PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 043-1
1 July 2018

AIDE-MEMOIRE

CROSS-CONTAMINATION IN SHARED FACILITIES

Editor: PIC/S Secretariat

e-mail: info@picscheme.org
web site: http://www.picscheme.org

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1. DOCUMENT HISTORY

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2. INTRODUCTION

2.1 Manufacturers of medicinal products must ensure that they are fit for their intended use, and do not place patients or target animals at risk due to inadequate safety, quality or efficacy.

2.2 To reliably achieve the quality objective, a significant Good Manufacturing Practice (GMP) requirement is that manufacturers pay appropriate attention to those factors that present risks of cross-contamination of the products being manufactured with other materials handled on the site or facility.

2.3 It is expected that the risk control measures should be identified, designed on the basis of the hazard presented by the materials being handled, and correctly implemented via a system of Quality Assurance (QA) incorporating Good Manufacturing Practice (GMP), and thus Quality Control (QC) and Quality Risk Management (QRM). The controls should be fully documented and their effectiveness monitored, and periodically reviewed taking account of technological and technical progress. The user of this Aide-Memoire should therefore be familiar with the general principles and guidelines applicable to QRM and take account of the factors included in the PIC/S Aide Memoire on the Inspection of QRM (PI-038). The cross-contamination risk management system must clearly link to the protection of the patient and/or target animals.

2.4 During inspections the GMP inspector should assess whether or not there is a systematic process for the risk management of cross-contamination and should assess the extent to which:

2.4.1 The evaluation of the hazards presented by the products is complete.

2.4.2 The design of facilities, utilities and equipment is appropriate to these hazards.

2.4.3 The processes and controls implemented are robustly in place and take account of:

2.4.3.1 Technical measures – e.g. premises and equipment design and installation.

2.4.3.2 Organisational measures – e.g. campaign processing, cleaning verification.

2.4.4 The above are periodically reviewed in a manner that is commensurate with the hazard of those products and processes throughout the lifecycle of the facility and products.

2.4.5 That the mitigating technical and organisational controls are based on scientific knowledge and experience with the process.

2.4.6 That the level of effort, formality and documentation of the cross-contamination risk management and implemented controls are commensurate with the level of the hazard.

2.5 Considerable technical progress has been made in the design of pharmaceutical production equipment, technology and quality control as well as the areas of auxiliary systems such as Air Handling Unit (AHU) systems and material handling systems. These innovations together with the increased emphasis on formalised Quality Risk Management have brought potential for greater flexibility for the campaign manufacture of certain materials in shared facilities that previously would have been handled in dedicated and/or segregated facilities provided that operations are completely and comprehensively separated when necessary.

3. PURPOSE

3.1 The purpose of this document is to assist GMP inspectors in the assessment of the risks to the product from cross-contamination in shared facilities. This document provides guidance for GMP inspectors to use in preparation for, and performance of, inspections.

3.2 This Aide-Memoire should also contribute to a harmonised approach for inspection of shared facilities within the Pharmaceutical industry between the different PIC/S Members.

3.3 This Aide-Memoire may also be useful in support of inspector training but this is not its intended purpose and it should not be seen as a substitute for training and knowledge of an inspector.

4. SCOPE

4.1 QRM of controls related to cross-contamination should be an integrated part of the planning and content of all GMP inspections (including for medicinal products as well as for active pharmaceutical ingredients), however this Aide-Memoire is specifically targeted at medicinal product manufacture. This Aide-Memoire promotes a risk-based approach and should guide the inspector to make both the optimal use of the inspection time and the optimal evaluation of GMP compliance.

4.2 This Aide-Memoire focuses on inspection of products containing starting materials having a ‘higher hazard’ level manufactured in a shared facility. The inspector should adapt the inspection approach to the hazard associated with the products manufactured. As such, less emphasis will be required on some areas for lower hazard products.

4.3 The concepts of hazard and risk have been used throughout this document and definitions apply as per PIC/S PE 009 Annex 20 Quality Risk Management. It is recognised that the level of risk established and accepted by the manufacturer relates to the potential for cross-contamination. However, it is important that inspectors consider the risk management process and controls in the context of the hazard of materials handled on a site to ensure that the hazards have been adequately addressed. The level of effort, formality and documentation of the quality risk management process

should be commensurate with the level of (initial) risk posed by the hazard. The lack of scientific evidence to adequately assess the hazardous material risk should preclude the use of a shared facility.

4.4 Inspectors should take account of any local and/or, national requirements in addition to the points recorded in this Aide-Memoire. For example, regional differences for dedicated facility requirements (e.g. for beta-lactam products) may require modification, or preclude the use, of some of the observational questions included in this Aide-Memoire.

4.5 The existence of this separate Aide-Memoire document does not suggest that specific inspections of cross-contamination control systems are performed. It is expected that elements of this Aide-Memoire would form part of most inspections; however, the time and depth of this part of the inspection should be commensurate with the nature of the products manufactured and the hazards they present.

4.6 At the time of issue, this document reflected current experience and practices. It is not intended to be a barrier to technical innovation or the pursuit of excellence or to limit or create new GMP requirements.

4.7 This Aide Memoire makes reference to the setting of health based limits for permitted exposure of patients or target animals but does not prescribe a specific methodology to be used. The setting of suitable evidence and health based limits is documented in PIC/S PI 046 “Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities”.

4.8 The health based limits approach will require specific application and consideration for each of the following situations:

4.8.1 Shared facilities for human products only, or

4.8.2 Shared facilities for both human and veterinary medicinal products, or

4.8.3 Facilities dedicated for veterinary medicinal products but shared between different medicinal products for different animal species.

4.8.4 Inspectors should ensure that manufacturers take into account specific requirements of either patients and/or target animals in each relevant situation.

4.9 Extrinsic contamination e.g. by microbial spoilage organisms and by materials of construction of premises, packaging and equipment are important GMP factors but are outside the scope of this specific Aide-Memoire.

4.10 This Aide-Memoire is not intended to address the safety of the inspector against the hazards but inspectors should be mindful of the hazards they may be exposed to during inspection.

5. AIDE-MEMOIRE

5.1 This Aide-Memoire should be used with the following general comments:

5.1.1 During an inspection attention should be paid to the risk management of cross-contamination; however, the amount of time allocated will depend upon the hazard level of the molecules, the type and number of products handled, and the degree to which facilities are proven to be separated and dedicated.

5.1.2 It is important during an inspection that possible mechanisms for cross-contamination are considered and commensurate inspection time is allocated to each on a risk basis. The primary mechanisms include but are not limited to:

- Surface to Surface
  - o Originating from inadequately cleaned shared equipment/tool surfaces through failures or inadequate design of cleaning/equipment
  - o Originating from contact with contaminated cleaning equipment
  - o Originating from personnel gowning

- Airborne to air/surface
  - o Originating from poorly controlled and unintended release into the environment due to inadequate control of dust, gases, vapours, sprays or organisms after which the contamination settles on product contact surfaces
  - o As above but resulting from loss of primary containment
  - o From recirculation in air handling systems between areas where filtration is inadequate
  - o From inadequately controlled exhausts
  - o Micronized powders and materials that have been aerosolized present higher risk due to their extended dwell time in the air

- Direct or indirect contamination from process or equipment failure
  - o Back flow from waste or vacuum systems
  - o Technical failure of equipment
  - o Spillage and leaks

- Originating from movement and mix up of personnel, materials or equipment or parts.

1. Cross-Contamination Hazard Assessment and Risk Management

Prior to the inspection inspectors should be aware of the site's product range. Consideration should be given to the level of hazard presented by the products handled in the context of the use of shared facilities/equipment. Therefore, during preparation for inspection, inspectors should request manufacturers to provide information relating to:

Type of products manufactured including:

- A list of dosage forms of both human and veterinary products which are manufactured on the site.
- A list of dosage forms of any investigational medicinal products (IMP)/Investigational New Drugs (IND) manufactured on the site for any clinical trials, the phase of clinical development they are in, and when different from the commercial manufacturing, information of production areas and personnel.
- A list of any research and development compounds manufactured in common areas with commercial products.
- A list of hazardous substances handled (e.g. with high pharmacological activity, particular critical toxicological effects, or highly sensitising properties such as beta-lactams).
- Health Based Exposure Limit and assessment for each substance.
- Any non-medicinal products manufactured onsite.
- Product types manufactured in a shared facility.

Lists should include the International Non-proprietary Names (INN-names) or common name (as available) of active pharmaceutical ingredients (API) used and their strength.

Inspectors may need to consult with toxicological experts within their own agencies prior to, during, or following inspections should specific assessment of manufacturer's hazard assessments be required.

Facility design drawings and block flow diagrams for plant and process, identifying utilities, equipment, material flow, waste flow, flow of dirty and clean mobile equipment, pressure differentials, airflow and movement of people may be required prior to or during the inspection if not already provided in the Site Master File.

The completeness and accuracy of information provided prior to the inspection should be verified on site.

Inspectors may need a method for triaging products in order to identify any products that may be regarded as higher hazards that require specific attention during the inspection.

The outcome of the QRM process completed by the manufacturing site should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product(s).

Inspectors should assign adequate time to preparation by review of the above information prior to inspections, particularly where higher hazard products are manufactured.

Nr.	*Inspection prompt*	*Reference PE 009-14 (Part I and Annexes)*
1.1	Does the level of sharing of premises/ equipment / utilities etc. that takes place require time allocated on inspection to evaluate the risks?	3.6
1.2	Are hazards presented by neighbouring facilities or other buildings in the facility relevant to the facility and building being inspected (e.g. Air Handling Units (AHU) outlets and intake locations)?	3.6
1.3	Does the site have an adequately documented policy and strategy for implementation for control of cross-contamination that reflects the hazards associated with products made or planned to be made? • Does the policy and strategy clearly state any product classes manufactured or excluded from manufacture at the site or clarify circumstances under which higher hazard products may be introduced?	4 principle, 5.18.
1.4	Are appropriate controls in place for New Product Introduction with respect to cross-contamination control?	Annex 15; 11.
1.5	Are appropriate controls in place for retiring or re-designation of equipment / facilities with cross-contamination control in mind?	3 principle
1.6	Have **all** products been identified including all products currently manufactured at site (for any country/market), legacy products which have been manufactured in recent years and non-medicinal products?	5.18
1.7	Do the products manufactured in shared facilities pose a significant hazard that may present a cross-contamination concern?	3.6
1.8	Have the hazards associated with the products been identified adequately?	5.18, Annex 15; 10.6
1.9	Is the extent and reliability of the manufacturer's product knowledge commensurate with the hazard considering: • Commercial product, • Investigational Medicinal Products (IMP)/ Investigational New Drugs (IND) and what phase of clinical development they are at, • Any research and development compounds manufactured in common areas with commercial products, and • New medicinal products for animals? For contract manufacturers – is there sufficient knowledge on site about the products they manufacture to ensure cross-contamination can be controlled adequately?	5.18, Annex 13; 5, Annex 15; 10.6
1.10	Were the hazards identified in an appropriate manner (e.g. via Permitted Daily Exposure (PDE) / Acceptable Daily Exposure (ADE) approach or other appropriate compliance/safety references)?	5.18, Annex 15; 10.6

1.11	Is there a scientific basis for the hazard assessment? • Does the person performing the hazard assessment have appropriate education, training and experience? • Is there appropriate resource available to carry out the hazard assessment? • If hazard assessment is an outsourced activity, is it adequately controlled?	2.1, 2.10, 2.11, 5.18, 7, Annex 15; 10.6
1.12	Does the manufacturer have a procedure on hazard assessment and is it approved by the relevant personnel?	4.1
1.13	Has the hazard assessment been adequately documented and conducted in accordance with the procedure?	4.3, 4.8
1.14	Is the level of detail adequate to support the level of hazard and any conclusions in the assessment document? Note: Inspectors may need to refer to toxicology experts within their own agency.	1.12, 1.13, 3.6
1.15	Is there an adequate QRM approach for identification and management of contamination risk? Is there a procedure and is output adequately documented? Does the QRM process include: • Assessment (Identification, analysis & evaluation), • Control, • Communication, and • Review • Is the manufacturer's approach robust, scientifically valid and adequately addresses the hazard presented by the product? Note: Inspectors should refer to PIC/S QRM Aide Memoire PI-038.	1.12, 1.13, 3.6
1.16	If the facility has segregated grouped products then how is the cross-contamination risk controlled? Within the group (e.g. hormonal products, or different cytotoxics in the same facility) is there a scientific rationale for the grouping of the products and for the controls exercised in such areas? Is risk control adequate to address the potential impact outside the group/area?	5.19
1.17	Does the risk management study adequately address potential failure in controls? Does the manufacturer have an adequate strategy to address failures including but not limited to: • Anticipating human failures to follow systems (especially work which is manually performed), • Equipment breakdown, • Failure of primary containment, • Power outages affecting AHU, • Product/material spills,	1.12, 1.13, 3.6

	• Accidental exposure, and • Rework/reprocessing occurring out of sync with the campaign manufacturing plan?	
1.18	Has the manufacturer shown evidence / demonstrated that it has the skills, knowledge, competency, controls (including equipment, facility design, people skills, organisation, etc.) to manufacture the products in question in a shared facility?	2.1, 2.10, 2.11
1.19	Are the risks adequately communicated to all relevant personnel?	1.12, 1.13
1.20	Is the frequency of periodic review of newly available data adequate to determine if the original hazard analysis is still appropriate? • Is there a mechanism to ensure follow through from pharmacovigilance data analysis? • Is new scientific knowledge taken into account?	Annex 15;11.1, 11.7
1.21	Are changes to the product portfolio taken into account when reviewing the use of the hazard analysis? Examples include introduction of products associated with a potentially more vulnerable patient group or change in route of administration such as liquids for external use to liquids for internal use, introduction of intravenous products, and change to particle size (e.g. micronized form), new target species.	Annex 15;11.1, 11.7
1.22	Are control systems robust enough to ensure detection and identification of cross-contamination issues (e.g. where appropriate do the manufacturer's procedures consider that cross-contamination could be the possible cause for complaints and out of specification results)?	1.1
1.23	Is there a periodic review of the controls established in the risk assessment to ensure ongoing suitability? Do changes to manufacturing process/ infrastructure/ equipment/ utilities/ etc. take into account the potential impact on cross-contamination?	1.12, 1.13, Annex 15; 11.4, Annex 20; 31, 32.

2. **Technical measures - Equipment and Facility Design**

During the walk through of the facility the Inspector should obtain a high level view of the suitability of equipment and building design. In general, the inspector should be considering if the equipment and facility design reflect the hazards of the products manufactured.

Look out for signs of loss of containment such as powder on surfaces or lack of primary containment where it would be expected based on the nature of the hazard.

Consider the level of dedication within the facility (such as buildings, rooms, production lines etc.).

Review drawings of building, utilities, and equipment with particular emphasis on AHU zoning and any required separation.

Review layouts and flow charts of the production areas showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the process areas.

Consider personnel, equipment, and material flow charts, and general flow charts for each manufacturing process.

Consider the movement of free standing equipment (equipment that is not specifically mobile but could be located in different rooms dependent on process needs) in and out of processing areas. Consider also layouts of warehouses and storage areas. Consider the need for special areas for the storage and handling of highly hazardous materials. If applicable, higher levels of primary containment are expected for higher hazard product manufacture.

Ensure that personnel exposure and product contamination control are not in conflict.

Nr.	*Inspection prompt*	*Reference PE 009-14 (Part I and Annexes)*
	PREMISES	
2.1	Are appropriate design measures, in terms of premises, in place for prevention of cross-contamination and are they consistent with the output of the QRM process? Does the qualification of the facility support the cross-contamination strategy and design philosophy?	*1.12, 1.13, 3.1, 3.6, 3.7, 5.19*
2.2	Does the design of the premises including siting of equipment facilitate good containment relative to the type of products/materials handled? Particularly where there may be open handling of materials.	*3.6, 3.7,3.8, 3.14*
2.3	Have adequate structural design provisions such as air locks, air showers and segregated or enhanced gowning/de-gowning areas been incorporated and meet desired effectiveness?	*5.19*
2.4	Are the premises designed for ease of cleaning or decontamination e.g. to minimise collection points for powder that may be difficult to clean?	*3.9*

2.5	Are wash rooms adequately designed to ensure they are not a risk of cross-contamination or recontamination?	*3.7*
2.6	Where appropriate, have dedicated utilities such as AHU, water systems, compressed air/gas and effluent/waste streams, for different products been incorporated? Could back flow in utilities cause a risk of cross-contamination?	*5.19*
2.7	Is the zoning design and associated AHU, pressure cascades and air flows appropriate?	*3.12*
2.8	Do the designed air flows take account of occurrences such as operation of local extract, vacuum transfer systems and doors opening?	*3.12*
2.9	Is there appropriate local extraction or containment to control the spread of dust/vapours at source?	*3.12, 3.14*
2.10	Where AHU recirculation is used, are adequate controls in place for the filtration system to ensure that airborne contamination is removed? Is reliance on filtration in the AHU system appropriate for the hazard presented?	*3.12, 5.21*
2.11	If the site operates a low power mode or switch off AHU out of hours has this been assessed, justified and demonstrated to be effective (depending on the extent of the hazard) in controlling cross-contamination? • Has consideration been given to the impact during power down and power up or power failure? • Could there be any unintended consequences (e.g. loss of containment or pressure reversal)? • Has the company documented an assessment for the time needed to return to a clean status once power is switched back on after power off / reduced power?	*3.12*
2.12	Are there appropriate mechanisms in place to detect failure of control mechanisms, particularly where higher hazard products are manufactured (e.g. AHU failure)?	*4 principle*
EQUIPMENT		
2.13	Are appropriate design measures, in terms of equipment, in place for prevention of cross-contamination and are they consistent with the output of the QRM study? Does the qualification of the equipment support the cross-contamination control strategy and design philosophy?	*3.34,1.6, Annex 15; 3*
2.14	Has appropriate use been made of dedicated / single use disposable equipment and/or disposable parts?	*5.21*
2.15	Is there appropriate emphasis on the use of primary containment? Where primary containment is used is it fit for purpose?	3, 3.1, 3.6, 3.14, 3.34

2.16	Where open processing is used are the controls and rationale appropriate?	*3.34,* 5.20, 5.21
2.17	Is the equipment designed to facilitate ease of cleaning and confirmation of cleanliness (e.g. visual inspection, swabbing)? Where cleanliness cannot be confirmed then has use of dedicated equipment or parts been considered?	*3.36, 5.21*
2.18	If Clean In Place (CIP) or Clean out of Place (COP) systems (e.g. skids for vessel cleaning, or washing machines for parts) are utilised, are they appropriately designed? Have the systems been confirmed to not represent a potential for cross-contamination themselves?	*Annex 15; 3*
2.19	Are CIP/COP cycles adequately specified, monitored, recorded and reviewed?	*3.38, 4.8*
2.20	Has the manufacturer adequately identified difficult to clean parts of equipment and is this supported by appropriate justification? Is there a clear procedure to define how this should be conducted?	*3.38, 4.1*
2.21	Have maintenance, In Process Control (IPC) and sampling (including equipment, personnel protective equipment/clothing, tools and change parts) been considered as part of contamination control? Where appropriate, have control measures been implemented?	*5.21*
2.22	Does the manufacturer have an adequate location, equipment and controlled process for cleaning process or product related contaminants (i.e. dust, powders, particulates etc) from pre-filters?	*5.21*

3. Organisational measures – general organisational controls, campaign organisation, equipment cleaning and inspection, cleaning validation and verification, personnel

Organisational measures supplement design of premises and equipment to prevent cross-contamination. In this section, the inspector is investigating the extent to which these measures are robust and sufficient to reduce the risk and control the hazards present.

For higher hazard products, a greater emphasis should be placed on primary containment measures in addition to organisational controls.

In general, for greater hazard materials redundant measures would be expected such that single control failures, particularly where these may be undetected, do not lead to critical risks to the patient.

Organisational measures should not be seen as a replacement for inadequate or inappropriate design of facilities and equipment.

Cleaning validation is the output of cleaning studies providing assurance that the method can be consistently applied and is effective. During the cleaning validation studies cleaning verification should be conducted. Cleaning verification may also be required as part of an ongoing program of assuring cleanliness post cleaning validation.

Any analytical methods used during cleaning verification should be validated and swabbing requirements should be defined in an approved document.

A periodic review should be conducted of all qualitative and quantitative data generated as part of ongoing cleaning verification.

Nr.	*Inspection prompt*	*Reference PE 009-14 (Part I and Annexes)*
	GENERAL ORGANISATIONAL CONTROLS	
3.1	Where relevant, have appropriate organisational controls been implemented to address risks identified in the risk assessment?	*1.6, 5.19*
3.2	Is contaminated/dirty equipment adequately pre-cleaned or protected before being moved to a general cleaning area?	3.8, 3.14
3.3	Have mobile or fixed equipment/accessories been identified and is equipment status clear and secure to prevent mix up. Is the process adequately documented?	3.8, 5.13
3.4	Are dedicated equipment/parts clearly labelled and controlled appropriately?	3.8, 5.13
3.5	Does the hazard level warrant consideration of periodic surface or airborne sampling? Is the sampling program suitable to detect spread of contamination from a controlled area to verify that containment measures are effective?	1.12, 1.13, 3.12, 5.21, 6.15

	If periodic monitoring is required is this conducted satisfactorily, with adequate action taken, to address instances where contamination is identified? Is the test method fit for purpose?	
3.6	Based on the level of hazard is the control and monitoring of effluent/waste streams adequate to control the risk of cross-contamination or recontamination from the waste stream?	1.12, 1.13, 5.21
3.7	Any time product or starting materials are exposed to the environment is control adequate to prevent cross-contamination?	5.20, 5.21
3.8	Are material storage and handling measures adequate to prevent cross-contamination and reflective of the material hazards? • Are materials kept adequately sealed until point of use? • Are the outside of containers cleaned to prevent cross-contamination (e.g. after sampling or dispensing)? • Are sampling tools adequately cleaned, dedicated or disposable? • Is the area where materials are sampled or dispensed adequately cleaned between different products (or dedicated where the hazard requires this)? • Are arrangements for storage appropriate for the hazard? • Is labelling adequately controlled to prevent mix up of materials?	3.1, 3.18, 3.22, 3.24, 5.9, 5.11
3.9	Have controls for spillages been determined and personnel trained, particularly for higher hazard products?	5.4, 5.11
3.10	Does the manufacturer have adequate systems to detect, record and assess impact of situations such as spillages or other unusual events that could lead to cross-contamination?	1.4viii
3.11	Is the equipment/facility subject to adequate preventative maintenance to prevent potential cross-contamination? For example, are there any issues with duct work or transfer line leaks that may contaminate other areas?	3.1,3.2, 3.8, 3.10
3.12	Are there any contract services (e.g. contract testing, contracted cleaning services, contract manufacture for other markets) that may introduce hazardous substances? • If so, are they appropriately identified, assessed and controlled? • Are contract service providers appropriately trained regarding control measures employed by the manufacturer?	7 principle
3.13	Are internal laundry practices and facilities controlled to prevent-cross-contamination between different products? Do external laundry contractors have appropriate controls to prevent cross-contamination with other manufacturer's products? Where appropriate, are decontamination processes applied and are they effective?	2.18, 7 principle, 7.3,7.4, 7.6, 7.9

CAMPAIGN MANUFACTURE ORGANISATION		
3.14	Is the manufacturer's overall strategy for campaign manufacture in shared facilities adequate to prevent cross contamination?	*5.20, 5.21*
3.15	Does the manufacturer adequately minimise the opportunities for cross-contamination of equipment in the processing area? • Is equipment, that is not required for manufacture removed from the area? If movement of equipment is necessary is it confirmed clean and is the previous use of the equipment compatible with the location it will be moved to? • Does the manufacturer adequately protect, or re-clean afterwards, equipment that is not required for production but cannot be removed from the area? Is this appropriate for the nature of the product hazard? • Is movement of ancillary equipment (e.g. IPC test equipment) and materials between campaigns (of different products) and areas adequately controlled?	*1.12, 1.13, 3.34, 5.21*
3.16	Is there an adequately detailed procedure(s) for campaign change over including cleaning of product contact equipment, cleaning of non-product surfaces e.g. AHU, exterior of equipment, walls, floors etc.	*3.1, 3.2, 3.7, 3.9, 4.1*
3.17	Is there an adequate procedure to describe cleaning of non-product contact equipment such as phones, chairs, fire extinguishers, computer keyboards etc.?	*3.1, 3.2, 3.7, 3.9, 4.1*
3.18	Where appropriate is there a procedure that adequately specifies decontamination practices (e.g. biologicals).	*3.1, 3.2, 3.7, 3.9, 4.1*
EQUIPMENT CLEANING AND INSPECTION		
3.19	Is there a procedure for developing the cleaning methods of equipment that requires adequate assessment, detail and evidence (i.e. are use of equipment drawings, equipment manufacturers manual and physical examination of equipment specified)?	*4.1, 4.3, 4.4.*
3.20	Is the equipment cleaning coordinated with area cleaning to prevent re-contamination?	*3.1, 3.2*
3.21	Does the level of detail in cleaning instructions reflect the hazard level and reflect the complexity of equipment, for example: • Are all variables specified in adequate detail? • Has an appropriate cleaning agent been selected? • Is the concentration and other relevant parameters such as contact time of the cleaning agent specified? • Are hard to clean areas clearly specified? • Is control of cleaning equipment and re-use of cleaning equipment (e.g. mop handles) specified?	*1.12, 1.13, 4.3, 4.4, Annex 15; 10.5*

	Are records of cleaning adequate to reflect the level of control required?	
3.22	Do manual cleaning, COP and CIP processes adequately define the level of preparation/dismantling of equipment required for consistent application?	1.12, 1.13, 4.3, 4.4, Annex 15; 10.4
3.23	Are diagrams or photographs depicting dismantled equipment used to support consistency and error proofing of cleaning?	1.12, 1.13, 4.3, 4.4
3.24	Are effluent and waste from the cleaning process controlled in a manner that does not allow cross-contamination or recontamination?	5.21
3.25	Is the process of visual inspection for cleanliness of equipment adequately controlled and specified? Where visual inspection of closed process equipment is not possible at each turnaround, has the cleanliness of the equipment and transfer lines been adequately proven during validation?	4.3, 4.4, Annex 15; 10.2
3.26	Is the visual inspection process, where applicable, clearly described and conducted in a manner to ensure potential contaminants will be seen? Does the manufacturer have adequate justification where visual inspection cannot be conducted?	4.3, 4.4, Annex 15; 10.2
3.27	Where visual inspection is conducted, is it a requirement that the equipment is dry and inspected before reassembly?	4.3, 4.4, Annex 15; 10.2
3.28	Has it been demonstrated that personnel have the skills, knowledge and competency to conduct visual inspection in a consistent manner?	2.10, 2.11, Annex 15; 10.2, 10.5
3.29	Are appropriate methods and tools used to help detect residues by visual inspection (e.g. use of a good light or mirror) adequately defined by procedure?	Annex 15; 10.2, 10.5
3.30	Is the person conducting the final visual inspection adequately independent of the cleaning operation?	1.4 iii
3.31	Has line clearance been effectively confirmed to ensure that any potential cross-contamination sources have been removed?	4.18c, 4.19f
3.32	Does the manufacturer have a system (e.g. deviation system) to record failures in cleaning such as: • Where execution of the prescribed cleaning instructions has failed to render the equipment clean, • Where, upon, visual inspection by the independent person, the equipment is found to not be clean, or • When swab/rinse sample failures occur?	1.4viii,x

CLEANING VALIDATION AND VERIFICATION		
3.33	Is the cleaning process validated and periodically verified in the appropriate manner and frequency required for the hazard presented?	Annex 15; 10.4, 10.10, 10.15
3.34	For cleaning validation/verification: • Does the validation protocol define an adequate structured approach to completing cleaning validation? • Where cleaning verification is used after each cleaning process, following or as part of the concurrent cleaning validation program, is there adequate assurance that the equipment has been demonstrated to be clean prior to further use? • Are the limits for the carryover of product residues established based on toxicological evaluation and justified by risk assessment? • Where manual cleaning is conducted has the validation adequately demonstrated that this method can be consistently applied by personnel? • If the cleaning process is manual is the reliability and effectiveness of the cleaning process confirmed through appropriate periodic verification? Note: This may be up to every turn-around for a higher hazard product. • Is the consistency and effectiveness of the automated cleaning process qualified and the methods validated? Do the methods include validated automated recipes that include appropriate cycle parameters and operator verification of selection of the correct cycle? • Have all variables and opportunities for malfunction (failure modes) of validated automated cleaning methods been identified, monitored and mitigated? • Have all variables and opportunities for failure in manual cleaning and verification been identified, monitored and mitigated? • Is the type of revalidation or ongoing verification frequency appropriate and has a sound scientific rationale been applied? • Are all deviations related to cleaning investigated and taken into consideration during the periodic review of cleaning validation/verification? • Are changes to any cleaning processes adequately assessed and recorded for impact on cleaning validation/verification?	1.4viii, Annex 15; 10.1, 10.3, 10.4, 10.6, 10.11, 10.15
3.35	On the occasions where visual inspection of equipment, or parts of equipment (e.g. closed systems or pipework), is not possible at routine turnaround does the manufacturer have other methods of assuring cleanliness such as a validated rinse method?	1.12, 1.13, Annex 15; 10.1, 10.2.
3.36	Has the manufacturer implemented visual inspection in line with the complexity of the equipment and its potential to retain residue?	1.12, 1.13, Annex 15; 10.1, 10.2.

3.37	Have individuals performing swabbing been confirmed as having the skills, knowledge and competency (recorded data and practical assessment) to ensure consistent application of the swabbing technique in accordance with the procedure?	1.8iii, 2.10, 2.11
3.38	Are the quantity and location of swab samples representative of the hazard and the equipment design including difficult to clean areas?	1.12, 1.13
3.39	Is there an appropriately validated analytical method for confirming that product residue has been removed in line with the acceptance criteria? • Has the analytical recovery of swab and rinse samples been adequately established? • Are the values appropriate for the hazard? • Has the recovery value been taken into account in calculating results?	Annex 15; 10.12
3.40	Have the following time dependent aspects been adequately included and established in the validation/verification approach? • Ease of cleaning at the end of the campaign and the maximum length of campaign manufacture? • The maximum dirty hold time of equipment?	Annex 15; 10.8, 10.9
3.41	Is the equipment clean hold process and hold time adequate to prevent recontamination of clean equipment? Is storage of cleaned equipment adequate to ensure that it is stored in a manner that protects it from contamination prior to use? Are the tools utilised in equipment disassembly, reassembly, cleaning subject to adequate control to prevent them being a potential source of contamination?	Annex 15; 10.8
3.42	Has the manufacturer adequately considered the potential effects of routine use of the equipment over time on the integrity of the equipment surfaces and the potential for any impact on the validated cleaning method e.g. pitting and wear during use?	Annex 15; 10.5

	PERSONNEL	
3.43	Have personnel been adequately trained and periodically assessed in processes to prevent cross-contamination and recontamination?	2.10, 2.11
3.44	Are the required working behaviours of personnel, to prevent opportunities for cross-contamination, defined in procedures and aligned to the hazard presented? Have the procedures been implemented and demonstrated to be effective?	2.10,2.11, 2.14, 4.1

3.45	Is there adequate supervision or oversight in processing areas to ensure that the required personnel behaviours are employed to prevent opportunities for cross-contamination?	1.4iii, 2.10,2.11, 2.14
3.46	Are all change/clothing requirements adequate to prevent cross-contamination for all personnel that may enter and exit manufacturing areas?	3.1,3.31
3.47	Is cleaning of protective clothing controlled in a manner to prevent cross-contamination?	3.1,3.31, 3.37, 5.21
3.48	Has the re-use of Personal Protective Equipment (PPE) been controlled to adequately protect it from recontamination and to prevent this being a source of cross-contamination?	5.21
3.49	Is the movement of people, between production areas, controlled to prevent cross-contamination in accordance with risk management principles for: • Production personnel, and • Support personnel (e.g. QC, maintenance, engineers and contractors, etc.)?	1.12, 1.13, 3.5, 3.27, 5.21

6. REFERENCES

PIC/S PE 009 Guide to Good Manufacturing Practice for Medicinal Products, Part I; Basic Requirements for Medicinal Products

PIC/S PE 009 Guide to Good Manufacturing Practice for Medicinal Products Annexes including PIC/S Annex 20 Quality Risk Management.

PIC/S PI 038 Aide Memoire on Assessment of QRM Implementation

PIC/S PI 046 Guideline on Setting Health Based Exposure Limits for use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities

7. REVISION HISTORY

Date	Version Number	Reasons for revision