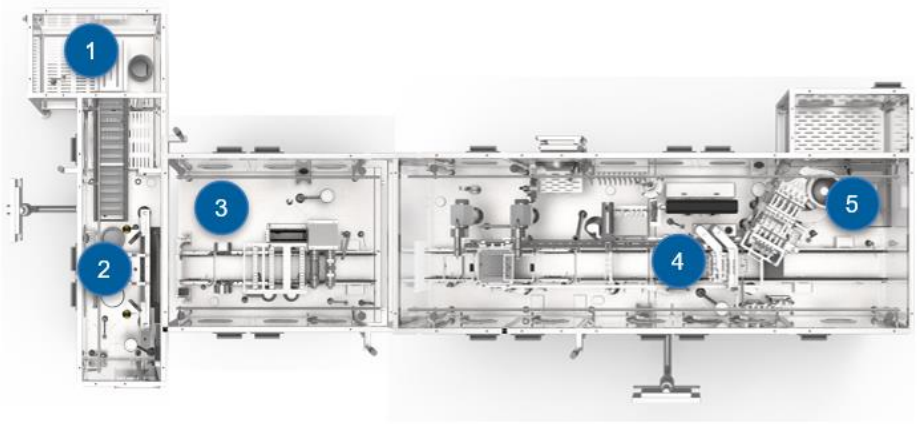
Environmental Monitoring Risk Analysis (EMRA)

PDA EU00192
Manage Your Aseptic Filling Line
4/5 September 2024

Robert Kibele, groninger & co. gmbh

PDA Parenteral Drug Association
PDA TRAINING

Recap: Overview of the filling line



Process Step Overview:

1. Opening of 1st bag
2. Opening of 2nd bag and transfer to grade A
3. Delidding/Delining and exposing container to grade A
4. Filling
5. Stoppering

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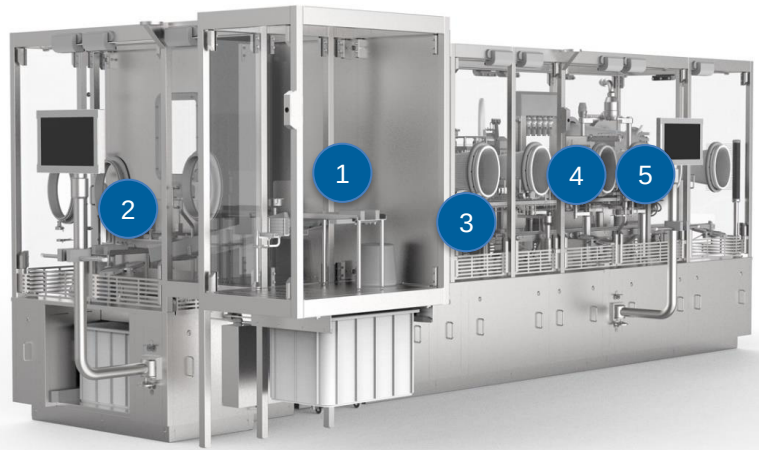
Recap: Overview of the filling line



Process Step Overview:

1. Opening of 1st bag
2. Opening of 2nd bag and transfer to grade A
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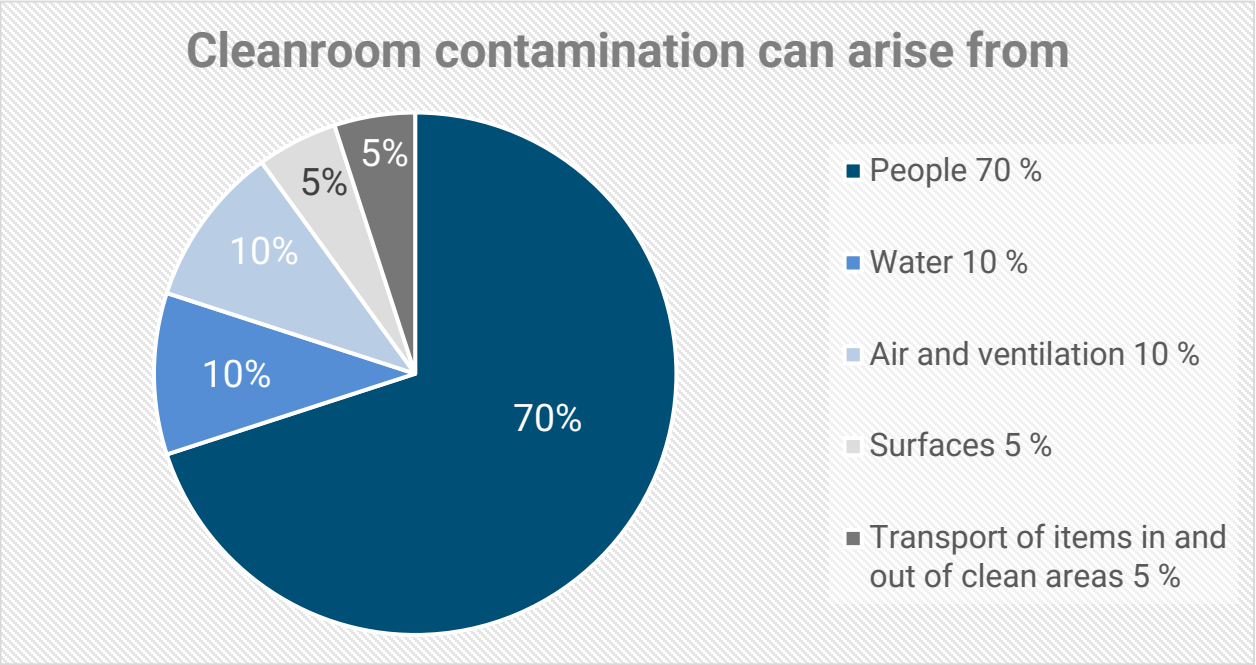
Sources of contamination



Reference: Sandle, 2020

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Regulatory basis

Annex 1, 9.4

"**Risk assessments should be performed** in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment."

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Quality risk management (QRM) process

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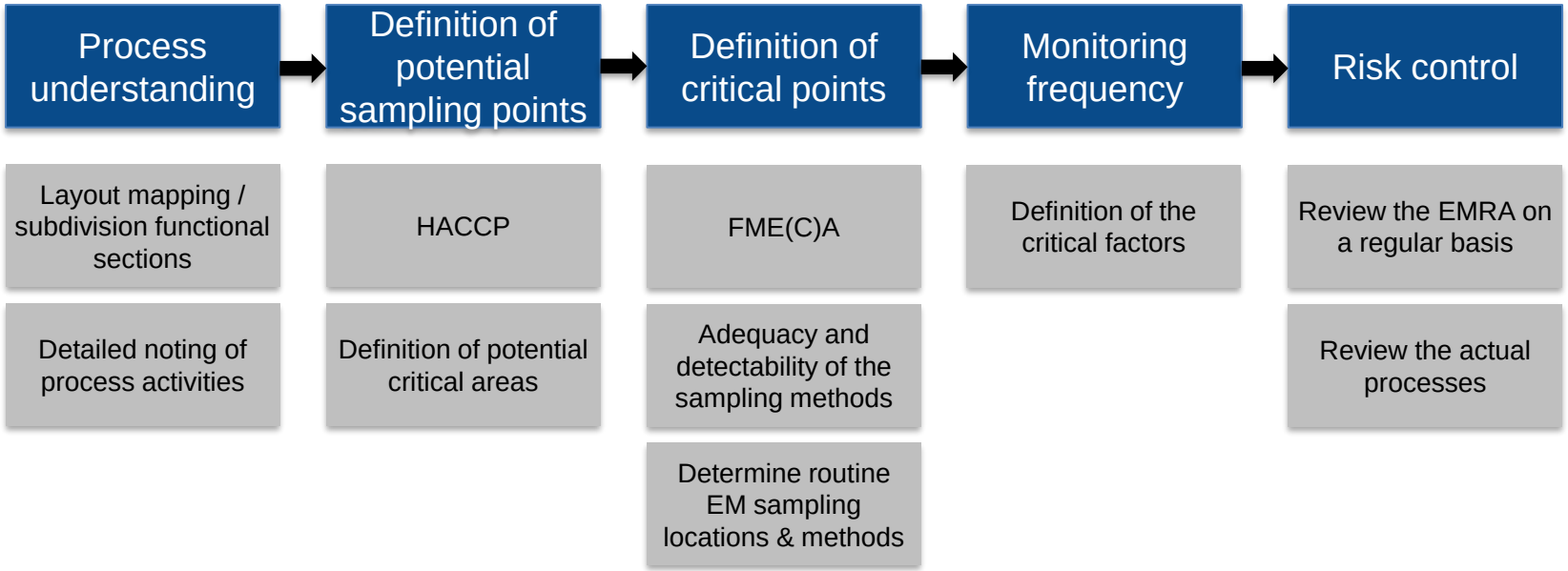
Creating a risk assessment – process flow



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Process understanding

Defining areas and subdivision

ISO 14644-1:2015-12
Cleanroom classification regarding air cleanliness in terms of airborne particle concentration

Define areas regarding air classification

Subdivision

The subdivision areas must be of equal size

Cleanroom area (m^2) less or equal to	Minimum Number of sampling locations to be tested (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7

N_L for larger areas can be found in ISO 14644-1.

ISO 14644-1 specifies the number of sampling points for operational qualification (OQ) purposes.

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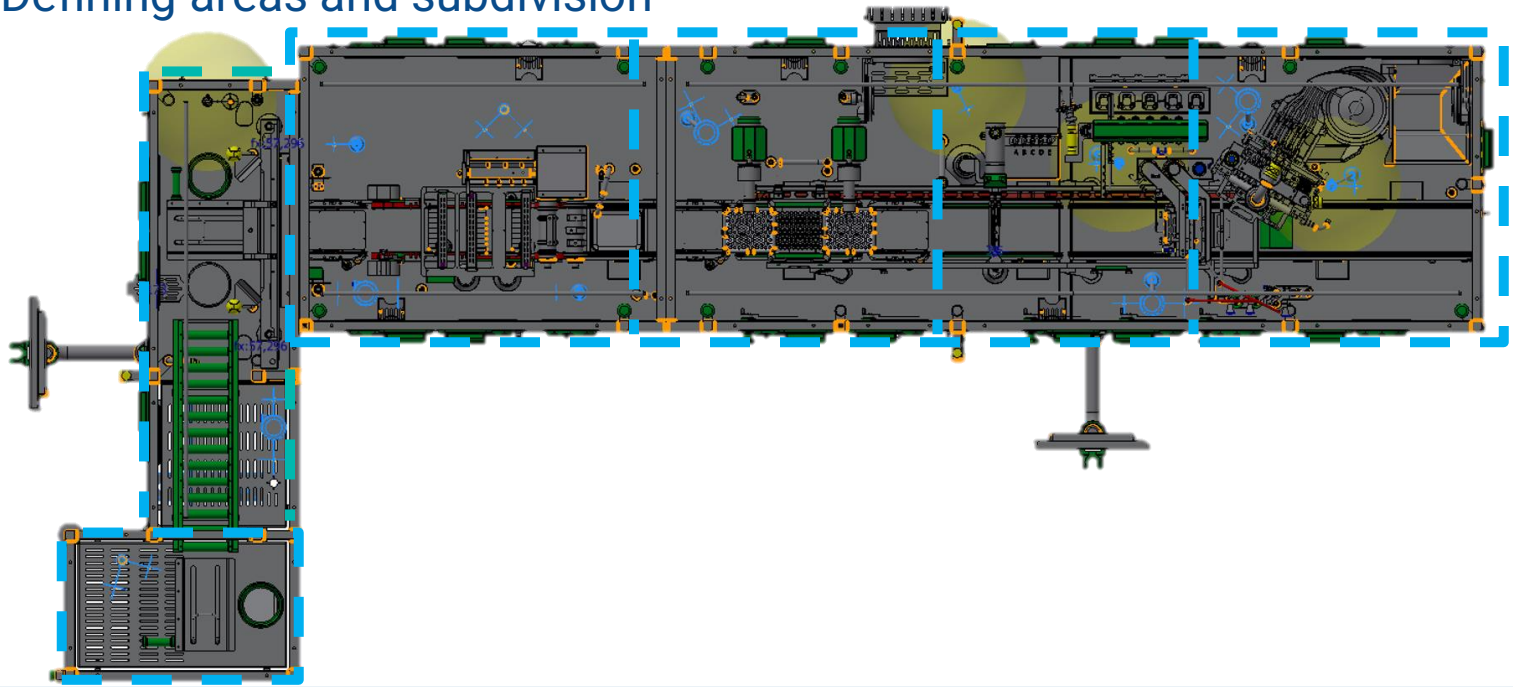
Process understanding

Defining areas and subdivision



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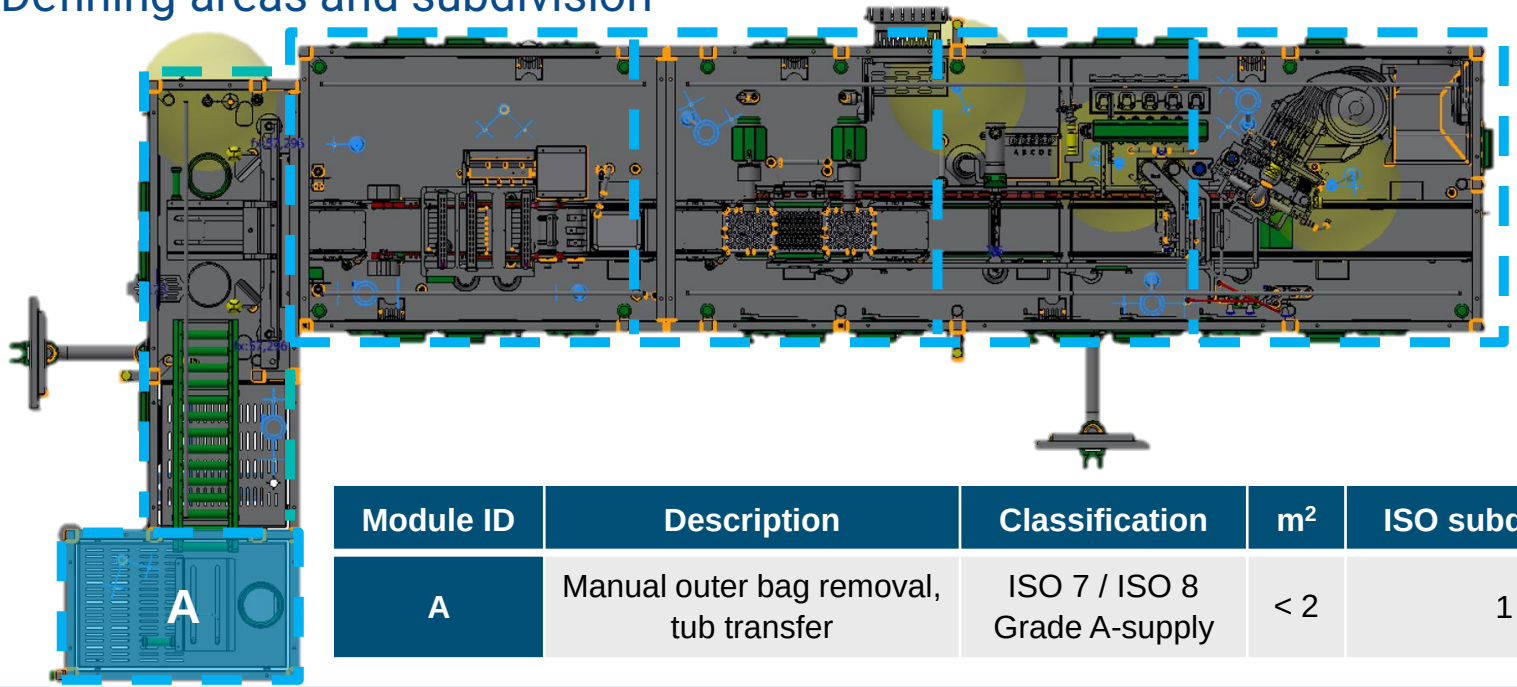
Process understanding

Defining areas and subdivision



Module ID	Description	Classification	m^2	ISO subdivision
A	Manual outer bag removal, tub transfer	ISO 7 / ISO 8 Grade A-supply	< 2	1

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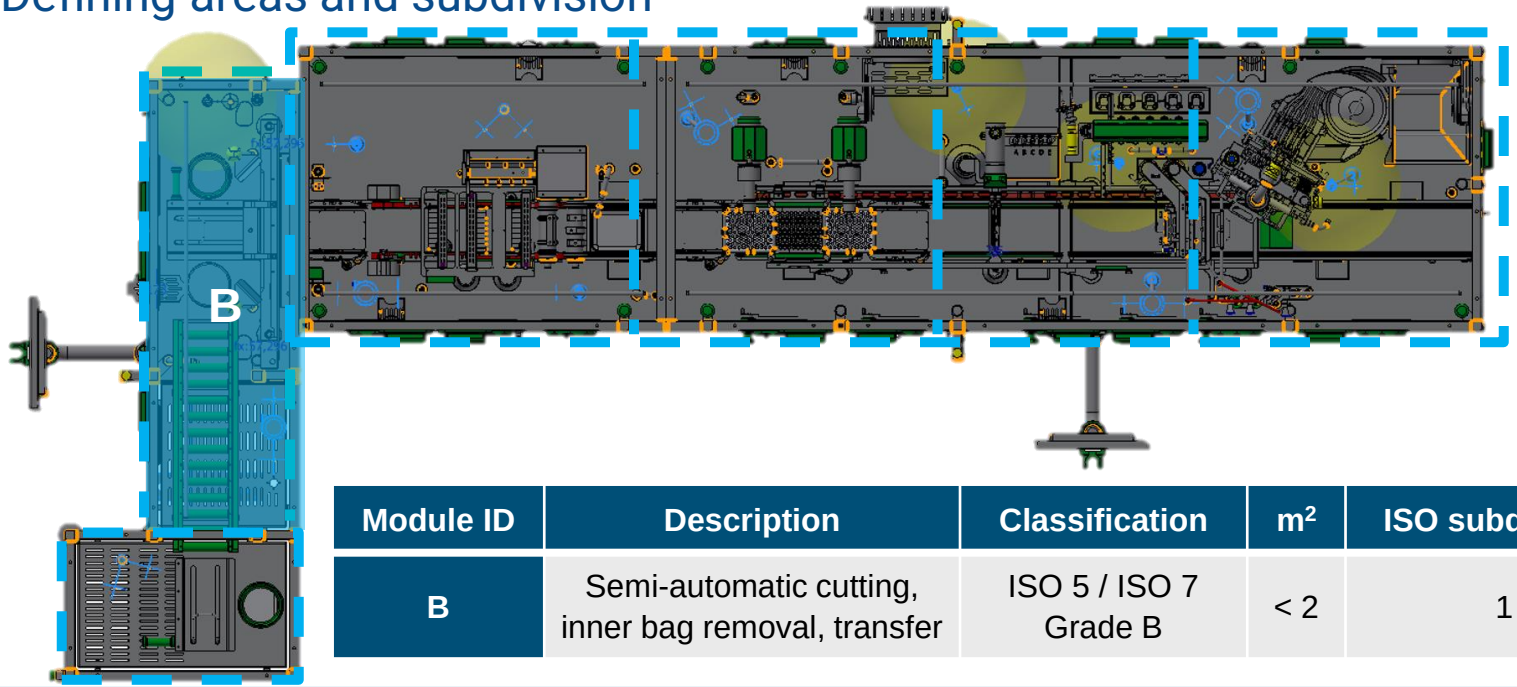
Process understanding

Defining areas and subdivision



Module ID	Description	Classification	m^2	ISO subdivision
B	Semi-automatic cutting, inner bag removal, transfer	ISO 5 / ISO 7 Grade B	< 2	1

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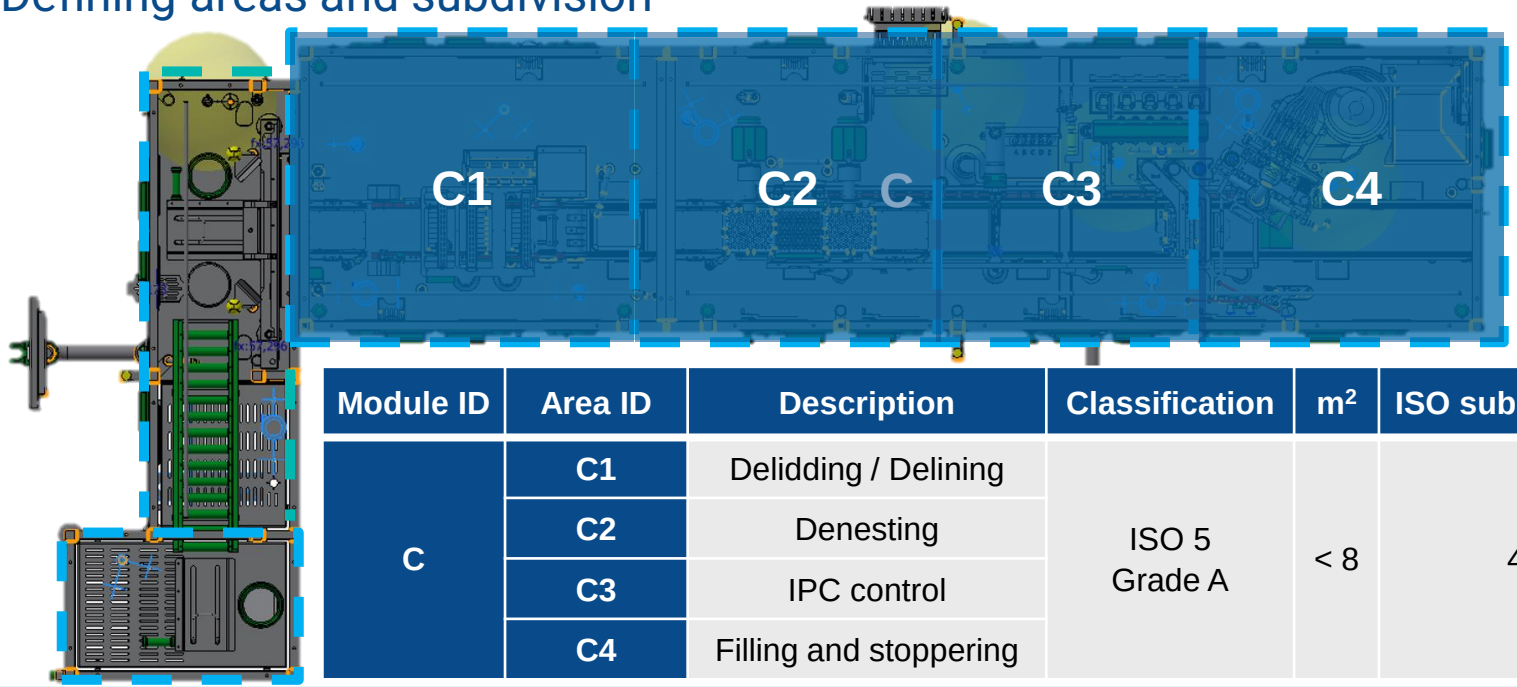
Process understanding

Defining areas and subdivision



Module ID	Area ID	Description	Classification	m²	ISO subdivision
C	C1	Delidding / Delining	ISO 5 Grade A	< 8	4
	C2	Denesting			
	C3	IPC control			
	C4	Filling and stoppering			

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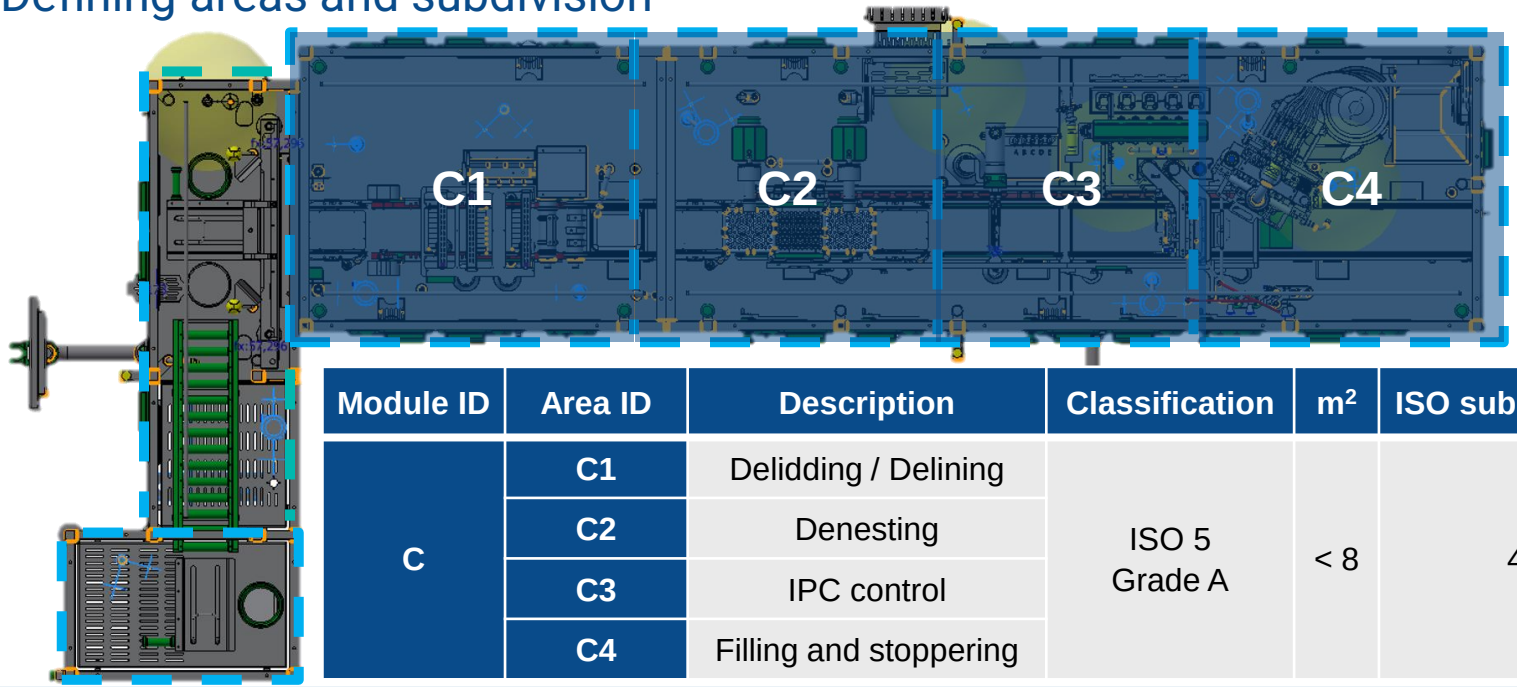
Process understanding

Defining areas and subdivision



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C	C1	Delidding / Delining	ISO 5 Grade A	< 8	4
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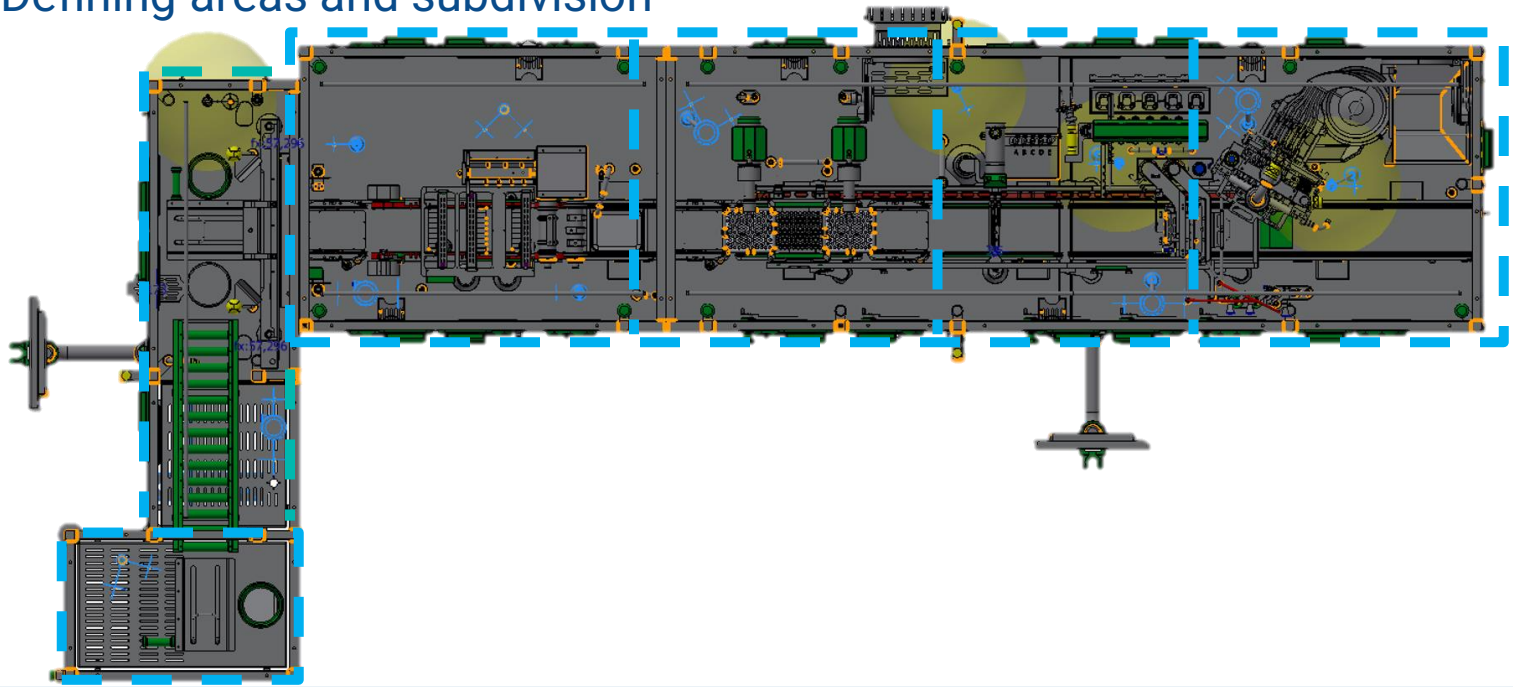
Process understanding

Defining areas and subdivision



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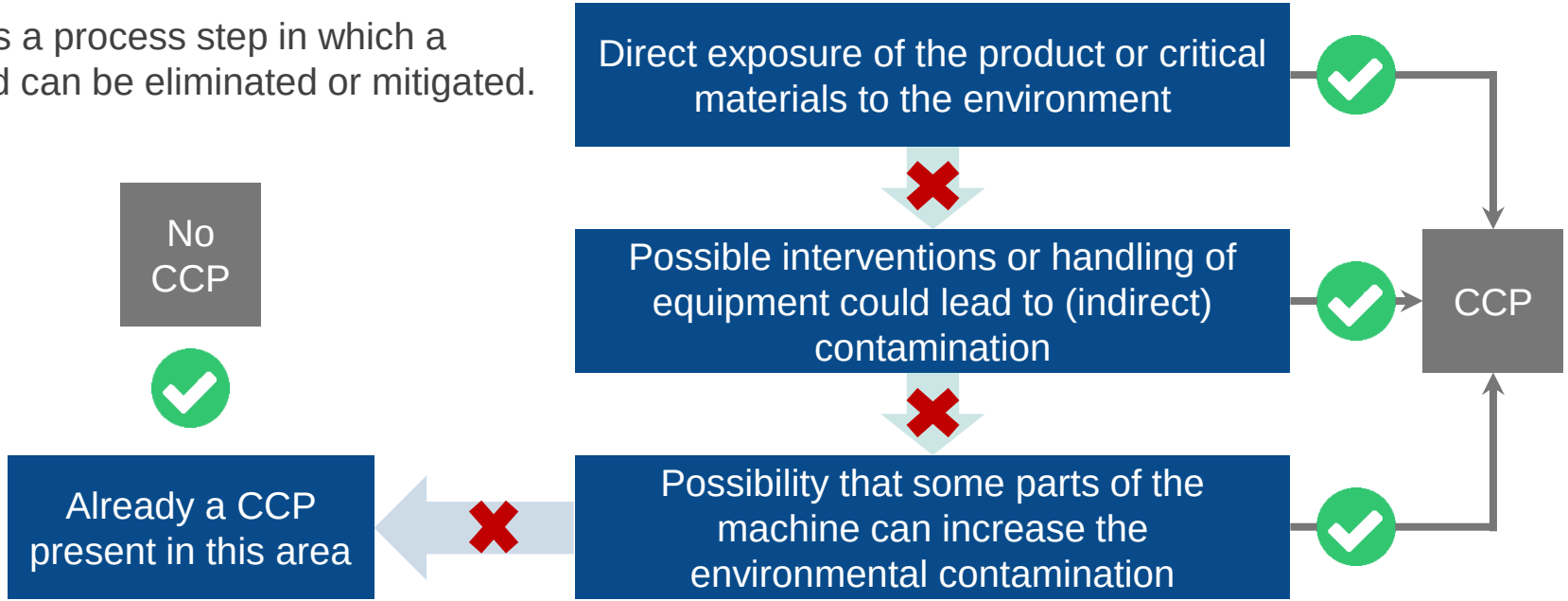
Definition of potential sampling points

HACCP

CCP is a process step in which a hazard can be eliminated or mitigated.



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Definition of potential sampling points

Critical areas – air sampling

Definition of critical areas according to Annex 1 (section 4.28 and 9.24)

Examples:

- Critical processes in general, like:
  - Filling process
  - Stoppering process
- In- and out-put of material within grade A, e.g. mouse holes and RTP ports
- Transport of open primary packaging containers and stoppers
- Transition between cleanroom classes (e.g. Grade C → Grade A or Grade A → Grade C)

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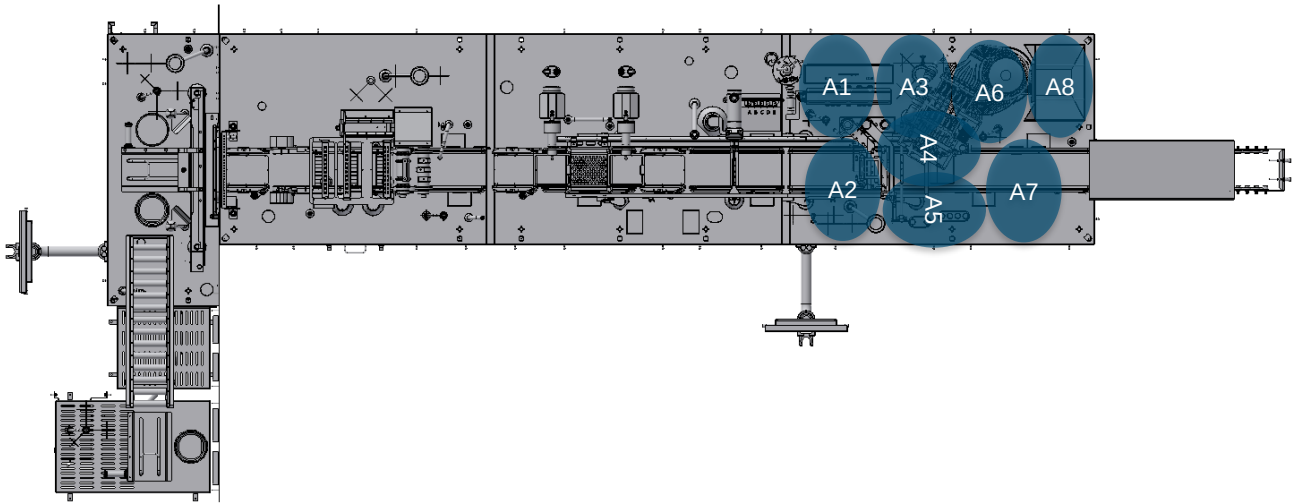
Definition of potential sampling points

Critical areas – air sampling



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Definition of potential sampling points

Critical areas – surface sampling

Definition of critical surfaces according to Annex 1 (Glossary):

Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

Examples:

- Needles
- Feeding and sorting equipment for stoppers and plungers
- Stoppering arms

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Definition of critical points

FMEA theoretical approach

The FMEA method is modified for establishing the Risk priority Number (RPN).
RPN = Severity (of the event) × probability (of the event occurring) × detection (probability that the event would not be detected before the user was aware of it)

Severity = impact of the failure on the product → considered a constant value (S = 1)
Detection = continuous for viables and particles during the whole process in the modules –> considered a constant value (D = 1)
Probability = for the product to be contaminated and varies according to the area or surface examined → the probability (occurrence) varies (P = X)

→ The probability it is the determining value to calculate the RPN

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Definition of critical points

FMEA theoretical approach – probability evaluation

Probability values

- P1: Assessment of the representativeness of the sampling from the process point of view
- P2: Assessment of the filling line design
- P3: Assessment of processing of product and primary packaging material

RPN = P1 x P2 x P3

- Values must be assigned according to the criticality
  - E.g. high risk, medium risk, low risk – 5, 3, 1 or 10, 5, 1

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Definition of critical points

FMEA theoretical approach – probability evaluation

Probability Evaluation for areas (air sampling) – Examples

Probability P1	Risk factor	Value	
$P1_a$	Process evaluation	High Filling and stoppering activities Automated critical operations (e.g. separation of primary packaging material) Set-up activities (e.g. filling needles)	**5**
		Medium Transit of open, empty primary packaging containers Temporary / short storage of primary containers and stoppers	**3**
		Low Transit of closed primary packaging containers and / or monitoring materials	**1**

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FMEA theoretical approach – probability evaluation

Probability Evaluation for areas (air sampling) – Examples

Probability P2	Risk factor	Value	
$P2_a$	Close to the mechanical parts in movement	Movement of mechanical parts above primary packaging material / open drug product	**5**
		Movement of mechanical parts nearby (not above) the assessed process	**3**
		No movements of mechanical parts nearby the assessed process	**1**
$P2_b$	Presence of RTP ports in the area	**Yes** There are RTP ports present which allow an input of materials from the outside.	**3**
		No	**1**
$P2_c$	Presence of connecting points to grade C (e.g. waste chutes, mouse holes)	**Yes** There are connecting points to grade C.	**3**
		No	**1**

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Definition of critical points

FMEA theoretical approach – probability evaluation

Probability Evaluation for areas (surface sampling) – Examples

Probability P2	Risk factor	Value	
$P2_a$	Close to the mechanical parts in movement	**Yes** Movement of mechanical parts nearby the assessed process	**3**
		No	**1**
$P2_b$	Type of surface material	Plastic, plexiglass	**5**
		Painted steel, PVC enameled steel, other metallic materials, PEEK, glass	**3**
		Stainless steel 316L, 304, 1.4435 or 1.4404	**1**
$P2_c$	Surface constitution	Irregular	**3**
		Regular	**1**

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Definition of critical points

FMEA theoretical approach – RPN calculation

- RPN calculation $RPN_{AIR/SURFACE} = (PX_a)\ x\ (PY_a + PY_b + PY_c)\ x\ (PZ_a + PZ_b)$
- The calculation consequently has a minimum and maximum value
- The risk is categorized in high, medium and low, e.g.:
  - Low risks values of ≤ 15 % of the value range
  - Medium risks > 15 % - 40 % of the value range
  - High risks > 40 % of the value range

Risk category	range value $RPN_{AIR/SURFACE}$	Risk category description
High	NNN – NNN	High risks that are above the acceptability. It is necessary to sample the area.
Medium	NN – NNN	Medium risk is acceptable. If there is no high risk in the evaluated module, it is necessary to sample the area considering the “highest” medium risk.
Low	N – NN	Low risk is acceptable. It is not necessary to sample the area in order to map the environment.

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Definition of critical points

FMEA theoretical approach – risk acceptance

Risk category	range value $RPN_{AIR/SURFACE}$	Risk category description
High	NNN – NNN	High risks that are above the acceptability. It is necessary to sample the area.
Medium	NN – NNN	Medium risk is acceptable. If there is no high risk in the evaluated module, it is necessary to sample the area considering the “highest” medium risk.
Low	N – NN	Low risk is acceptable. It is not necessary to sample the area in order to map the environment.

- More EM (locations) ≠ safer process
  - It is not about putting EM devices everywhere on the line. “*Sampling methods should not pose a risk of contamination to the manufacturing operations”* (Annex 1, 4.31 and 9.8)
- Support for the selection of solid EM positions:
  - CFD simulations
  - Particle studies
  - Smoke studies

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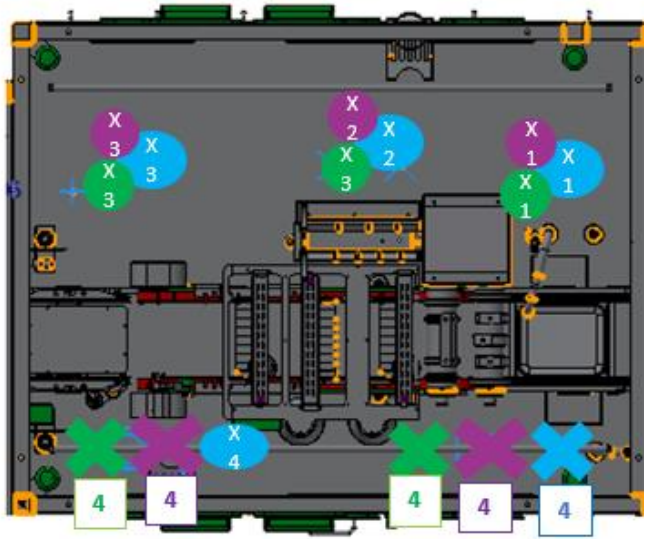
Definition of critical points

Determine routine EM sampling locations & methods – air



Description	Activity	ID	Value 1,3,5	Value 1,3,5	Σ	Value 1,3,5	Value 1,3,5	Value 1,3,5	Value 1,3,5	Σ	Value 1,3,5	Value 1,3,5	Σ	
The adhesive is loosened by the heating frame, then the lid and liner are removed and disposed of. Tub is moved via transport belt.	The vacuum rollers open the tubs	C1	5	3	8	3	3	3	1	10	1	5	6	480
	Transit of closed tub	C2	1	3	4	1	3	3	1	8	1	1	2	64
	Transit of closed tub	C3	1	3	4	1	3	3	1	8	1	1	2	64
	Transit of closed tub	C4	1	3	4	1	3	3	1	8	1	1	2	64

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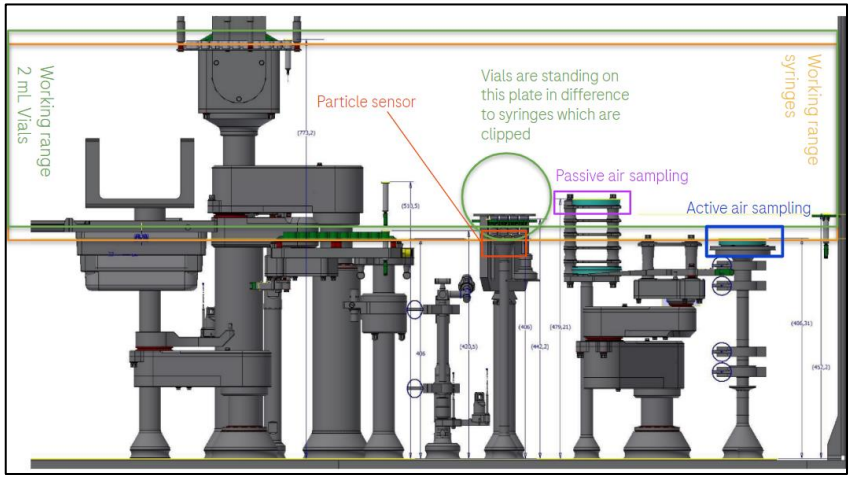
Definition of critical points

Determine routine EM sampling locations & methods – air

Annex 1, 9.7 / FDA CGMP, section X., A.:
The monitoring locations should be in a height representative of the working height during activities of the process

- The working range can be defined as the highest and lowest position of the opening of the primary packaging containers during processing
- Therefore, the sampling height can be defined as the lowest height of the open primary packaging containers



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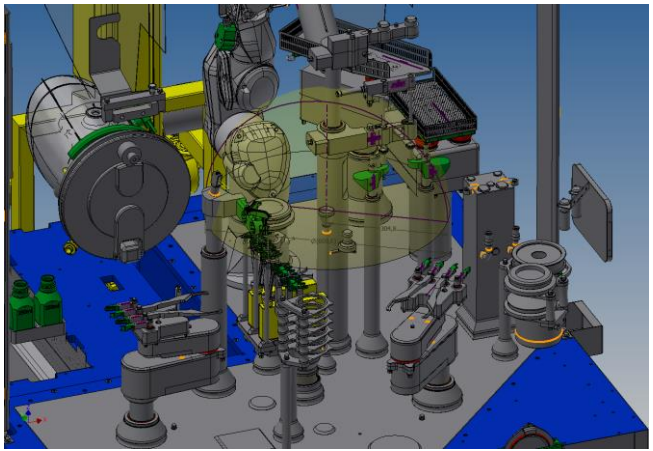
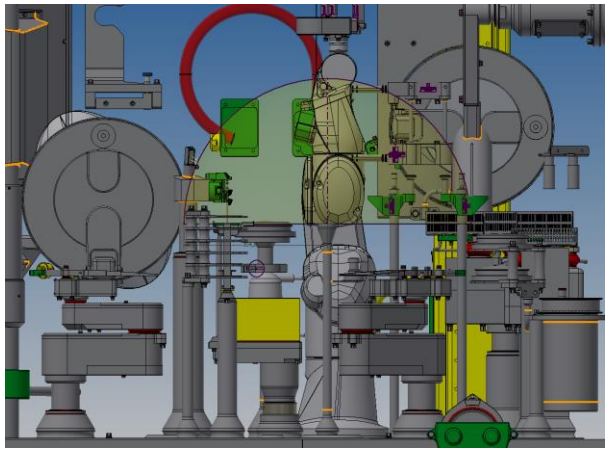
Definition of critical points

Determine routine EM sampling locations & methods – air

FDA CGMP, section IV., A.:
[…] *per-cubic-meter particle count […] at representative locations normally not more than 1 foot away from the work site […]*





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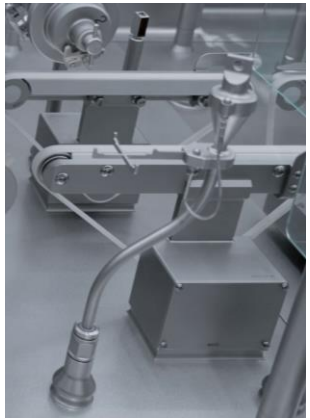
Definition of critical points

Widely used set-up for monitoring – air

Annex 1, 9.16 and 9.24:
For grade A, particle monitoring should be undertaken for the full duration […]
Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration […]



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Definition of critical points

Determine routine EM sampling locations & methods – surface

Module X	Filling and stoppering Contamination of the surfaces of this area is critical as it may leads contamination of primary packaging materials in contact with the product and / or the product itself.	S1	One pair of gloves	3	3	6	3	5	1	1	1	11	1	5	6	396
		S2	Needles (sample all needles with swab)	5	3	8	3	1	3	3	5	15	3	5	8	960
		S3	Feeding of the stoppers	5	3	8	3	1	1	1	5	11	1	5	6	528
		S4	Stopper track: final edge	5	3	8	3	1	3	3	5	15	1	5	6	720
		S5	Stopper piston	5	3	8	3	1	3	3	5	15	1	5	6	720
		S6	Top of the filling robot arm	3	3	6	3	1	1	1	3	9	1	1	2	108
		S7	Support for settle plates	1	3	4	1	1	1	1	3	7	1	3	4	112
		S8	Top of the stopper feeding arm	5	3	8	3	1	1	1	5	11	1	5	6	528
		S9	Outfeed conveyor	3	3	6	1	5	1	1	3	11	1	1	2	132

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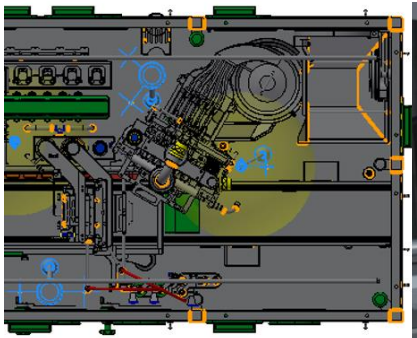
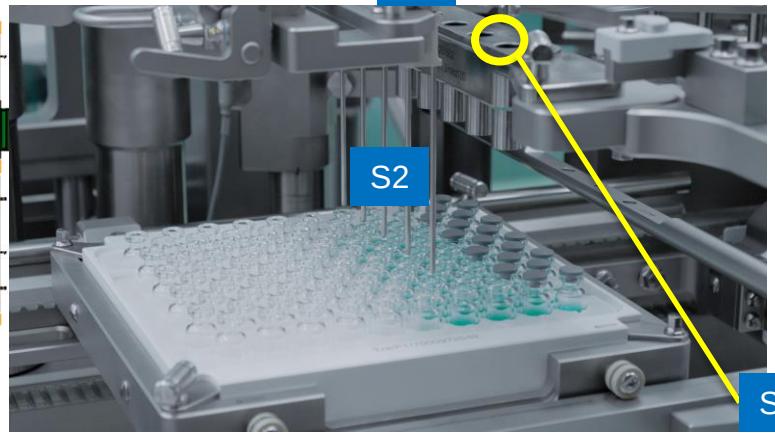
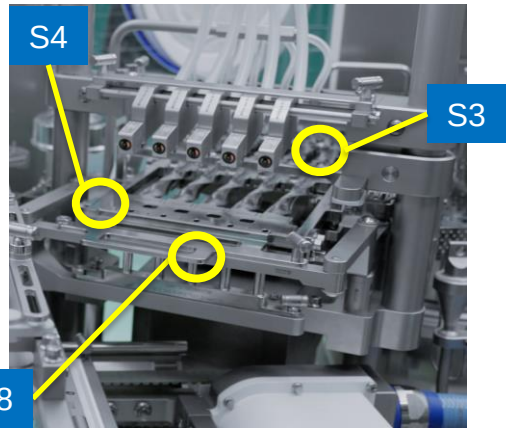
Definition of critical points

Determine routine EM sampling locations & methods – surface

S1 One pair of gloves







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Definition of critical points

Determine routine EM sampling locations & methods – surface

- Contact plates
  - 
    The plates are filled with sufficient medium to form a convex surface that supports the growth of the microorganisms. The contact plate is pressed against a flat surface for 10 seconds and then placed in an incubator for the time specified during method validation. → quantitative results
  - Contact plates are not suitable for sampling irregular surfaces and leave media residues
- Swabs
  - 
    Requires a suitable diluent in which the swab is stored before use. Area needs to be defined and method validated. → qualitative and quantitative (based on processing)
  - 
    Used for irregular surfaces which cannot be sampled with contact plates. Can be used for flat surfaces if template is used to define the sample size

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Monitoring frequency

Example – based on the level of criticality

Level of criticality	Description	Frequency
High	Aseptic filling where no further processing takes place. Here the risk of contamination would have a considerable product impact because contaminants could not be reduced or removed by further processing.	**Total particle**: In continuous **Settle plates**: In continuous. **Active air**: Each shift and/or each batch (start, middle, end) **Surfaces**: At the end of the batch
Medium	Indirect exposure of the materials in direct contact with the product is somewhat likely to introduce contaminants. This may apply to areas where little or no open processing occurs or where risk mitigation significantly reduces the risk (de-bagging).	**Total particle**: At least 1 m^3 per batch or in continuous in grade A air supply areas **Settle plates**: One sampling per batch (> 2 h up to < 4 h) **Active air**: At least 1 m^3 per batch **Surfaces**: At the end of the batch
Low	Indirect exposure to the environment is highly unlikely to introduce contaminants that could affect the finished product. If a contaminant were to be introduced, sufficient downstream controls and/or the use of preservative agents are highly likely to remove and significantly reduce contaminants.	Not Applicable

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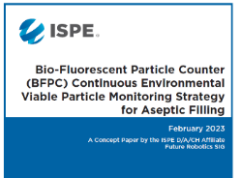
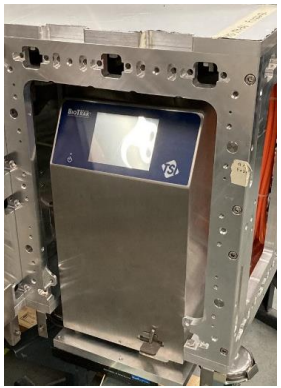
Bio-fluorescent particle counters

Developments in environmental monitoring



Annex 1, 9.28:
The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers […]

- Consideration of sampling position
- Space requirements in the machine base
- Accessibility from cleanroom (viable findings)
- Possibility for simultaneous operation of conventional active viable sampling and BFPC for validation purposes
- Implementation of strict SOP for handling AFU counts



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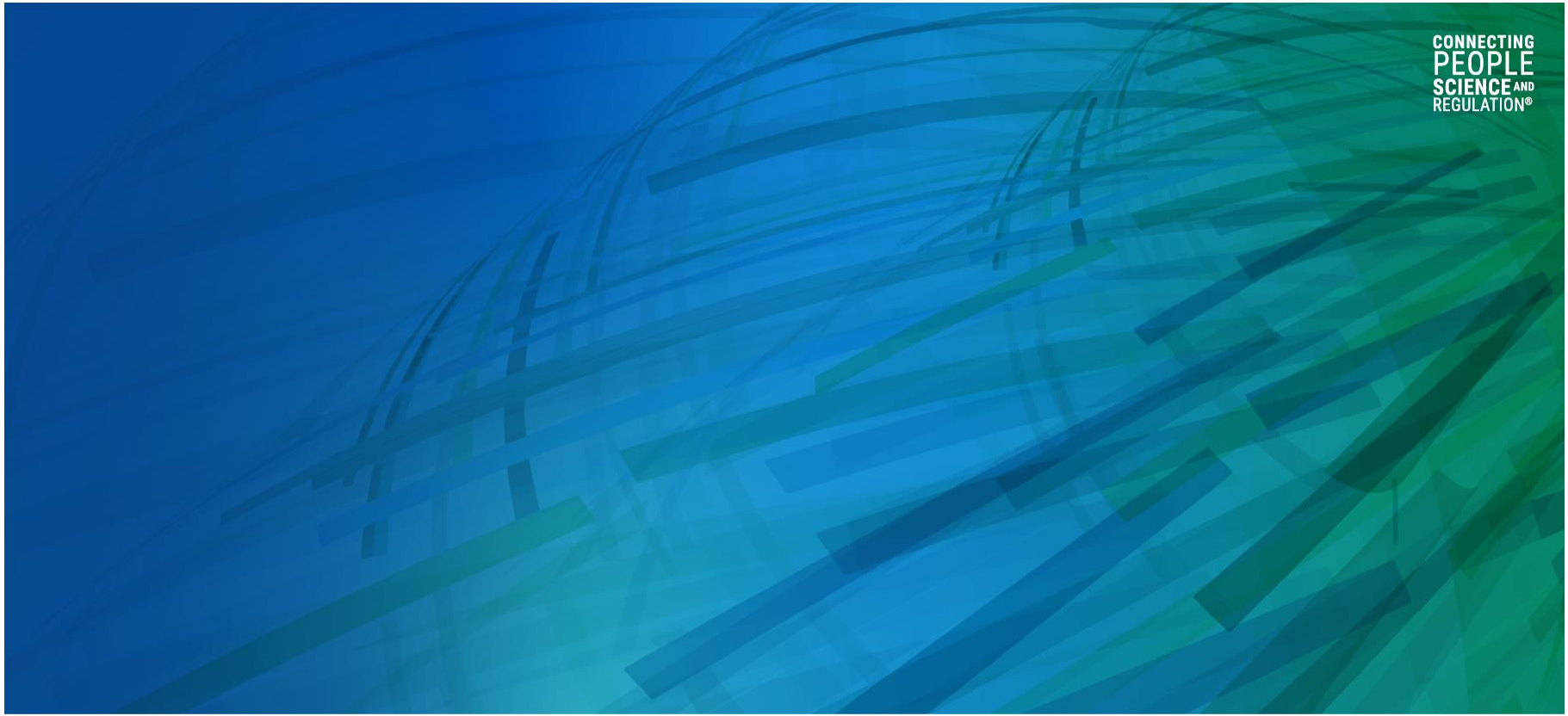

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