prevents unpleasant surprises during an inspection later.

Step 7: Risk-Rank Identified Gaps

Not all gaps are equal. Use the quality risk management tools described in Chapter 6—such as failure mode and effects analysis (FMEA) or hazard analysis and critical control points (HACCP)—to risk-rank your gaps. Focus your resources on the highest-risk gaps first. Document the risk ranking and the rationale for prioritization.

Step 8: Define Additional Controls and Acceptance Criteria

For each identified gap, define the additional controls needed, the acceptance criteria, and the monitoring or verification method. Where possible, prioritize higher-level controls (engineering controls, design changes) over lower-level controls (administrative procedures, PPE). This aligns with the hierarchy of contamination controls discussed in Chapter 3.

Step 9: Document, Approve, and Communicate

Write the CCS document (or master index), have it reviewed and approved through your quality management system, and communicate it to all relevant personnel. The CCS should be a controlled document with a defined approval workflow, version history, and change control process. Importantly, communicate the CCS beyond the people who wrote it—production operators, maintenance technicians, and warehouse staff all contribute to contamination control and should understand how their work fits into the broader strategy.

Step 10: Establish the Review Cycle and Lifecycle Triggers

Define how often the CCS will be reviewed (at least annually is common practice), who is responsible for the review, and what triggers an unscheduled review. Section 5.7 discusses lifecycle management in detail.

5.5 The CCS Elements of Annex 1 §2.5 (i–xvi) — What Each One Means in Practice

Annex 1 §2.5 lists 16 elements (i–xvi) that should be considered within the CCS. The phrase “should include (but are not limited to)” is important—it means that all 16 must be considered, but the depth of your controls for each will depend on your risk assessment, and additional topics beyond the listed 16 may also be relevant to your facility. A site using terminally sterilized products will have different control priorities than one performing aseptic filling. The following discussion explains each element in practical terms.

(i) Plant and Process Design Including Documentation

Your facility and process design are your first lines of defense against contamination. This element covers how your manufacturing areas are laid out, how personnel, materials, and products flow through the facility, and how the design itself prevents contamination. Your CCS should describe the

design philosophy, reference the relevant facility drawings, and explain how the design supports contamination prevention. Key questions: Does your facility design separate clean and dirty flows? Are there adequate airlocks and pass-throughs? Is unidirectional flow maintained in critical areas?

(ii) Premises and Equipment

This element addresses the physical environment and the equipment within it. Your CCS should describe how cleanrooms are constructed, how equipment is qualified, and how both are maintained to prevent contamination. Surface finishes, ease of cleaning, equipment design (eliminating dead legs, minimizing crevices), and the qualification status of critical equipment all belong here.

(iii) Personnel

Personnel are consistently the dominant contamination source in sterile manufacturing environments, as discussed in Chapters 1 and 3. This element covers gowning procedures, aseptic technique training, personnel monitoring, health screening, behavior rules in classified areas, and maximum occupancy limits. Your CCS should describe how you manage the human contamination risk and how you verify that your controls are effective—through gown qualification, personnel environmental monitoring, and intervention assessment during media fills.

(iv) Utilities

Water systems, HVAC, compressed gases, steam, and other utilities are potential contamination vectors. Your CCS should describe the grade of each utility, the monitoring strategy, the alert and action limits, and the maintenance program. Pay particular attention to water for injection (WFI) systems, where biofilm formation is a persistent risk, and to HVAC systems, where HEPA filter integrity is essential to maintaining classified environments.

(v) Raw Material Controls and In-Process Controls

Materials entering your facility—active pharmaceutical ingredients, excipients, primary packaging components, and process consumables—carry contamination risk. Your CCS should describe incoming material testing, sampling plans, supplier qualification, and any material-specific decontamination or depyrogenation steps. In-process controls, such as bioburden testing before sterilization, belong in this element as well.

(vi) Product Containers and Closures

Containers and closures (vials, stoppers, syringes, ampoules) are the final barrier between your product and the environment. This element addresses container-closure integrity testing, washing and depyrogenation processes, and the validation of sterilization or decontamination methods for components. Container-closure integrity is especially critical for products with extended shelf lives.

(vii) Vendor Approval

Annex 1 specifically mentions key component suppliers, sterilization of components, single-use systems (SUS), and critical service providers. Your CCS should describe how you qualify and monitor vendors whose products or services directly affect contamination risk. This includes component suppliers, contract sterilization providers, SUS manufacturers, and environmental monitoring service providers.

(viii) Management of Outsourced Activities

If any contamination-critical activity is outsourced—such as contract sterilization, sterility testing, or fill-finish operations—your CCS must describe how responsibilities are defined, how information is transferred between parties, and how you verify that the outsourced activity meets your contamination control requirements. This is especially relevant for sponsors using CMOs for sterile manufacturing.

(ix) Process Risk Management

This element connects your CCS directly to the quality risk management framework described in Chapter 6. Your CCS should reference the risk assessments that informed your contamination controls and explain how risk is managed throughout the product lifecycle. Risk assessment feeds into every CCS review.

(x) Process Validation and Ongoing Process Verification

Your CCS should describe how your contamination control measures are validated and how you verify their continued effectiveness. This includes process validation (demonstrating that your manufacturing process consistently produces sterile product), cleaning validation, sterilization validation, and the continued process verification activities that confirm ongoing control.

(xi) Validation of Sterilization Processes

This element addresses validation of all sterilization methods used at your site—moist heat, dry heat, radiation, ethylene oxide, filtration—and is distinct from element (x) because it focuses specifically on the assurance that sterilization processes consistently achieve the required sterility assurance level. Your CCS should describe the method selected for each product and component, the rationale for that selection, and the validation approach. Chapters 9 through 15 cover individual sterilization methods in detail.

(xii) Preventive Maintenance of Premises and Equipment

Annex 1 §2.5(xii) specifically calls out preventive maintenance—both planned and unplanned—as a CCS element. Equipment that is not maintained will eventually fail, and equipment failure is a contamination risk. Your CCS should describe the preventive maintenance program for all contamination-critical equipment, including HVAC systems, autoclaves, filling equipment, HEPA

filters, and water system components. The maintenance schedule, calibration program, and spare parts strategy all contribute to contamination control.

(xiii) Cleaning and Disinfection

Cleaning removes residues; disinfection reduces microbial load. Both are essential to contamination control. Your CCS should describe the cleaning and disinfection programs for each classified area, the agents used, the rotation schedule, the contact times, and the validation evidence supporting their effectiveness. Chapter 27 provides detailed guidance on cleaning and disinfection.

(xiv) Monitoring Systems

Environmental monitoring, water monitoring, compressed gas monitoring, and other measurement systems provide the data that tells you whether your contamination controls are working. Annex 1 §2.5(xiv) also specifically references the feasibility of introducing scientifically sound alternative methods that optimize detection of environmental contamination—a nod toward rapid microbiological methods. Your CCS should describe what you monitor, where, how often, with what methods, and what limits apply. It should also describe how you trend the data and how you respond when limits are exceeded. Chapter 21 covers environmental monitoring program design.

(xv) Prevention Mechanisms

When things go wrong—an environmental monitoring excursion, a sterility test failure, a deviation from a cleaning procedure—your response is part of your contamination control strategy. Annex 1 §2.5(xv) groups trend analysis, detailed investigation, root cause determination, and corrective and preventive actions (CAPA) together as prevention mechanisms. Your CCS should describe how you connect individual events to systemic patterns and how you use trending data to drive improvement. The emphasis on “comprehensive investigational tools” signals that inspectors expect more than superficial root cause analysis.

(xvi) Continuous Improvement

The final listed element is arguably the most important. Annex 1 §2.5(xvi) states simply: continuous improvement based on information derived from the above. This closes the loop—your CCS is not a static document but a system that learns from its own data. Contamination control is also a cultural exercise. If your operators do not believe in the importance of gowning procedures, if your managers do not allocate resources for preventive maintenance, if your quality team does not follow up on adverse trends, then no amount of documentation will protect your product. Your CCS should describe how senior management is involved in reviewing CCS effectiveness, how you foster a culture of contamination awareness, and how you drive continual improvement. This connects directly to the PQS and ICH Q10 management review expectations.

5.5.1 Additional CCS Topics Referenced Elsewhere in Annex 1

The 16 elements of §2.5 are explicitly described as a non-exhaustive list ("should include but are not limited to"). Several additional topics are addressed elsewhere in Annex 1 and are commonly included in a comprehensive CCS. These include: material, equipment, and component transfer procedures between classified areas (e.g., Annex 1 §4.10–§4.12); establishment of maximum hold times where relevant (examples appear in multiple sections, including §7 for sterilized garments and §8 for components/packaging and process timing); specific process considerations for technologies such as Form-Fill-Seal and lyophilization (§8); and the principles for managing personnel, material, and product flows through cleanroom grades/zones and critical zones (e.g., segregation, airlocks, transfer disinfection, barrier technology) described across Premises, Personnel, Utilities, and Production. While these topics are not enumerated as §2.5 elements, they should be considered in your CCS where they are relevant to your facility and processes.

5.6 Risk Assessment Within the CCS

The CCS is a risk-based document. This means that the depth and rigor of your controls for each element should be proportionate to the contamination risk that element represents to your product and your patient. A simple compliance checklist—treating every element with equal weight regardless of risk—is not what Annex 1 intends.

Risk assessment within the CCS connects directly to the ICH Q9(R1) framework, which is discussed in detail in Chapter 6. For the purposes of CCS development, the key principles are: identify the hazards (contamination sources and routes), estimate the probability and severity of harm, evaluate whether your existing controls are adequate, and decide what additional controls are needed. The CCS documents the outcomes of this risk assessment and the rationale for your decisions.

One concept that deserves particular attention is residual risk—the contamination risk that remains after you have applied all your controls.

> **IN PLAIN TERMS — Residual Risk**
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> Residual risk is the contamination risk that remains after you have applied all your controls. No manufacturing process can eliminate contamination risk entirely. The question is whether the remaining risk is acceptable—and your CCS must document both the residual risk level and the rationale for accepting it. If residual risk is unacceptable, you need additional controls, a process redesign, or a different manufacturing technology.

Annex 1 §2.4 makes a critical point about risk assessment: contamination control measures are typically assessed individually, but *their collective effectiveness should be considered together.* This means you should not evaluate your HVAC system in isolation from your gowning program, or your cleaning validation separately from your environmental monitoring. The CCS risk assessment must

consider how all your controls interact—because a weakness in one area can undermine the effectiveness of controls in another.

A practical example illustrates this point. Consider a facility that has excellent HVAC design (Grade A unidirectional airflow, appropriate pressure differentials, validated HEPA filters) but poor gowning compliance (operators frequently adjusting face masks, touching exposed skin, entering classified areas with improper gown integrity). The HVAC controls are individually strong, but their effectiveness is degraded by the personnel controls. A CCS risk assessment that evaluates each element separately might rate both as "acceptable." A holistic assessment would recognize that the combined system has a vulnerability that needs to be addressed.

5.7 The CCS as a Living Document: Lifecycle Management

Annex 1 §2.3 is explicit: the CCS should be actively reviewed and, where appropriate, updated, and its effectiveness should form part of the periodic management review. A CCS that is written once and never revisited is not compliant—and it is not effective.

> **IN PLAIN TERMS — Lifecycle Management**
> Lifecycle management means treating your CCS as a living document that evolves as your facility, processes, products, and knowledge change. It includes scheduled periodic reviews, triggered reviews in response to specific events, effectiveness metrics, and a formal change control process. The CCS is never "finished"—it is continuously maintained.

In practice, CCS lifecycle management involves two types of review: periodic scheduled reviews and event-triggered reviews.

5.7.1 Periodic Reviews

Most sites establish an annual CCS review cycle, aligned with the annual product quality review or management review process. During the periodic review, the multidisciplinary team evaluates whether the controls described in the CCS are still appropriate, whether the monitoring data supports continued effectiveness, and whether any changes to the facility, processes, or regulatory requirements require updates to the CCS. The outcome of the periodic review should be documented, approved, and reflected in an updated (or re-confirmed) version of the CCS.

5.7.2 Event-Triggered Reviews

Certain events should trigger an unscheduled CCS review. These include:

- Regulatory changes affecting contamination control requirements
- Significant process changes or new product introductions
- Facility modifications (new cleanrooms, HVAC changes, equipment replacement)

- Adverse environmental monitoring trends (sustained excursions, new organisms)
- Sterility test failures or major contamination deviations
- Audit or inspection findings related to contamination control
- Closed CAPAs that revealed systemic contamination control gaps
- Closed investigations that identified new contamination sources or routes
- Introduction of new materials, consumables, or reagents that contact the product or classified environment
- Technology changes (e.g., transition from conventional cleanroom to RABS or isolator)
- Changes in outsourced activities or contract manufacturing arrangements

5.7.3 Measuring CCS Effectiveness

Annex 1 requires that the effectiveness of the CCS forms part of the management review. But how do you measure whether your CCS is effective? The answer lies in your data. Environmental monitoring trending, sterility assurance metrics, deviation rates, contamination-related CAPA effectiveness, audit findings, and product quality review outcomes all provide evidence of CCS effectiveness. Section 5.12.1 provides a practical set of key performance indicators (KPIs) that you can use to evaluate your CCS.

5.8 When Contamination Controls Fail to Connect

CASE STUDY — Catalent Indiana, LLC / Novo Nordisk, Bloomington, Indiana (2025)

What happened: In mid-2025, the FDA inspected a fill-finish facility in Bloomington, Indiana, owned by Novo Nordisk following the completion of Novo Holdings' acquisition of Catalent (enterprise value ~US$16.5B, closed 18 December 2024), after which Novo Nordisk acquired selected Catalent fill-finish sites. The FDA Warning Letter (MARCS-CMS 718189, November 20, 2025), based on the June 23–July 14, 2025 inspection, cited significant cGMP violations. The letter described repeated deviations involving extrinsic "mammalian hair" contamination found in or around vial stopper regions and criticized the facility for releasing batches in which customers subsequently found contamination. According to Scholar Rock's public disclosure (October 10, 2025), the FDA determined the site's inspection classification was Official Action Indicated (OAI)—the agency's most serious post-inspection classification.

What went wrong: The FDA Warning Letter specifically cited failures to adequately investigate more than 20 deviations linked to possible mammalian hair contamination, and to establish adequate written procedures to prevent microbiological contamination of sterile drug products (21 CFR 211.113, 211.192). The facility had contamination control elements in place, but the FDA's findings indicate these elements were not functioning as an integrated system. Investigations did not determine root causes, did not assess impact on other lots, and did not evaluate whether similar issues had occurred in other batches. Additional details were reported in a copy of the Form 483 circulated by media; details should be confirmed against the underlying Form 483/EIR when available.

The CCS lesson: This case illustrates precisely why Annex 1 mandates a formal, documented, and integrated CCS. Having individual contamination control elements is not sufficient. If those elements are not connected through a single strategic document that links risk assessment, monitoring, investigation,

trending, and CAPA, contamination signals can be missed and systemic problems can persist. A functioning CCS with effective lifecycle management would connect recurring complaints, equipment issues, and environmental monitoring results into a single risk picture—enabling earlier detection and corrective action.

Sources: (1) FDA Warning Letter, Catalent Indiana, LLC (MARCS-CMS 718189), November 20, 2025. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/catalent-indiana-llc-718189-11202025. (2) Scholar Rock public statement, October 10, 2025 (OAI classification). https://scholarrock.com/our-company/newsroom/update-on-third-party-manufacturing-site/. (3) Novo Holdings. "Novo Holdings Completes Acquisition of Catalent." 18 December 2024. https://novoholdings.dk/news/novo-holdings-completes-acquisition-of-catalent. (4) Additional details were reported in a copy of the Form 483 circulated by media (STAT News); details should be confirmed against the underlying Form 483/EIR when available.

5.9 Common Mistakes in CCS Development and Implementation

Having reviewed CCS documents from multiple sites and examined regulatory inspection findings, several patterns of failure emerge consistently. Recognizing these common mistakes can help you avoid them in your own CCS.

Mistake 1: Treating the CCS as a One-Time Compliance Document

Some sites write a CCS to satisfy an inspection requirement and then file it away. This defeats the purpose. The CCS must be a working document that is referenced during deviation investigations, cited in management reviews, and updated when conditions change. If your CCS has not been revised in over a year, that is a warning sign.

Mistake 2: Writing a Document Index Instead of a Strategy

A CCS that lists document numbers without describing the controls themselves, the rationale for those controls, or how effectiveness is measured is not a strategy. Inspectors have identified this pattern repeatedly. Your CCS must describe what you do, why you do it, and how you know it works.

Mistake 3: Excluding Key Stakeholders

A CCS written entirely by the quality assurance department, without input from engineering, microbiology, production, or utilities, will have blind spots. Contamination control is inherently multidisciplinary—your CCS must reflect that. If the people who operate and maintain your equipment did not contribute to the CCS, the document will not accurately represent your facility's contamination control landscape.

Mistake 4: Omitting Risk Assessment Outcomes and Residual Risk

A CCS that describes controls but does not include the risk assessments that informed those controls—or that fails to document residual risk—is incomplete. Inspectors will ask why you chose

specific controls and how you know they are sufficient. Without documented risk assessments, you cannot answer these questions credibly.

Mistake 5: No Review Cycle

A CCS without a defined review schedule and documented review history is not a living document. Establish a review cycle (at least annual), assign responsibility, and document every review—even if the outcome is that no changes are required.

Mistake 6: Treating Legacy Systems as Exempt

Annex 1 §2.3 states that where existing control systems are in place and appropriately managed, they may not require replacement but should be referenced in the CCS and their interactions understood. Some sites interpret this as permission to exclude legacy equipment or processes from the CCS. It is not. Every control that contributes to contamination prevention—whether new or legacy—belongs in the CCS.

Mistake 7: Confusing the CCS with Other Documents

The CCS is not a validation master plan, not a site master file, and not an environmental monitoring program. While the CCS references and connects to all of these, it is a distinct document with a distinct purpose: to describe how all your contamination controls work together as an integrated system. Keep the boundaries clear.

5.10 CCS for Multi-Product and Contract Manufacturing Sites

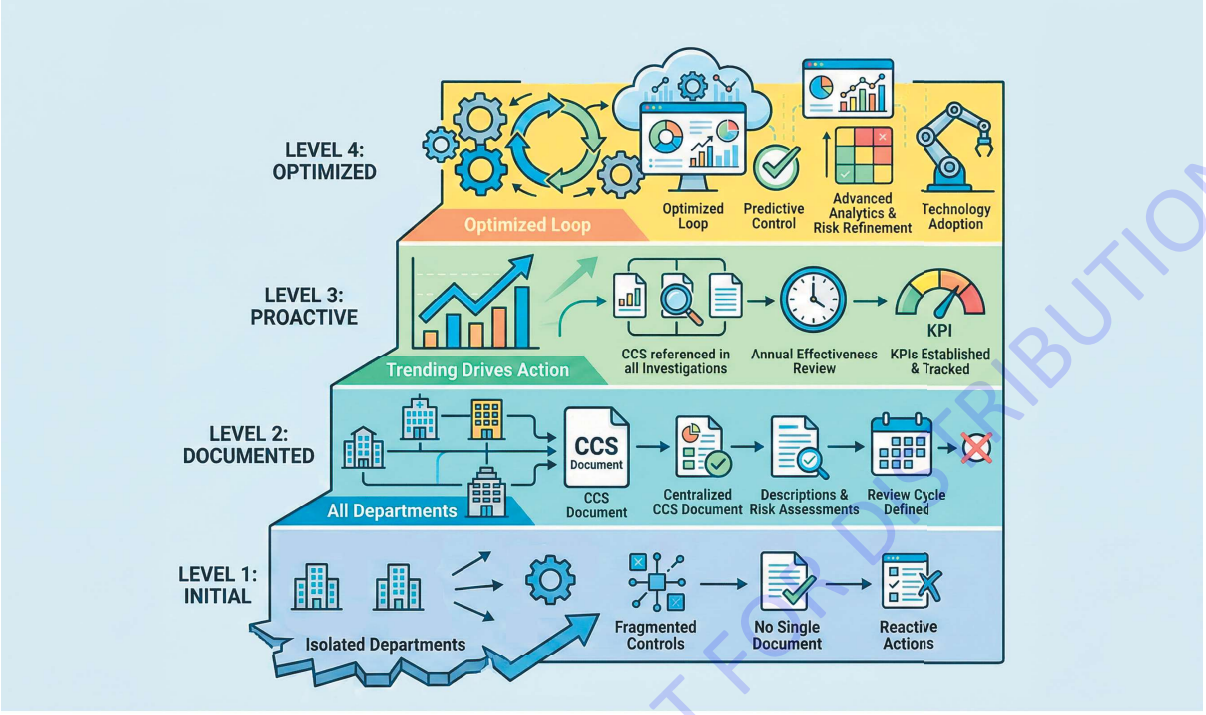
Multi-product sites and contract manufacturing organizations (CMOs) face unique challenges in CCS development. When your facility manufactures multiple products—potentially for multiple sponsors—you need to manage the CCS at two levels.

Site-wide CCS elements include facility design, HVAC, utilities, cleaning and disinfection programs, environmental monitoring, personnel gowning, and general maintenance. These are common to all products manufactured at the site and form the backbone of the CCS.

Product-specific CCS elements address the unique contamination risks of individual products, such as specific bioburden limits, product-specific hold times, dedicated equipment, or particular sterilization methods. For a CMO, product-specific elements may include sponsor-defined requirements that go beyond the site's standard controls.

Annex 1 §2.5(viii) specifically addresses management of outsourced activities, requiring clear definition of responsibilities and availability of critical information between parties. For CMOs, this means the CCS must clearly document which contamination controls are the responsibility of the CMO and which are the responsibility of the sponsor. For sponsors using CMOs, your own quality oversight program should include review of the CMO's CCS (or relevant sections) and verification that your product-specific requirements are addressed.

FIGURE 5.2 — CCS Maturity Model



Most sites begin at Level 1 (fragmented controls) or Level 2 (documented but not fully operationalized). The goal is to progress toward Level 3 (proactive, data-driven) and ultimately Level 4 (optimized, predictive). Progression requires investment in data analytics, cross-functional collaboration, and a strong quality culture.

5.11 Regulatory Inspection Expectations: How Inspectors Assess Your CCS

When a regulatory inspector arrives at your facility, the CCS is increasingly one of the first documents they request. Understanding how inspectors assess the CCS helps you prepare effectively.

Inspectors evaluate the CCS on three dimensions. First, they check that the document exists, is approved, and covers all required elements. Second, they assess whether the CCS is operationalized—meaning it is actively used in daily operations, referenced in deviation investigations, and reflected in training materials. Third, they verify that the CCS is maintained—meaning it has been reviewed within the defined review cycle and updated in response to changes.

Common inspection questions about the CCS include: "Show me your CCS." "When was it last reviewed?" "Who approved it?" "How do you know your CCS is effective?" "Show me a deviation investigation where the CCS was referenced." "What triggered the last update to your CCS?" If you can answer these questions confidently, with documented evidence, you are well prepared.

Since Annex 1 came into operation on 25 August 2023 (with point 8.123 postponed until 25 August 2024), CCS has increasingly appeared in publicly shared MHRA inspection-finding discussions. For example, a UK radiopharmacy inspection-findings summary reported CCS-related deficiencies (e.g.,

'no active CCS' and CCS not adequately addressing effectiveness of controls). The level of emphasis and the specific expectations may vary by inspection scope and site risk profile.

> **⚠ REGULATORY OBSERVATION — CCS Absent or Inadequate — MHRA Inspection Findings at UK Radiopharmacy Units (2024–2025)**
>
> *MHRA inspections of UK radiopharmacy units, as summarized by Dr. Maggie Cooper, UKRG Secretary (May 2025). Source: https://cdn.ymaws.com/www.bnms.org.uk/resource/resmgr/ukrg/resources/ukrg_mhra_findings_document.pdf*
>
> In a publicly shared summary of MHRA inspection findings at UK radiopharmacy units, the following CCS-related deficiencies were reported as Critical and Major findings under the heading "Sterility Assurance": (1) The site had no active contamination control strategy (CCS). (2) The contamination control strategy did not adequately address the effectiveness of controls and monitoring measures to establish a robust assurance of contamination prevention. (3) Compliance with EU GMP Annex 1 was not assured—a risk assessment to address the gaps with Annex 1 requirements did not describe suitable actions or mitigations. (4) The Annex 1 gap assessment had no evidence of actions with target dates or steps taken to assess and mitigate the currently identified risks. The summary noted that this was the first time since the 2022 Annex 1 update that CCS-related findings had appeared in MHRA inspections of these facilities. For your site, these findings reinforce that having no CCS, or having a CCS that does not link controls to effectiveness evidence, is a tangible inspection risk under the current regulatory framework.

> **✓ LESSONS LEARNED — What "Operationalized" Means in Practice**
>
> The CCS must be more than a document in a folder. It must be referenced in SOPs, training materials, deviation investigations, and management reviews. It is the strategic backbone that connects all your contamination control activities. When you investigate a deviation, you should be asking: which CCS element does this affect? When you train a new operator, the CCS should frame why each gowning step matters. When you conduct a management review, CCS effectiveness metrics should be on the agenda. If your CCS is not actively referenced in your daily quality operations, it is not operationalized—regardless of how thorough the document itself may be.

5.12 Building Your CCS: A Practical Starting Template

Table 5.2 provides a practical CCS development checklist organized by the Annex 1 §2.5 elements. You can use this as a starting framework to assess your current state and identify gaps.

Table 5.2 — CCS development checklist. Use this framework to assess your current contamination control documentation against the 16 Annex 1 §2.5 elements. The Status column can be marked as complete (☑), in progress (◔), or not started (□).

CCS Element (Annex 1 §2.5)	Key Questions for Your Site	Status
(i) Plant/process design	Is facility layout documented? Flows defined?	□
(ii) Premises/equipment	Equipment qualified? Surfaces suitable?	□
(iii) Personnel	Gowning validated? Max occupancy defined?	□
(iv) Utilities	Water/HVAC monitored? Limits justified?	□
(v) Raw materials	Incoming testing defined? Suppliers qualified?	□
(vi) Containers/closures	Integrity testing validated? Depyrogenation documented?	□
(vii) Vendor approval	Critical suppliers audited? SUS qualified?	□
(viii) Outsourced activities	Responsibilities defined? Information transfer?	□
(ix) Process risk management	Risk assessments current? Residual risk documented?	□
(x) Process validation	Validation current? CPV in place?	□
(xi) Sterilization validation	Methods validated? BIs/CIs used?	□
(xii) Preventive maintenance	PM schedule current? Calibration tracked?	□
(xiii) Cleaning/disinfection	Agents qualified? Rotation documented?	□
(xiv) Monitoring systems	EM program justified? Trends reviewed?	□
(xv) Prevention mechanisms	Root cause methods defined? Trending systematic?	□
(xvi) Continuous improvement	Management review includes CCS? CI program?	□

5.12.1 CCS Effectiveness: Key Performance Indicators

Annex 1 requires that the effectiveness of the CCS forms part of the management review. The following indicators can help you measure whether your CCS is delivering the intended outcome. These represent the types of data that demonstrate whether your contamination controls are working as a system.

Table 5.3 — Example KPIs for CCS effectiveness measurement. These metrics should be trended over time and reviewed as part of the annual CCS and management review cycle.

KPI Category	Example Metric	What It Tells You
Environmental monitoring	EM excursion rate (action limit) per period	Whether classified environments are consistently controlled
Sterility assurance	Sterility test failure rate per period	Whether your overall sterility assurance system is effective
Deviation/CAPA	Contamination-related deviation rate; CAPA effectiveness (recurrence rate)	Whether investigations identify true root causes and CAPA prevents recurrence
Personnel	Gown qualification failure rate; personnel EM recovery rate	Whether your personnel controls are adequate

KPI Category	Example Metric	What It Tells You
CCS maintenance	Time since last CCS review; number of triggered reviews completed vs. due	Whether the CCS is being maintained as a living document
Process capability	Media fill success rate; process hold time compliance	Whether your aseptic processes and validated parameters are under control

DID YOU KNOW?

EU GMP Annex 1 (2022) foregrounds Quality Risk Management (QRM) early in its text (§2.2) and introduces the CCS immediately after (§2.3)—placing it in the opening paragraphs of the entire regulation. Annex 1 (2022) is among the first major GMP frameworks to explicitly require a documented, facility-wide CCS as an integrated strategy. The Annex 1 glossary defines the CCS as "a planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding." The aligned PIC/S Annex 1 carries the same requirement, and PIC/S member authorities—comprising 57 Participating Authorities (as of 2026)—now apply the CCS expectation in their inspections, making it a de facto global standard for sterile manufacturing sites.

The CCS is not what you write — it is what you do. A 200-page CCS that sits in a drawer while your facility runs on undocumented institutional know-how is not a contamination control strategy.

5.13 How This Chapter Connects to Regulatory Requirements

The CCS concept connects to multiple regulatory frameworks. The following table maps the key topics covered in this chapter to specific regulatory requirements.

Table 5.4 — Regulatory alignment: connections between Chapter 5 content and specific regulatory requirements.

Regulatory Document	Specific Requirement	Chapter 5 Connection
EU GMP Annex 1 (2022), §2.2–2.7	CCS must be implemented, actively reviewed, and its effectiveness included in management review.	Sections 5.2, 5.7, 5.11
EU GMP Annex 1 (2022), §2.5	16 CCS elements (i–xvi) that should be considered within the CCS.	Sections 5.5, 5.12 (Table 5.1, Table 5.2)
ICH Q9(R1) — Quality Risk Management	Risk assessments should be science-based and use appropriate tools (FMEA, HACCP, etc.).	Section 5.6 (detailed tools in Ch. 6)
ICH Q10 — Pharmaceutical Quality System	Senior management oversight, continual improvement, quality culture.	Section 5.5 (element xvi); Sections 5.7 and 5.12.1

Regulatory Document	Specific Requirement	Chapter 5 Connection
FDA 21 CFR 211.113	Written procedures to prevent microbiological contamination of sterile drug products.	Sections 5.2.2, 5.8 (case study)
FDA 21 CFR 211.192	Thorough investigation of unexplained discrepancies, with written record.	Section 5.5 (element xv); Section 5.8 (case study)
PIC/S GMP Guide	Aligned with EU GMP Annex 1 CCS requirements through PIC/S harmonization.	Section 5.2.2

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