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“Quality Risk Management Process for multi product on fermentation and microfiltration equipment Case study from class B1 product to other products”

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Quality Risk Management Process (QRMP) is one of main tools to evaluate and manage areas of business and government including finance, insurance occupational safety, public health, through the systematic approach based on scientific knowledge

In pharmaceutical world the "ICH guidance Q9 Quality Risk Managements" provides specific guidance to manage the quality risk.

General Quality Risk Management Process

The present quality risk process management is based on a systematic process for the assessment, control, communication and review of risks to the quality of the Active Pharmaceutical Ingredients (API) or any Intermediate or Drug Product across the product lifecycle.
The model implemented in the present process is outlined in the following diagram and it is fully according with model proposed in the ICH Q9.

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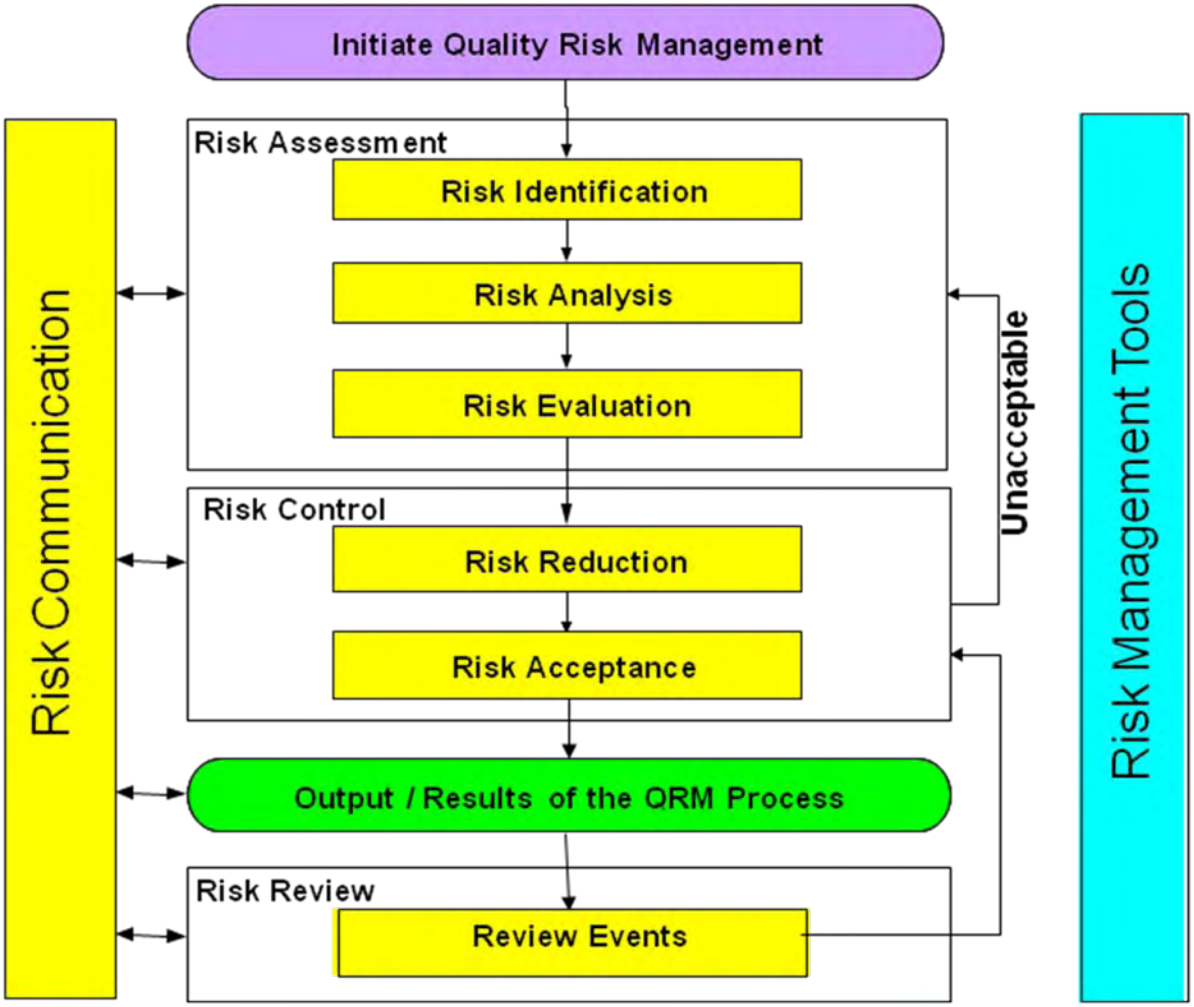

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Risk Identification

Defining the Risk Question

Which is the risk of cross contamination and regulatory deviation related to a multiproduct use of fermentation and microfiltration area?

Risk Analysis

Identifying an appropriate Risk Assessment Method/Tool

According to the key role of detection in reducing the overall risk of the process, the FMEA methodology has been used to analyze, basing on scientific knowledge, processes and equipments.

Risk Analysis

Define meaning of risk components

Severity (SEV)

- Cross-contamination
- Regulatory deviation

Occurrence (OCC)

- Likelihood of occurrence of the single severity risk components

Detection (DET)

- Detection degree for each potential contaminant

Define the scales for severity, probability and detection

Linear : 1,2,3,4,....

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Severity Scale

How severe the EFFECT is ?

Severity Ranking Table		
Rank	**Classification**	**External and Internal Effect**
10	Liability	Failure could injure the customer or an employee.
9	Reliability / reputation at risk	Failure would create non compliance with regulations.
8		Failure renders the unit inoperable or unfit for use. Supply to the customer could be interrupted.
7	Customer quality inconveniences	Failure causes a high degree of customer dissatisfaction (impact on finished product).
6		Failure results in a subsystem or partial malfunction of the product (impact on next step / intermediate).
5	Reduced yield or special handling required	Failure impact equipment that could be not suitable for use.
4		Failure impact equipment and its suitability for next use (corrective action to be taken).
3		Failure impact equipment during production operation.
2		Failure may not be readily apparent to the customer, but would have minor effects on the customer’s process or product. (Failure impacts equipment not yet used)
1	Unnoticed	Failure would not be noticeable to the customer and would not affect the customer’s process or product.

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Occurrence Scale

How often does the CAUSE occur?

Occurrence Ranking Table		
Rank	***Classification***	***Suggested criteria Probability***
10	Very high	It happens in most of the cases
9		It happens frequently in no preventive action is taken
8	High	It happens frequently (process is not robust enough)
7		It has already occurred several times in the past
6	Moderate	It may occur with a moderate probability
5		It may occur if triggered by concurrence of causes
4		It may occur in case of concurrence of events
3	Low	It may occur only if triggered by external factor
2	Very low	It may occur in case of disastrous event
1	Remote	No known occurrence

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Detection Scale

How high is the risk that the implemented control is not effective to detect the issue?

Detection Ranking Table		
Risk ranking	***Detectability***	***Suggested criteria***
10	Extremely low	The implemented control is certainly not able to detect the event
9	Remote	It is not sure that the implemented control is able to detect the event
8	Low	The implemented control is not able to detect the event until the next QA check.
7		The implemented control could not able to detect the event until the next batch / campaign.
6	Moderate	The implemented control could not able to detect the event until the next analytical check
5		The implemented control could not able to detect the event that could be recurrent
4	High	The implemented control could not able to detect the event until the next production check
3		The implemented control is able to detect the event but there is no automatic corrective action.
2	Almost certain	The implemented control is able to detect the event and to avoid its occurrence.
1		The implemented control is able to prevent the event and to avoid its occurrence.

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Risk Priority Number (RPN) definition

For each risk factor the risk priority number

$$RPN = (SEV) \times (OCC) \times (DET)$$

has been calculated

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Determine the RPN threshold for action

Threshold for action have been individuated and reported in the following table

RPN Actions Thresholds			
From	**To**	**Risk classification**	**Action(s)**
1	100	Trivial	No action (acceptable level of risk)
100	300	Low	Reduce risk to ALARP (As low as reasonably possible), considering cost/benefit
300	500	Intermediate	Reduce risk to ALARP (As low as reasonably possible)
500		High	**Risk must be reduced**

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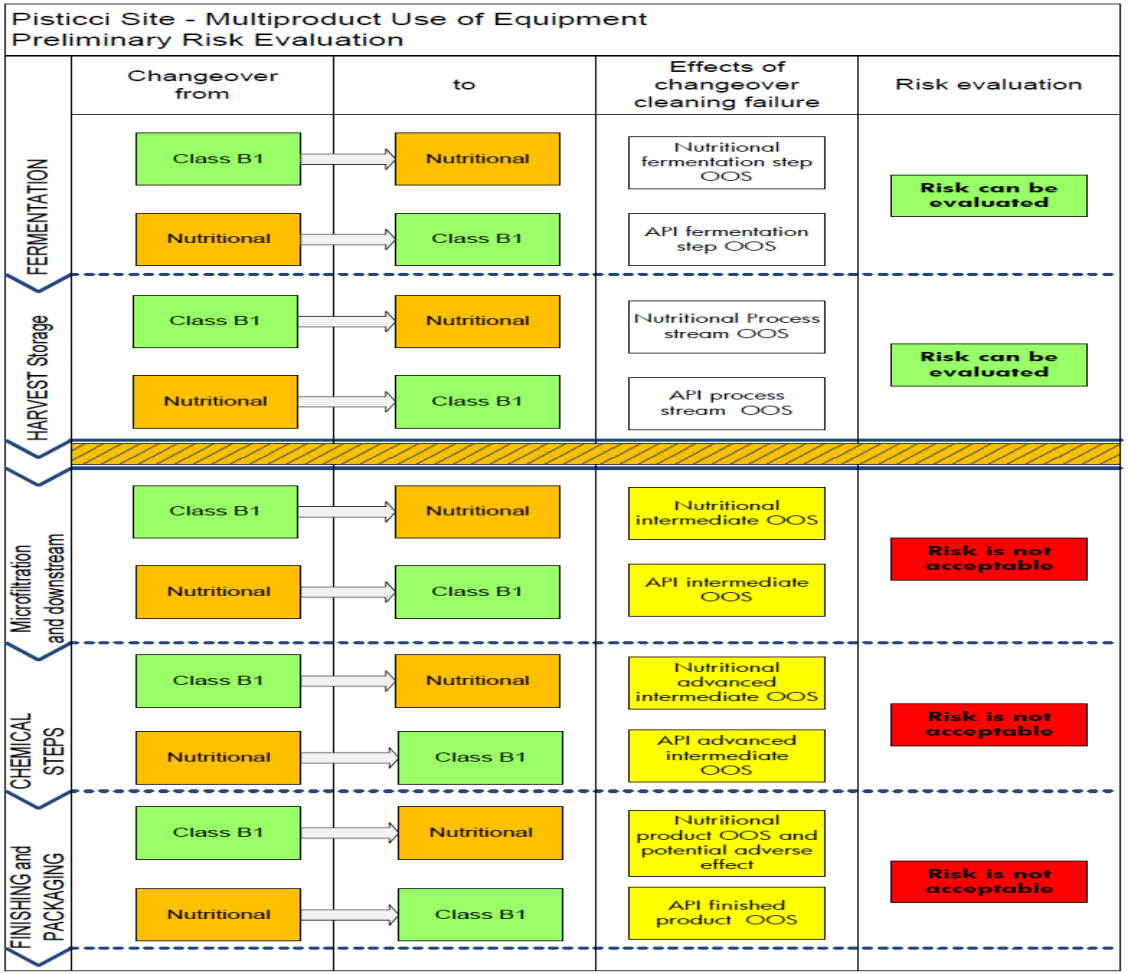
Collect and organise information

Preliminary evaluation



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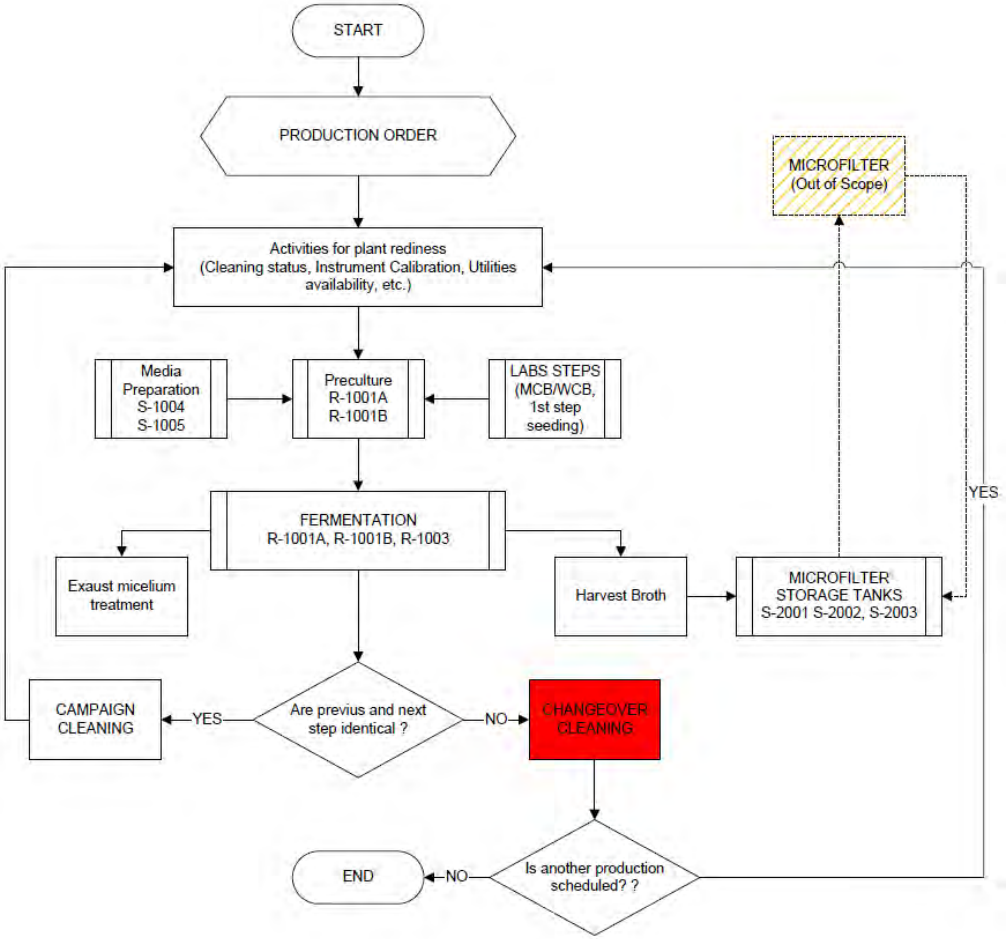
Collect and organise information

QRM application boundaries



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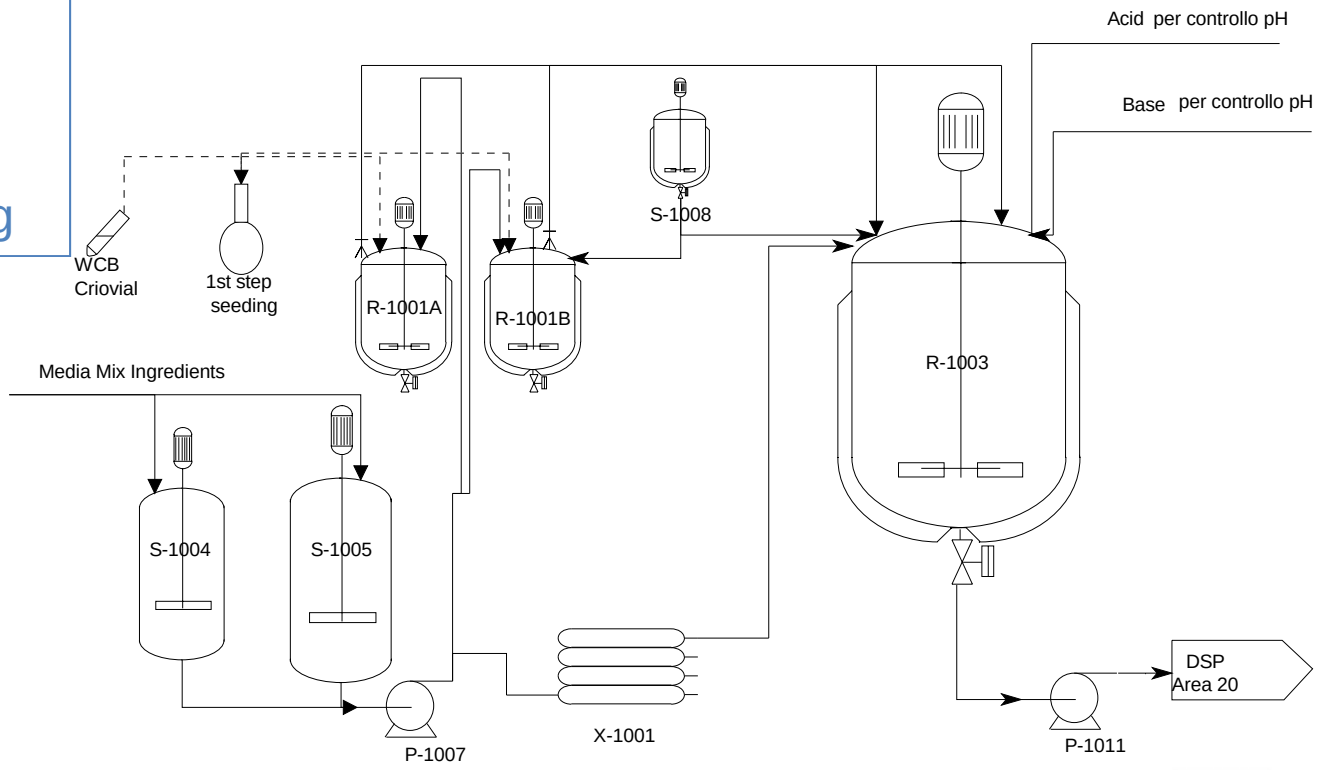
Collect and organise information

Flow chartering

Area 10
Fermentation 1st line - Equipment Flow Sheet



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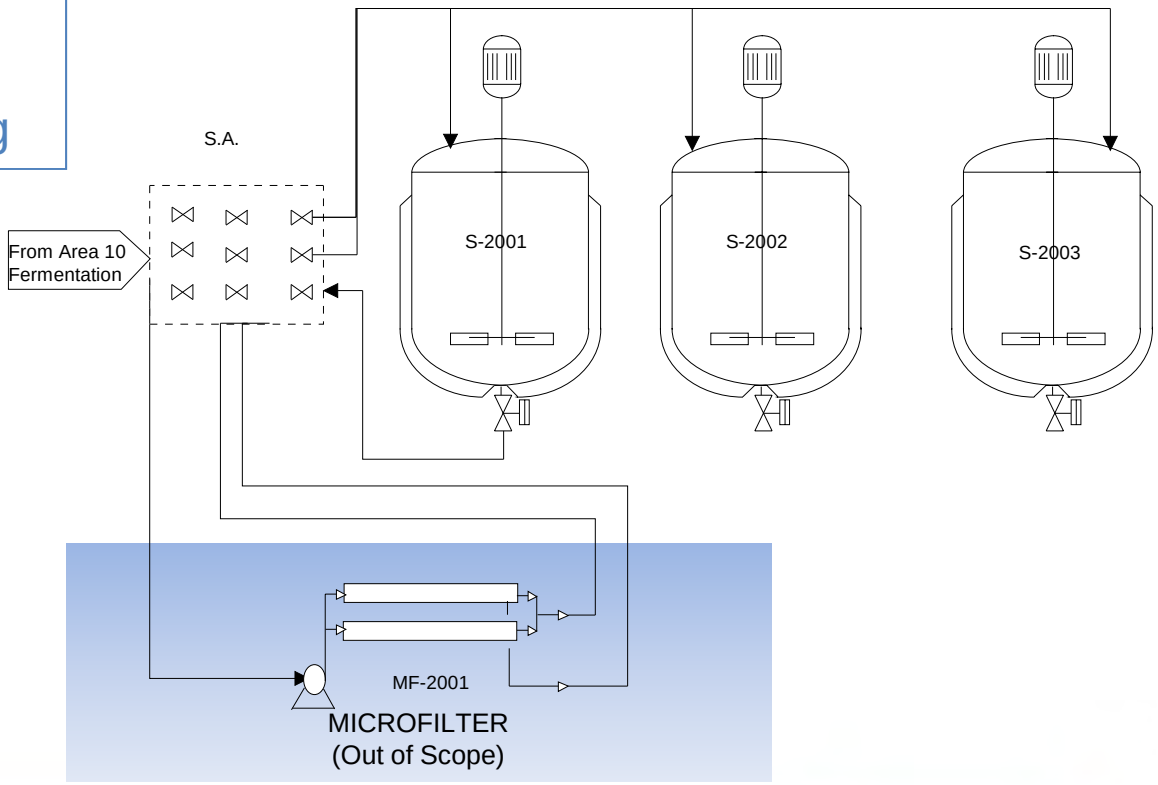
Collect and organise information

Flow chartering

Area 20
Microfiltration Equipment Flow Sheet



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APPLY THE TOOL

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FMEA analysis

- Fermentation area
  - Outcomes summary

Process step	Potential failure modes with higher RPN (first three)	RPN	Comments
Change Over Cleaning from B1 to Nutra	Break down of supplied utilities	45	Detection measures in place; back up system available
	Distributed Control System (DCS) sequence failure	40	Validation of autometed system performed
	Human error	30	Procedure in place, double check on critical controls performed, training program implemented
Change Over Cleaning from Nutra to B1	Break down of supplied utilities	36	Same consideration of previous scenario. Lower RPN due to lower severity score
	Distributed Control System (DCS) sequence failure	32	
	Human error	24	

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FMEA analysis

- Microfiltration area
  - Outcomes summary

Process step	Potential failure modes with higher RPN (first three)	RPN	Comments
Change Over Cleaning from B1 to Nutra	Distributed Control System (DCS) sequence failure	60	Validation of autometed system performed.
	Break down of supplied utilities	45	Detection measures in place; back up system available
	Human error	30	Procedure in place, double check on critical controls performed, training program implemented
Change Over Cleaning from Nutra to B1	Break down of supplied utilities	48	Same consideration of previous scenario. Lower RPN due to lower severity score
	Distributed Control System (DCS) sequence failure	36	
	Human error	24	

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RESULTS FROM CLEANING OPERATIONS

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Table 1 – Sampling by rinsing (Changeover cleaning from B1 to Nutra)

Area	Equipment, line to be sampled	Analysis Description	Maximum Measured Value	Acceptance Criteria (1)
10	R1001A	HPLC Assay	< 0,4 mg/L (2)	< 0,63 mg/L
		pH	8.8	< 10
	R1003	HPLC Assay	Not Detectable < 0,09 mg/L (3)	< 0,11 mg/L
		pH	7,3	< 10
20	R-1001A/B -S.A.2000 S -2001 Line Loop Area 20 (concentrate)	HPLC Assay	Not Detectable < 0,09 mg/L (3)	< 0,22 mg/L
		pH	8,4	< 10
	S-2002 Loop Area 20 (permeate)	HPLC Assay	Not Detectable < 0,09 mg/L (3)	< 0,22 mg/L
		pH	8,4	< 10

(1) As per Cleaning Validation Protocol PV-0000-006-1.0

(2) HPLC Assay Limit of Quantization (LOQ) for B1 (Teicoplanin) = 0,4 mg/L

(3) HPLC Assay Limit of Detection (LOD) for B1 (Teicoplanin) = 0.09 mg/L

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Table 2 – Sampling by swab (Changeover cleaning from B1 to Nutra)

Area	Equipment, line to be sampled	Analysis Description	Maximum Measured Value	Acceptance Criteria (1)
10	R-1001A	HPLC Assay	< 0,0024 mg/dm2 (2) (4)	< 0,69 mg/dm2
10	R-1003	HPLC Assay	Not Detectable < 0,00053 mg/dm2 (3) (5)	< 0,17 mg/dm2

(1) As per Cleaning Validation Protocol PV-0000-006-1.0
(2) HPLC Assay Limit of Quantization (LOQ) for B1 (Teicoplanin) = 0,4 mg/L
(3) HPLC Assay Limit of Detection (LOD) for B1 (Teicoplanin) = 0,09 mg/L
(4) 0,4 mg/L (HPLC LOQ is equivalent to 0,0024 mg/dm2 - See Internal report PI-10-056)
(5) 0,09 mg/L (HPLC LOD is equivalent to 0,00053 mg/dm2 - See Internal report PI-10-056)

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Table 3 – Sampling by swab (Changeover cleaning from Nutra to B1)

Area	Equipment, line to be sampled	Analysis Description	Maximum Measured Value	Acceptance Criteria (1)
10	R-1003	HPLC Assay	Not Detectable < 0,0006 mg/dm2 (2) (3)	< 0,17 mg/dm2

(1) As per Cleaning Validation Protocol PV-0000-006-1.0
(2) HPLC Assay Limit of Quantization (LOQ) of Vitamin K1= 0,1 mg/L
(3) 0,1 mg/L (HPLC LOQ is equivalent to 0,0006 mg/dm2 - See Internal report PI-10-055)

EVALUATION

FMEA analysis has been carried out for fermentation and microfiltration steps.

Principal outcomes :

- Potential failure in critical steps individuated
- Potential effect and causes evaluated
- The already implemented preventive action have been considered
  - Validation performed on system and analytical method
  - Suitable detection method in place
  - No issues from cleaning checks results
- Risk Priority Numbers for all the risk factor resulted less than the threshold for action

CONCLUSIONS

On the basis of the performed Quality Risk Management Process the risk of using the same fermentation and microfiltration equipment for different products (B1 APIs and nutritional) has been considered acceptable since there is no impact on the quality of the steps and/or intermediates manufactured

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QUESTIONS ?

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THANK YOU
FOR YOUR ATTENTION

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