Feedback from the Industry on Implementation of the Annex 1

Richard Denk

Senior Consultant Aseptic Processing & Containment

SKAN AG

PDA Parenteral Drug Association

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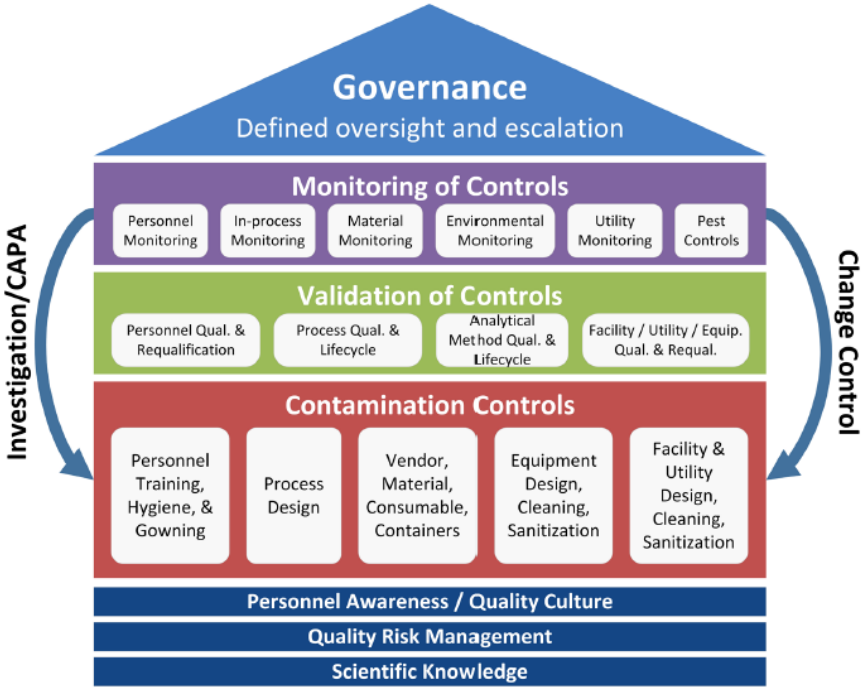
Quality Risk Management QRM and Contamination Control Strategy CCS



Quality Risk Management QRM and Contamination Control Strategy CCS

- PDA FDA Joined Conference Washington DC September 2023

Implementation of Annex 1

- Quality Risk Management QRM and Contamination Control Strategy CCS implementation
- Investigate the most critical steps for your sterile product. Where do you have open sterile Container, Filling path, Stopper Transfers until your Container is closed
- Investigate the transfers from C to A or B to A. Are they validated? Do they provide appropriate Transfer Technologies
- Investigate your current manual interventions. Can they be eliminated or automated.
- Does an upgrade of your installation to a RABS is possible or better replace to an Isolator?

Implementation of Annex 1

Have a look at some critical requirements implementing Annex 1

First Air

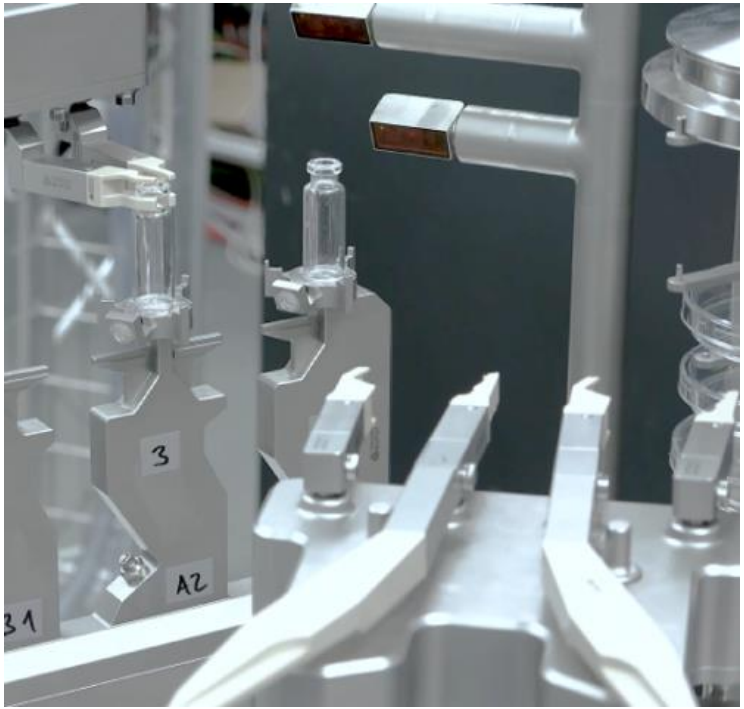
4.4 For the manufacture of sterile products, there are four grades of cleanroom/zone.

Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing
c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

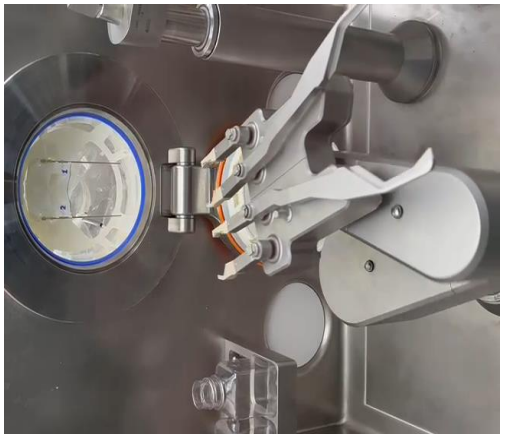


First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

First Air

- Installation Filling Path

- Installation Filling Path



First Air

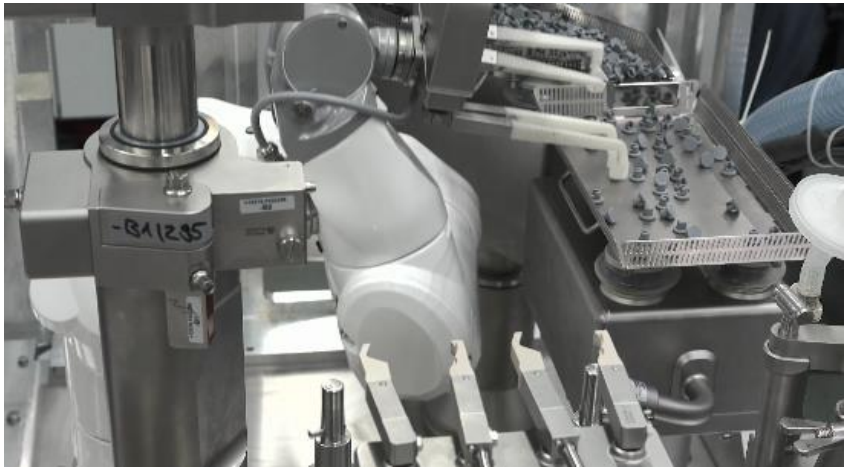
- Vîable Monitoring

- Viable Monitoring

First Air

- Stopper Transfer

- Stopper Transfer



Indirect Product Contact Parts

5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

Stopper Transfers

- Stopper Bowl and Stopper transfer concerns and important to consider:

  - Evaluate the risk of your current technology e.g.,

  - How does the design of your stopper bowl and transfer looks like. It is easy to clean? Does the vaporized or sprayed hydrogen Peroxide reach all surfaces?

  - Does the assembly of the stopper transfer parts support aseptic assembly and reduce the risk of contamination?

Stopper Transfers

- Stopper Bowl and Stopper transfer Design to meet Annex 1 requirements

  - The design shall provide first air protection in critical zones und unidirectional airflow that sweeps over and away from exposed products during processing

  - The design shall allow to install all components without touching critical surfaces and avoid working above critical surfaces

Material Transfers

- E-Beam, Material Airlocks, RTPs

8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

Material Transfers

- RTP – Single Use

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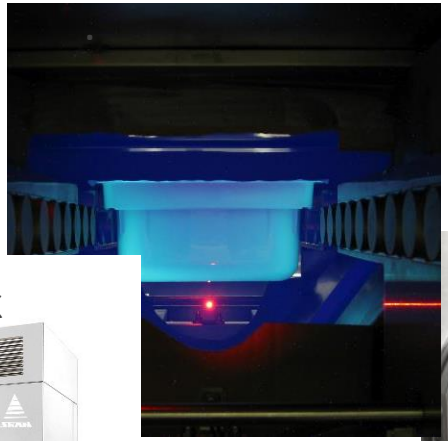
- E-Beam



- H2O2 Airlock

- AT Sterile Connector

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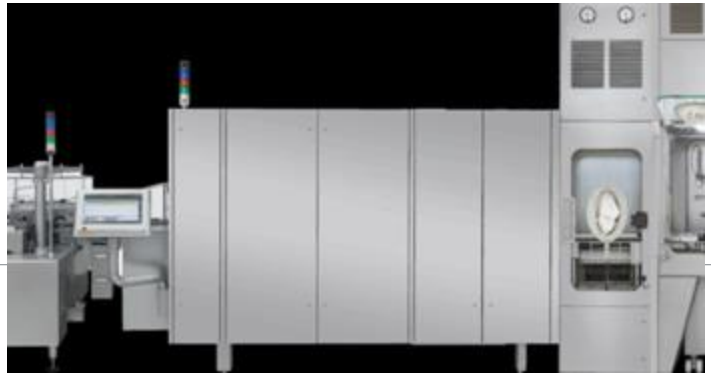
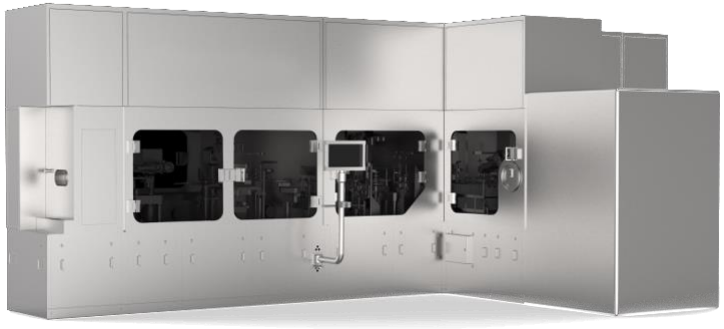


- Dry Heat Tunnel

Barrier

- RABS/cRABS or Isolator
- Europe and Noth America are Isolator focused based on Information from the FDA during ISPE and PDA Conferences
- PDA Survey from 2018, 50% Conventional Installations and 50% Barrier of new installation
- ISPE Survey from 2022 20% Conventional and 80% Barrier.

Retrofit Existing Installations



Source: Groninger RoboCell

Retrofit Existing Installation

- What is important to consider?

  - Does the current installation meet the new Annex 1, like first air, transfer etc.?
  - Investigate if current interventions are needed or could they be avoided or replaced through other technologies or automated system.
  - Is it possible that all your planned interventions and monitoring performed in the Barrier without open door?
  - Cost is no excuse not to invest in advanced technologies

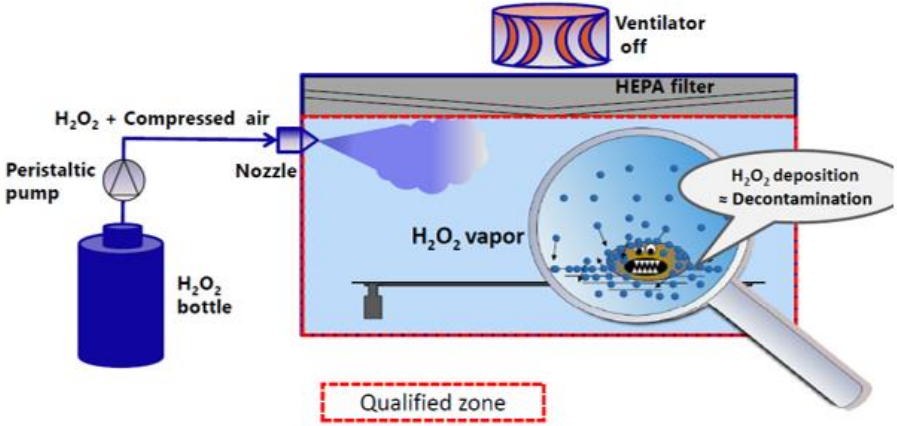
Decontamination

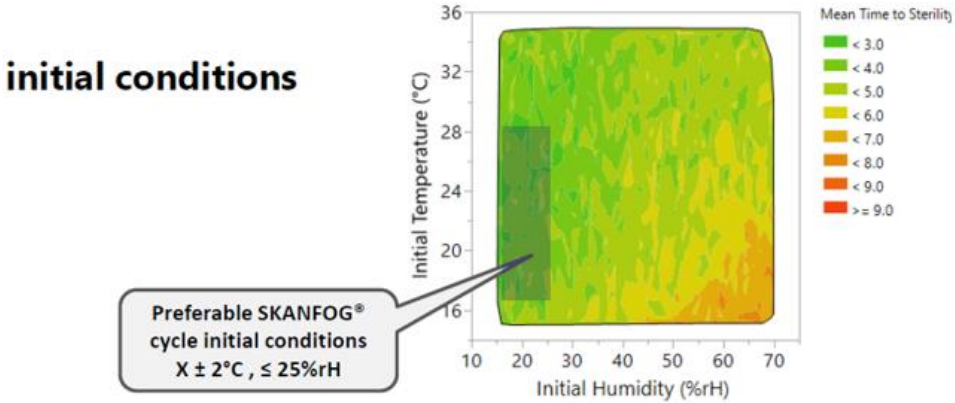
- Isolators

4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.

i. For isolators

The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.





Gloves

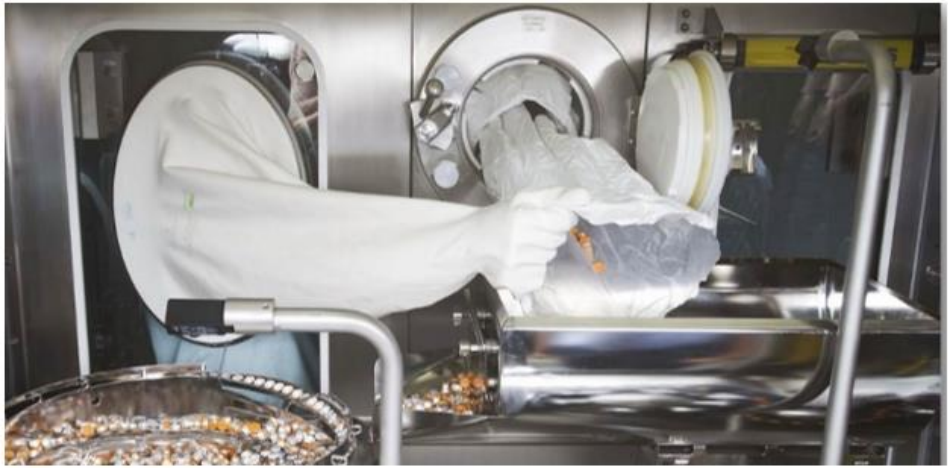
- In Isolators

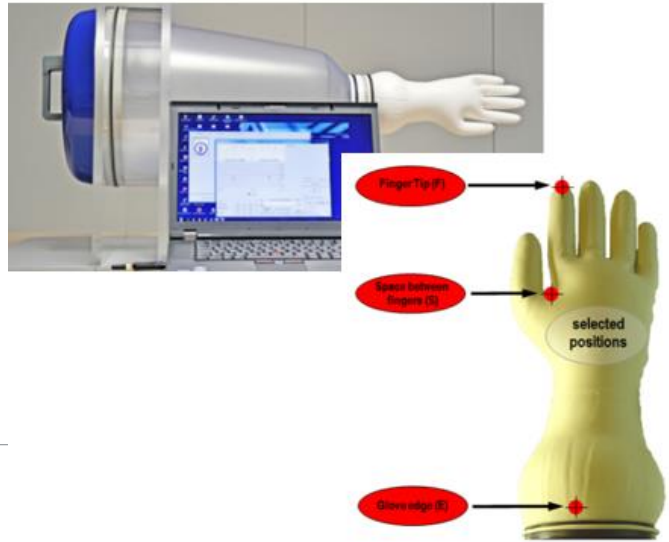
4.21 The materials used for glove systems (for both isolators and RABS), should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

i. Isolators:

a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length.
Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.
For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.

b. Integrity / leak testing of isolator systems should be performed at defined intervals.





Cleaning

- Cleaning before Decontamination
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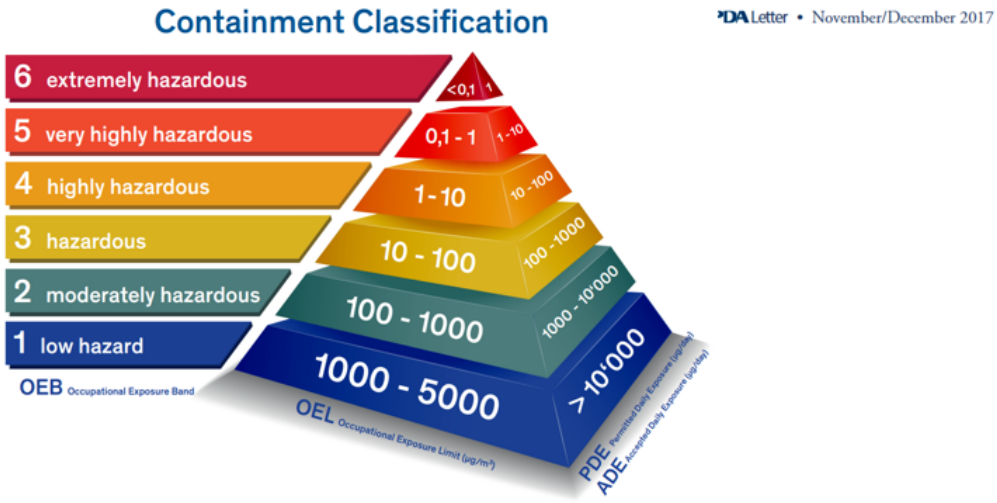
5.4 The cleaning process should be validated to be able to:

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

Table 1 Proposed EH&S and GMP surface limits for non-product contact surfaces and air limits inside of isolators

Occupational Exposure Bands (OEBs) Acceptable worker exposure (µg/m³) *(8-hour time-weighted average). The acceptable exposure is the conservative end of the OEB.*	Limit for surface with no direct product contact inside the isolator (µg/dm²) *Acceptable based on GMP and occupational health criteria.*	Limit for "public" surface with uncontrolled possibility of unprotected hand contact (µg/dm²) *Driven by occupational health criteria only.*	Limit for airborne API inside of isolator after cleaning at product changeover (µg/m³) *Driven by GMP criteria only.* **
OEB 1: range 1000-5000 ug/m³ Exposure limit: 1000 ug/m³	Visually clean	Visually clean	10000
OEB 2: range 100-1000 ug/m³ Exposure limit: 100 ug/m³	Visually clean	100	1000
OEB 3: range 10-100 ug/m³ Exposure limit: 10 ug/m³	100	10	100
OEB 4: range 1-10 ug/m³ Exposure limit: 1 ug/m³	10	1	10
OEB 5: range 0.1-1 ug/m³ Exposure limit: 0.1 ug/m³	1	0.1	1
OEB 6: range less than 01 ug/m³ Exposure limit: 0.01 ug/m³ or lower	0.1 or lower	0.01 or lower	0.1 or lower

** This limit is safe under the assumption that as a maximum, the total API burden of the previous product suspended in 1 m³ of air inside the isolator would go into one single therapeutic dose of the following products. Please also consider above that for simplification reasons the PDE/OEL ratio of 10 was assumed in regard to cross-contamination. Be aware that this needs to be justified for each product and product sequence due to difference in adjustment factors and administration route.



Cleaning

- Cleaning before Decontamination
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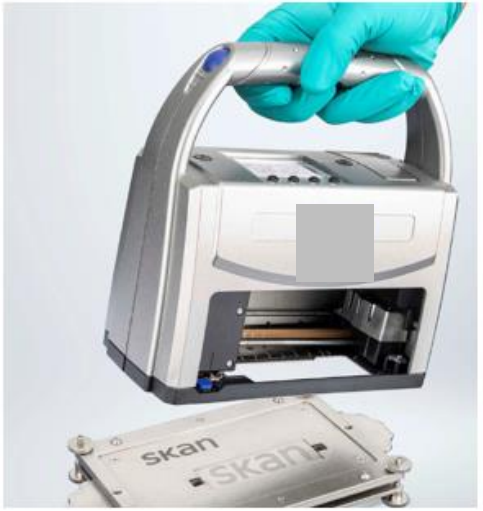
CLEAN IP

CLEAN Indicators & Prints

- SKAN contamination dosing printer technology is designed to help our customer to establish suitable contamination control strategies.
- No more random and uncontrolled spiking studies where the pattern distribution is left to chance.
- By using our SKAN patented printing approach you will be able to reliably and accurately deposit contamination patterns on your manufacturing and surrogate materials.



CLEAN IP

CLEAN Indicators & Prints

Your challenge

- Development and test of a suitable cleaning strategy
- Identify for different materials the visual threshold when your API or residues becomes visible
- Check residual contamination after the cleaning process

Robotics

2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).

Thank you