**Contamination Control Strategy Template:**

**Aseptic preparation**

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1. Introduction

Include an introductory section in your CCS - suggested wording

*A Contamination Control Strategy (CCS) is implemented across this facility in order to define all critical control points and to assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to the quality and safety of aseptically prepared medicines (under Section 10 exemption).*

*The importance of maintaining microbiological, endotoxin and particulate quality of products is understood and applied through a series of overarching controls. The CCS considers all integral elements of aseptic preparation, including Quality Risk Management (QRM) principles (described in ICH Q9). It supports risk assessment of contamination control and monitoring (detectability of contamination event) systems. The CCS promotes the consideration of isolated contamination events within wider performance parameters and holistic application of CAPA.*

*The CCS requires active review and will drive continuous improvement of the preparation and control methods, with updates when new methods or technologies are implemented.*

1. Definitions and abbreviations

Include a table of definitions and abbreviations you have used in the CCS.

1. Purpose

Describe the purpose of your CCS - suggested wording:

*The CCS serves as an overview of the quality assurance arrangements in place which contribute to a state of environmental control. This document has been structured to describe these controls and will often refer to more detailed policies and procedures containing said controls. The CCS can also be used as an effective tool when reviewing the impact of change or deviations to existing controls in order to understand the areas impacted by that change or deviation.*

1. Scope

Describe the scope of your CCS. (It is essential to include areas outwith pharmacy e.g. plant rooms where aseptic teams should have suitable oversight and understanding of the maintenance activities which may impact on the facility).

Suggested wording:

*The CCS describes all control measures, and aids units in considering and assessing the overall state of control in terms of microbiological, non-viable particulate and endotoxin/pyrogenic contamination.*

*The CCS is applicable to all activity carried out on site, including plant areas, which may be accessed by contractors or Estates departments.*

Explanatory note: Although significant consideration will be given to microbiological and non-viable particulate contamination, chemical contamination will also require inclusion under certain elements.

1. Responsibilities

Include roles of relevant staff involved in the development and maintenance of the CCS.

In addition, responsibilities for compliance with the various concepts, procedures and policies described in the CCS should be defined in the individual procedures referenced.

1. Site Overview

Provide an overview of your unit - suggested wording:

*This site operates under Section 10 exemption regulatory framework. Aseptic preparation of sterile medicines from licensed starting materials using closed system transfers in response to a prescription for individual patients is carried out. Products are assigned a maximum expiry of 8 days and stored between 2-8°C wherever stability data permits. All activity is carried out under the supervision of a pharmacist.*

*Open systems may be utilised for emergency eye drop preparation under defined circumstances.*

Information to be considered within this section of the CCS :-

1. Site Description
2. Product range – include product presentation e.g. syringes, pumps etc. Include IMPs.
3. High level description of facilities and equipment (1-2 paragraphs)
4. High level description of preparation activity - include reference to any relevant site documents and include these in the table at the end of this section (site master file, quality manual)

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Site Master File |
|  | Quality Policy / Manual |
|  | Capacity / contingency plans |

1. Contamination Control Strategy

## **Design of Plant and Process**

Introductory text – suggested wording

*Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable subjected to ongoing verification, according to relevant sections of Good Manufacturing Practices guidelines (Annex 1, MHRA, 2022)*

Explanatory note: For the purposes of this template, plant is considered to be fixed equipment such as the Air Handling Unit and associated HVAC equipment (e.g. heating, cooling, dehumidification, extract, ductwork, energy recovery, and recirculation systems) involved with supplying filtered air to the terminal HEPA filters located in the cleanroom ceiling. There are separate sections for any utilities such as water or gas systems, where relevant. Premises are considered to be the cleanrooms themselves (see section ii).

* 1. Design of Plant

Introductory test - suggested wording :-

*Air handling plant (AHP) has been designed, installed and qualified to provide the requisite environment for the preparation of aseptic medicines.*

Controls to be considered within this element of the CCS :-

1. High level description of the plant room(s) containing:

* AHP
* Heating / Chiller plant
* Humidity Control where applicable
* Building Management System (BMS) / Control system
* Pre-filters / HEPA filters (grade and location in AHU)
* Planned Preventative Maintenance programme (or reference section 9)
* Schematic of ductwork

Explanatory note : The above may be included in other site documents such as the Site Master File. It is not necessary to duplicate information. Where it is contained in sufficient detail in another document which is part of the PQS, cross reference to this document may be sufficient.

The above may all be incorporated into a single, or multiple HVACs, be stand-alone or shared. Provide a high level overview of the plant, include references to original URS/IQ/OQ and describe the general approach to maintenance (annual/biannual/quarterly/monthly/weekly service and checks). Reference should be made to the Technical agreements with Estates/contractors in the table below. Include alarms and out-of-hours response to failures.

Include reference to any risk assessments available for AHP failure and impact on contamination control.

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Site Master File |
|  | URS for AHU if separate from cleanrooms and general premises |
|  | DQ/IQ/OQ/PQ of plant |
|  | Validation policy |
|  | Calibration policy / standard operating procedures |
|  | Alarm and OOH call out |
|  | Technical Agreements with service providers / Estates |
|  | Planned preventative maintenance schedule |
|  | Planned preventative maintenance reports and repairs |

## Design of Processes

Introductory test - suggested wording :-

*Processes are designed to reduce the potential for contamination. A general hierarchy of control is applied to products prepared, and only when one method of preparation is deemed not feasible or impractical, is the next level considered.*

*Several products may be qualified under a single process validation and link to an Aseptic Process Simulation (APS) which covers all stages of every relevant product included. Each process is subject to a Process Risk Assessment and is performed using an appropriate method such as FMEA, the output of which is a series of mitigating actions used to educate the APS design for that process or require changes to systems and/or equipment to lower the risk.*

*Periodic review of any unmitigated risks is performed in order to establish if developments in techniques, equipment or methods can be applied to further reduce the exposure to risk.*

Controls to be considered within this element of the CCS :-

1. Details of each process used - this would generally be any process for which the unit has an APS (Aseptic Process Simulation, or media fill)
2. Link each preparation process activity to the corresponding process risk assessment – identification and assessment of contamination risks to the final product
3. Material transfer
4. Operator entry

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Product list |
|  | Process maps |
|  | Risk assessments associated with process maps / activities |
|  | Standard operating procedures |

## **Premises and Equipment**

Introductory text – suggested wording :-

*In line with the definition of Premises vs. Plant in section i), it is also necessary to differentiate between Premises and Equipment. As already stated in section i), Premises is considered to be fixed items such as doors, transfer hatches, cleanrooms (walls, floors and ceilings), and fixed benches etc. that make up the fabric of the facility beyond that which is included in the definition of Plant.*

*Equipment is defined as the removable items (although in reality this may be difficult to do) such as isolators, autoclaves, LAFs, balances, extract hoods, computer systems etc. Technology solutions such as isolators, robotics and continuous monitoring systems are routinely considered as solutions for reducing the risk of contamination from extraneous sources.*

Explanatory note : There may be alternative definitions which for specific reasons may be more appropriate for a site, this template has been structured with the above definitions in mind, but alternative approaches may be suitable where this is clearly defined within the CCS or supportive documents.

## Premises

*Manufacture / preparation of sterile pharmaceuticals is carried out within a GMP compliant*

*cleanroom facility containing Grade A, B, C and D zones. Entry of personnel is achieved through*

*change areas and airlocks. Transfer of materials is carried out through dedicated interlocking*

*transfer hatches. HEPA filtered air is supplied to all critical areas at high level, with associated*

*extract at low level. A positive pressure cascade is maintained. All exposed surfaces are smooth*

*and constructed from impervious material. Recesses are limited.*

Controls to be considered within this element of the CCS :-

1. Provide an overview of the facility or reference to the relevant documents which contain the relevant information including:

* Cleanroom layout – include a floorplan. Determine the suitability of the layout, risk assess process flows and potential for mix up and contamination
* Construction materials
* Classification of each cleanroom – include a table with rooms and classifications
* Pressure cascade
* Airflow pattern
* Personnel flow
* Product flow
* Use of airlocks and transfer hatches
* Include storage areas

1. A description of the activity carried out in each cleanroom / area / zone may be necessary for larger facilities.
2. If there are any specific design features which are relevant, provide an overview where these are not detailed above. Examples of relevant aspects may be:

* Cleanrooms are designed with no uncleanable recesses, all corners formed with coving and the entire cleanroom is lined with welded vinyl
* Light fittings are designed to be changed from a walk-on ceiling to avoid the need to breach the cleanroom when changing bulbs
* Transfer hatches are fitted with local extract / active filtered air supply / air bleed from the higher to lower grade areas
* PAL / MALs are fitted with magnetic interlock mechanisms with a delay of x seconds to prevent ingress of dirty air during transit
* Use of a contamination control mat at entrance to change rooms – cleaned daily

1. Cleanroom qualification and classification – and requalification

* Installed filter system leakage and integrity testing
* Airflow tests – volume and velocity
* Airflow visualisation
* Particle concentration
* Pressure cascade
* Microbiological airborne and surface contamination
* Temperatures and humidity

Include information on how the facility operates and is classified, e.g. premises are designed to permit and maintain appropriate conditions for the activity carried out in that area. Cleanrooms are classified according to EU GMP classifications using methodology described in ISO 14644. Airflow visualisation studies have been performed to demonstrate appropriate protection of the critical zone and identify appropriate monitoring locations.

1. Details of planned and unplanned maintenance

## Equipment

Controls to be considered within this element of the CCS :-

1. Describe the equipment in use, e.g. positive / negative pressure closed isolators / open isolators / LAFs / BSCs. Where closed isolators are used, a justification for the background environment is required, this would normally be carried out using a risk assessment, reference this here. Open cabinets such as LAF / BSCs must be located in a Grade B background. Describe the activities for which the equipment is used.
2. Where isolators are used, describe the transfer devices (e.g. VHP systems / interlocked +ve pressure hatch etc.), integrity test methods and frequency etc.
3. Isolator systems are likely to include control panels (HMIs) which display operating conditions and alarms. These systems should also be described. Define what is considered a critical alarm (note, critical alarms must be acknowledged and addressed immediately following your PQS, this is a requirement of Annex 1)
4. Describe any other relevant equipment that contributes to the control of either microbiological, particulate or endotoxin / pyrogen contamination.
5. Include biodecontamination programme (see element (xiii)), glove change processes
6. Describe impact of potential loss of contamination barrier, e.g. glove/sleeve integrity.
7. Include qualification and classification – and requalification

* Installed filter system leakage and integrity testing
* Airflow tests – volume and velocity
* Airflow visualisation
* Particle concentration
* Microbiological airborne and surface contamination

1. Describe frequency of requalification testing
2. Planned preventative maintenance/ servicing /equipment out of use policy

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Site Master File |
|  | URS for AHU if separate from cleanrooms and general premises |
|  | DQ/IQ/OQ/PQ of plant |
|  | Validation policy |
|  | Calibration policy / standard operating procedures |
|  | Alarm and OOH call out |
|  | Technical Agreements with service providers / Estates |
|  | Planned preventative maintenance schedule |
|  | Planned preventative maintenance reports and repairs |
|  | Inventory log |

## **Personnel**

Introductory text – suggested wording :-

*Operators are the single greatest source of microbial and particulate contamination within the cleanroom. Validated procedures have been developed and implemented for operator entry to reduce risk. Operators should be appropriately qualified and trained in the design and validation of processes and be able to apply knowledge and skills to reduce risk of contamination. Evidence of acquisition of required knowledge is available and operators are signed off as competent in activities. Competency is re-evaluated periodically.*

Controls to be considered within this element of the CCS :-

1. Staff training e.g. induction, GMP, hygiene (reporting skin conditions), cleanroom practices, contamination control, aseptic techniques, safety implications of loss of product sterility, basic elements of microbiology, environmental monitoring
2. Cosmetic and jewellery policy
3. Cleanroom behaviour / comportment controls
4. Operator number restriction within cleanroom
5. Cleanroom garments – describe garment fabric specification and design e.g. non-shedding, durable, continuous filament thread, no pockets or pleats
6. Cleanroom clothing required for each grade of cleanroom
7. Use of sterile masks, sterile goggles, sterile gloves, socks etc. (include specification details as required).
8. Cleaning and sterilisation of cleanroom garments – processes and certification
9. Gowning processes and validation of these processes
10. Operator qualification / competency assessment for: Gowning, aseptic technique, transfer disinfection, glove donning/un-donning etc.
11. Operator disqualification
12. Access arrangements for visitors, untrained staff, maintenance contractors etc.

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Training programmes |
|  | Training records |
|  | Gowning procedures and validation |
|  | Authorisation certificates / statements |
|  | Garment, mask, glove specifications |
|  | Technical agreement with Cleanroom garment supplier – gamma irradiation certificates |

## 

## **Utilities**

Introductory text - suggested wording

*All aseptic units will be served by a variety of utilities. Utilities are designed, installed, maintained and monitored to ensure compliance with acceptance criteria. The potential for contamination of the clean work space arising from each of these utilities have been assessed and documented.*

Controls to be considered within this element of the CCS :-

1. Heating/cooling systems

Design; risk of breakage, leakage and contamination, presence of traps

1. Tap water systems - hand-washing facilities and potable water supply

Tap design allowing hands–free use (“elbow” type)

Use of water supplies - hand washing only or cleaning of any critical equipment e.g. work trays

If a dishwasher is used to clean work trays, check suitability of the water supply

Position of pipework e.g. in ceiling void space

1. Sinks & drains

Sink design – availability of anti-splash sinks, flood prevention

Position of sinks & drains relative to critical points/processes for contamination control e.g. room transfer hatches, storage of critical components

1. Pest control

Risks of ingress of pests

Pest control provision for the building - storage areas, loading areas subject to monitoring

1. Trending of operational parameters for utilities

Several of the above are suitable for trending to ensure no adverse trends are noted which may indicate loss of contamination control e.g. potable water CFU counts

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Tap water monitoring schedule and records |
|  | Sink and drain cleaning SOP, schedule and records |
|  | Pest Control Technical Agreement with provider |
|  | Pest Control Records |

## **v) Starting material control**

Introductory text - suggested wording :-

*For units operating under Section 10 all starting materials must be sterile. Most starting materials will be licensed products.*

Controls to be considered within this element of the CCS :-

1. Specifications

Use of terminally sterilised licensed products where possible. Most are licensed products but where this is not possible then sterile starting materials produced by UK MS holders should be used.

All exceptions to this must be listed and subject to individual risk assessment prior to use (Babiven; HAS; clinical trials materials). Sampling, testing (including microbiological and endotoxin) and release processes to be described.

1. Receipt and acceptance

All deliveries are checked for accuracy against the order and placed into storage by trained operators.

Soiled, wet or damaged goods are not accepted.

ULMs are placed into a quarantine area awaiting formal acceptance by trained staff

1. Storage

All starting materials are stored in a manner that protects them from contamination:

Cleaning of ambient storage areas

Training of cleaning staff where they are not Pharmacy staff

No eating, drinking, smoking in the store

Refrigerators/freezers are subject to cleaning on a regular schedule

Regular stores “walk round” audits are undertaken

Describe arrangements for recalled stock

1. Supplier approval – see (vii) Vendor approval

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Risk Assessments for all unlicensed starting materials |
|  | Storage SOPs |
|  | Temperature mapping and recording |
|  | Temperature excursion |
|  | Cleaning SOPs, schedule & records |
|  | Cleaner’s training records |
|  | Records of regular storage are audits and any CAPAs arising |

## **Product containers and closures**

Introductory text – suggested wording :-

*Processes associated with the packaging, finishing, storage and transport of sterile products should not compromise the sterile product (Annex 1, 2022). Final product containers are selected for their suitability for the intended application. They are procured from approved suppliers and may undergo inspection / testing on receipt as described below.*

Controls to be considered within this element of the CCS :-

1. Container closure specifications

Consider - syringe/cap specifications and suitability

Syringe size - no syringe filled to over 80% to avoid plunger instability and potential for leaks/ingress of contamination

All components to be purchased sterile, CE or UKCA marked. Exceptionally, if not CE / UKCA marked for IMP preparation, appropriately assessed prior to introduction

1. Integrity qualification

Integrity Study data verifying compatibility of syringe/cap combination to be obtained and held on file. Any change subject to change control. Consideration should be given to retention of integrity during surface sanitisation and transfer processes.

1. Sterilisation of components

No components should be sterilised on site.

1. Use of triple wrapped packaging

Where possible, component are sourced in triple sterile wrapped packs to provide a high degree of sterility assurance and avoid transfer of contamination to clean zone

1. Inclusion of container/closure in process validation

Process validations are designed to use the same container/closure system as the actual products prepared. The types of container/closure systems validated should cover the whole range of product types prepared

1. Single use systems

No container/closure systems are re-used

1. Systems for processing and approving components for use

New components are introduced via a change control process and subject to validation to determine suitability

1. Supplier approval – see (vii) Vendor approval

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Specifications |
|  | Integrity qualification |

## **Vendor approval**

Introductory text – suggested wording :-

*A sound vendor management program is a fundamental part of ensuring all starting materials (raw materials, product containers and closures, etc) and equipment meet their specification and do not compromise contamination control.*

*All raw materials, components and equipment used within the facility must be assessed and utilised correctly to ensure there is no risk from increased contamination associated with their use. In order to manage this, appropriate approval of suppliers is necessary.*

*Vendor approval is also be applied to all key component suppliers, and suppliers of critical services, e.g.*

* *Sterilisation services,*
* *Servicing and maintenance of facility and key equipment, including local Estates*
* *Laundry services*
* *Contract labs*
* *Suppliers of sterile consumables (syringes, needles, disinfectant solutions and wipes)*

Controls to be considered within this element of the CCS :-

1. Assessment of Suppliers – qualification, requalification, audit

Include detailed information on vendors e.g., details of contract/agreements, specifications for products/processes supplied, any audit reports and reports from routine evaluation, (annually)

1. Lists of approved suppliers
2. Contracted products
3. Use of Bona fide checks if not contracted supplier
4. Development of SLA / TAs

e.g. Sourced via regional framework with associated centralised vendor qualification which is held on file **at the site.** Availability of NHS audit reports may assist in TA development.

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Supplier approval policy/SOP and associated forms |
|  | SLAs/QTAs with individual suppliers of materials and services |
|  | List of approved suppliers |
|  | Audit reports from supplier audits |

## **Management of outsourced activities**

# 

# Introductory text – suggested wording :-

# *All outsourced activities are clearly detailed in written contracts and/or technical agreements. All activity should be controlled to ensure it meets GMP requirements and does not compromise contamination control. Written contracts are available for relevant activities and include clear definition of roles and responsibilities of both the contract giver and acceptor. Contracts/TAs/SLAs include assurance that the principles of contamination control are followed by the contract acceptor relevant to the activity they provide. Evidence is provided that all outsourced products meet acceptable quality standards*

Controls to be considered within this element of the CCS :-

1. Details of all outsourced activity
2. Contracts and service / technical agreements / audit arrangements and should include reference to performance of the provider against the requirements of the TA

e.g. sterilisation – sufficient evidence should be given to contract giver to ensure process is

operating correctly. Requires audit and expert review of the sterilisation process.

1. Provide details or refer to quality agreements, supplier qualification documents of the outsourced activity such as microbial or release testing performed by an external laboratory.

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Supplier approval policy/SOP and associated documentation |
|  | Quality assessment policy/SOP |
|  | SLAs/QTAs with individual suppliers of materials and services |
|  | List of approved suppliers |

**ix) Process risk assessment**

Introductory text – suggested wording

*The aseptic process is clearly defined and described e.g. via a process map. Each activity is risk assessed and mitigations put in place. Contamination control is designed into each stage of the preparation process (describe design parameters).*

Explanatory note: Units must establish an appropriate mechanism to assess the risk of each process using QRM principles (e.g. FMEA etc). Due to the range of processes in place for Section 10 facilities, a matrix approach is advised. Describe the way in which this is executed here, including how required mitigation is applied and how often residual risks are reviewed. Flow charts may be a useful way of presenting this information. If this is contained in other documentation already part of the PQS, simply cross reference this information and provide a summary.

Controls to be considered within this element of the CCS :-

References to risk assessments and the processes to which they apply should be added. This is likely to link to the process design philosophy in section i)b), describe any feedback mechanisms here.

The following table contains an example of how this could be presented:

|  |  |  |  |
| --- | --- | --- | --- |
| APS Reference | Process Risk Assessment # | Description | Products qualified by this APS |
| Kit 111 | PRA111 | Draw up of diluent from a vial into a syringe, reconstitution of a vial, draw up of ‘drug’ and addition to an IV bag as final container | Etoposide  Carboplatin  Etc. |
| Kit 222 | PRA222 | Draw up of diluent in a vial, draw up of drug concentrate, serial dilution using 3 x syringe to syringe transfers, cap syringe as final container | Preparation of allergy challenge products |

Consider product segregation and change over during work sessions and non-routine items requiring specific starting materials / consumables / final containers.

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Process maps |
|  | Associated risk assessments |
|  | Method SOPs |
|  | Worksheets |

1. **Process validation**

Introductory text – suggested wording

*Validation of aseptic processes and operator technique is assessed using aseptic process simulations (APS). Appropriate media is used as the starting material instead of pharmaceutical products. APS imitate critical process activities and steps and also take into account routine interventions. Design is based on preparation worksheets*

*As part of the risk assessment consideration is given to non-routine interventions and potential impact on product quality. The risk assessment is re-visited as processes and procedures change and innovative medicines are introduced to assure ongoing validity of validation.*

Controls to be considered within this element of the CCS :-

Describe how the outputs from process risk assessments links to design of APSs, and subsequently production processes. This should also include a list of expected, allowed interventions which may take place during routine activity.

1. Describe number of tests required for a new process
2. Describe frequency of process re-qualification
3. Describe operator qualification for the process (note new requirements of Annex 1)
4. Rotation of processes around clean air devices
5. Choice of media for APSs – see element (xii)
6. Acceptance criteria for APSs (EM results performed while carrying out the APS should be considered)
7. Justification of batch size
8. Use of matrix approach
9. Associated environmental monitoring required alongside the APS
10. CAPA required for OOS results

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Aseptic Process Simulation programme |
|  | Aseptic Process Simulation validation reports |
|  | Operator validation |
|  | Risk assessments |

1. **Validation of Sterilisation Processes**

See CCS element (x) – refer to aseptic filtration criteria (Section 8, Annex 1, 2022)

1. **Preventative maintenance**

Introductory text – suggested wording

*Arrangements for ongoing preventative maintenance is considered for plant, premises and equipment.*

Controls to be considered within this element of the CCS :-

Describe or reference documents which describe the approach to maintaining equipment and premises (planned and unplanned). This is likely to include the following key aspects:

1. Supplier selection and approval
2. Technical Agreements
3. Permit to work (PtW) system and process for accepting equipment back into use following maintenance if not included in PtW
4. Service intervals for key plant and equipment
5. Process for validating and bringing the facility back online following shut down
6. Access arrangements and training of contractor staff where they access unsupervised

## **Cleaning and Disinfection**

Introductory text – suggested wording :-

This element of the CCS covers cleaning and disinfection of the cleanroom and also transfer of materials.

*An important part of maintaining contamination control is through design and implementation*

*of effective cleaning and disinfection programs / processes for premises and equipment.*

*Validation of disinfectants and cleaning methods is essential to the provision of assurance*

*(include reference to validation methodology and availability of reports).*

*Processes for the transfer of materials between zones have also been validated (include*

*methodology). Ongoing monitoring of effectiveness is achieved by (include methodology).*

Controls to be considered within this element of the CCS within this element of the CCS :-

1. Describe / list disinfectants used & rationale for this – note: cleaning v disinfection
2. Use of a sporicide
3. Disinfectant rotation
4. Contact time
5. Validation studies relate to specific manner in which disinfectants are use
6. Validation for in use expiry dates for prepared products
7. Monitoring effectiveness of disinfectants
8. Age and condition of surfaces
9. Residue testing in critical zones
10. Locally cleaned equipment e.g. trays
11. Gassing isolators and surface decontamination –effectiveness of the vapour disinfectant and details of the dispersion system
12. Use of triple wrapped packaging and how these are treated differently (how long after first layer removed)
13. Transfer process – entry of materials in to Grade A workstation – an assessment of material transfer process, decontamination methods, assessment of the background environment – risk assessments should be available

|  |  |
| --- | --- |
| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Surface sanitisation SOPs |
|  | Transfer SOPs |
|  | Transfer validation policy and test reports |
|  | Specifications for wipes, sprays, etc |

1. **Monitoring systems**

Introductory text – suggested wording

*An environmental monitoring programme, which provides assurance of compliance with regulatory requirements is established. This programme also is designed to detect excursions from environmental limits triggering investigation and assessment of risk to product quality (annex 1, 2022). The environmental programme covers both viable and non-viable particles.*

Controls to be considered within this element of the CCS – viable particles :-

1. Use of risk assessments to determine :-

* Sampling/ test locations – during operations and at rest – risk based
* Frequency of monitoring – include continuous monitoring for non-viable particles and pressures
* Monitoring methods (including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimise the environmental detection of environmental contamination, and do not pose a risk of contamination to the product – Rapid Micro Methods (RMM)
* At rest and operational monitoring
* Acceptance criteria
* Risk assessment review

Explanatory note :- Environmental monitoring should be targeted at critical points of operator and material transfer and key interactions in the preparation process. In addition, results should be considered in conjunction with air changes, air flow patterns and pressure cascades.

The microbiological contamination control strategy covers CAPA associated with repeated results above alerts levels or results reported above regulatory action levels.

1. Identification of potential sources/routes of microbiological contamination
2. Risk assessments, mitigation and controls
3. Describe the monitoring programme
4. Media used – provide a description and refer to product specifications for settle plates, contact plates, liquid media etc.
5. Refer to alert and action limits noted in (ii) Premises and equipment
6. Alert and action limits. For Grade A – no growth i.e. every recovery requires an investigation.
7. OOS investigation, root cause analysis and CAPA
8. Trending, setting alert and actions levels, data patterns
9. Trending also applies to microbial speciation, A/B should be identified, C/D recommended
10. Media growth promotion – reference micro-organisms used / representation of facility flora / use of wild type micro-organisms
11. Describe environmental monitoring training

A similar approach should be taken for monitoring non-viable particles.

Temperature monitoring

Controls to be considered under this element of the CCS :-

1. Automated temperature monitoring systems
2. Temperature mapping – use of calibrated data loggers
3. OOS reporting and CAPA

Explanatory note : - Operator monitoring – could be considered under this element or under element (iii)

Aseptic process simulation – media used, process validation design – see element (x)

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| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Environmental monitoring programme |
|  | Media growth promotion |
|  | Validation reports |
|  | Alert and action limits |
|  | OOS / OOT action |
|  | Trend analysis |

1. **Prevention mechanisms**

Introductory text – suggested wording

*Principles described in Chapter 1 of the Good Manufacturing Practice Guidelines form the basis for the Pharmaceutical Quality System.*

*Having robust prevention mechanisms in place is a fundamental element of a contamination control strategy. The strategy describes the processes in place to identify, understand and document their contamination control risks and the actions taken to appropriately eliminate, reduce and mitigate them. Describing how this is achieved can be done through tools such as, trend analysis, detailed investigation, root cause determination (appendix 1), corrective and preventative actions (CAPA), and the need for more comprehensive investigational tools.*

*Risk management and risk assessment principles are applied and documented for the development and maintenance of the CCS including the rationale for decisions taken. ICH9 principles are used. All non-conformities are investigated to determine the impact on product quality and patient safety.*

Controls to be considered within this element of the CCS :-

1. Pharmaceutical risk management review arrangements
   * Describe risk assessment processes in place and how pharmaceutical RA principles are applied for contamination control risks.
   * Consider having a risk assessment tool/template that guides you through the RA process (consider including as an appendix for RA SOP).
   * Demonstrate how the risk assessment process identifies contamination control risks, what actions are necessary to mitigate/reduce the risk and that this is regularly reviewed for effectiveness (feedback mechanism).
   * Describe how contamination control risks and subsequent actions are considered, prioritised, reviewed and escalated within your PQS.
2. Deviation procedure
   * Describe the processes in place for management of deviations that includes CCS deviations.
   * Consider the use of RCA tools to identify root cause.
   * Describe how staff performing/leading an RCA have the skills, experience to do so. Consider using an independent person for RCA’s if appropriate.
   * Utilise information from the PQS e.g data/trends/reported incidents/training gaps to inform investigations and RCA process.
   * Set out how outcomes, findings, risks and actions of any investigations/RCA’s are documented and approved.
3. CAPA process
   * Describe the processes in place for corrective and preventative actions (CAPA) and how the actions required to mitigate/reduce any CCS risks identified.
   * Utilise PQS information to inform the CAPA and impact of actions taken.
   * Demonstrate how the PQS includes all relevant data relating to CCS risks.
   * Describe the processes for ensuring CAPA actions completed in a timely manner and demonstration that risks are reduced as expected.
   * Consider what measures are in place for cyclical/regular review of effectiveness implemented actions.
4. Escalation process
   * Demonstrate how staff escalate any contamination control risks they have identified and who they escalate to. Consider utilising a flow chart outlining the escalation process as an appendix to a relevant SOP.
5. Error management
   * Describe the processes in place for reporting near misses, errors and incidents and consider their effectiveness.
   * Explain how this process is embedded into the department’s culture demonstrating how errors etc. are reported (including trends), documented, appropriate actions taken and the mechanisms in place for regular review and analysis.
   * Ensure appropriate actions taken in response to any CCS risks identified.
   * Describe how your organisations risk/incident management processes are incorporated into aseptic unit processes to ensure risks are escalated appropriately e.g. reporting on Datix as necessary.

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| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Risk assessment SOP and associated templates |
|  | Deviation SOP |
|  | CAPA SOP |
|  | Root Cause Analysis tools/templates |
|  | Near Miss/Error monitoring tool |
|  | RCA – Training tools |
|  | SOP that includes escalation process for staff |

## **Continuous improvement**

## Introductory text – suggested wording

## *As part of a contamination control strategy it is imperative that a culture of continuous improvement is established. This is based on information from the current PQS and quality risk management processes. It is important that there are systems in place to continually review and identify where improvements are required.*

Controls to be considered within this element of the CCS :-

1. Audit – refer to iQAAPs audit process and reports
   * Describe the process of internal and external audit and how they are documented.
   * Demonstrate how contamination control principles are embedded within these processes
   * Consider how outcomes and actions are documented and describe the processes for feedback, review and demonstration of risk reduction.

1. Change control
   * Describe the processes involved in introducing a change, consider a standard approved template to be followed as an appendix to an associated SOP.
   * Demonstrate how the change control process incorporates contamination control and risk management principles, identifying any required changes and assess for success and risk reduction post implementation.
   * Encourage change management as a fundamental element of a PQS and that changes in practice are reviewed at PQS meetings.
2. Key performance indicators
   * Identify what your key contamination control KPI’s are e.g Out of spec micro results, broth validation failures, physical and microbiological monitoring failures.
   * Demonstrate how data is collected and how KPI’s are recorded and reported. Regularly report KPI data e.g monthly
   * Describe how KPI data is reviewed, trended and escalated if concerns identified, standards breached.
   * Examples from a CCS perspective include environmental monitoring non-conformances in all areas
   * Consider how you can demonstrate that appropriate actions have been taken in the event of a KPI standard breach and appropriate actions taken to address the issue.
   * Demonstrate how KPI’s are shared and escalated as required.

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| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | iQAAPs reports |
|  | Audit action plans |
|  | Trend analysis reports |
|  | KPI reports |

## **Feedback and Evaluation**

Introductory text – suggested wording :-

*The purpose of the CCS is not solely to document all the measures and controls in place but also to enable units to have an overview of their contamination control measures and how well they work or are utilised in preventing contamination. The CCS considers all aspects of contamination control and undergoes periodic review. The CCS is an integral part of the PQS.*

Controls to be considered within this element of the CCS :-

* Change controls
* Deviations, non-conformances and incidents
* Introduction of new equipment
* Results from routine data review and trend analysis that indicate CCS concerns.
* Training of staff.
* KPI’s relating to contamination control.

Explanatory note :- It is recommended that for each section of the CCS, consideration and reference to relevant risk assessments, validations, procedures, studies etc. should be made as appropriate. In addition to this it is also recommended that there is a mechanism of reviewing/analysing the data gathered by the controls in place to define if:

1. The measures are working in preventing contamination.
2. The residual risk of contamination is still acceptable or if additional risk reduction measures are required.
3. Units should review their CCS and assess for any improvements that are required implementing them as applicable as part of the PQS.

This will be a significant section of the CCS and will be supported by procedure(s) around data collection and evaluation. It should champion control over monitoring.

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| Reference documentation *(these are examples of the documents you should reference)* | |
| Reference no. | Environmental monitoring programme reports and data |
|  | Risk assessments |
|  | Change controls |
|  | Deviations |
|  | Non-conformances |
|  | Trend analysis reports |
|  | KPI reports |
|  | PQS/Quality meeting minutes and actions. |
|  | PQS reports |