Quality Risk Management for the Evaluation of Potable Water Final Rinse during the Cleaning Process of Granulator Jilter Bags

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Abstract *— The objective of this article is to describe the application of Quality Risk Management (QRM) approach to assess and manage the risk associated to the impact of using Potable Water during the final rinse process used to clean the exhaust cloth filter bags of the Fluid Bed Granulators at the Plant Y, facility. The Quality Risk Management tools were used to perform a holistic evaluation of the granulation exhaust cloth filters cleaning process performance, the manufacturing function of the filters and also any potential drug product quality attribute impact that could affect patient/customer safety. The resulting Risk priority number (RPN) of 45 for a "negligible" severity, according to QRM methodology, has a "Broadly acceptable" acceptability. "Broadly acceptable" criteria mean that these would be acceptable risks, no further risk control measures needed. No risk/benefit rationale required for acceptance.*

Key Terms — *Cleaning Process, Granulator, Quality Risk Management, Risk Assessment.*

OBJECTIVES

The objective of this report is to document the application of Quality Risk Management (QRM) approach to assess and manage the risk associated to the impact of using Potable Water during the final rinse process used to clean the exhaust cloth filter bags of the Fluid Bed Granulators at the Plant Y, facility.

SCOPE

The Quality Risk Management (QRM) approach was used to assess the risk associated to the impact of using Potable Water during the final rinse process used to clean the exhaust cloth filter bags of the Fluid Bed Granulators at the Plant Y, facility. The level of formality and documentation of the QRM approach will be leveraged with the level of risk to product safety, efficacy, quality and regulatory compliance. The scope of the QRM approach will be to formally assess the risk to quality based on:

- Process/Product: Current manufacturing process knowledge. Use of fluid bed granulator cloth filter bags during processing and cleaning cycle/process performance for the cloth filter bags.
- Patient: Link to the protection of the patient/customer. Critical to quality output indicators from the cleaning process performance will be assessed (e.g., visual inspection, chemical residues, bioburden).

BACKGROUND INFORMATION

An evaluation of the Site Cleaning Validation Program was carried out in Plant Y. As part of the evaluation it was identified that the current cleaning process for the exhaust cloth filter bags of the Fluid Bed Granulators had a final rinse using Potable Water. It was identified that the highest grade of water used in the final rinse step should be the highest grade of water used in the drug product manufacturing process. As part of the evaluation process, a request was obtained to perform a risk assessment associated to the impact of using Potable Water during the final rinse process used to clean the exhaust cloth filter bags of the Fluid Bed Granulators at the Plant Y, facility.

The Quality Risk Management (QRM) evaluation focused on critical to quality output indicators from the cleaning process performance

(e.g., visual inspection, chemical residues, bioburden) and their relationship to product quality and patient safety [1]. Quality Risk Management (QRM) and Process Excellence (PE) tools were used to perform a holistic evaluation of the granulation exhaust cloth filters cleaning process performance, the manufacturing function of the filters and also any potential drug product quality attribute impact that could affect patient/customer safety [2].

The QRM process, methodology and tools followed included the following:

- **QRM Process initiation:**
  - Risk assessment started with a scope and well defined problem description.
  - SIPOC (Suppliers, Inputs, Process, Outputs, Customers): This tool was used in the QRM process to provide a high level mapping of the extent of the situation and focus in two fundamental areas, cleaning process performance and customers/patient.
- **Risk Assessment/Control/Acceptability:**
  - Risk Assessment:
    - ✓ Critical to Quality Diagram (CTQ) was used to assess the cleaning process performance using potable water. Also the cleaning process performance and potable water rinse impact on drug product and patient/customer [3].
    - ✓ Risks were estimated quantitatively by using Failure Mode Effects and Criticality Analysis (FMECA) and relative ranking/risk indexing [4].
    - ✓ Drug Product Impact Assessment.
  - Risk Control:
    - ✓ Risk control involves decision making for risk reduction and/or risk acceptance.
    - ✓ The risk associated should be evaluated based on the assessment of severity, occurrence and detectability.
  - Risk Acceptability:
    - ✓ Risk priority number (RPN) will be used to characterize risk, Equation (1) [5].

$$RPN = Severity \times Occurrence \times Detection \quad (1)$$

- ✓ Quantitative and Qualitative ranking/risk indexing for severity, occurrence and detection are provided in Tables 1, 2 and 3 respectively. These tables were used for RPN determination/calculation. Also risk acceptability tables are presented in Tables 4 and 5.

Table 1
Severity Classifications

Classification	Description	Rank	
		Quantitative	Qualitative
Negligible	No real effect on performance	1	Low
Negligible	Cosmetic issue that does not affect product performance	2	
Negligible	Performance degradation of a single non-critical quality attribute	3	
Negligible	Performance degradation of a multiple non-critical quality attributes	4	
Negligible	Performance degradation of a single critical quality attribute	5	
Marginal	Performance degradation of a multiple critical quality attributes	6	Medium
Marginal	Product malfunction or product is ineffective without potential for injury, serious injury or death	7	
Marginal	Potential of non-serious injury	8	
Critical	Potential of serious injury	9	High
Catastrophic	Potential of death	10	

Table 2
Occurrence Classifications

Classification	Description	Likelihood	Rank	
		Chronological	Quantitative	Qualitative
Very High	Failure is almost inevitable	More than one occurrence per day	10	High
		One occurrence every three to four days	9	
High	Repeated failures	One occurrence per week	8	
		One occurrence every month	7	
Moderate	Occasional failures	One occurrence every three months	6	
		One occurrence every six months to one year	5	Medium
		One occurrence per year	4	
Low	Relatively few failures	One occurrence every one to three years	3	
Very Low	Only isolated failures	One occurrence every three to five years	2	Low
Remote	Failures is unlikely	One occurrence in greater than five years	1	

Table 3
Detectability Classifications

Classification	Description	Detectability	Rank	
		Failures Undetected by Control Systems	Quantitative	Qualitative
Almost certain	Existing controls will almost certainly detect a failure. Failure would be evident to trained personnel and/or would be detected prior to execution.	≤1 in 1500000	1	High
Very High	Very high chance that existing controls will detect a failure. Events identified by on-line, at-line instrumentation.	1 in 150000	2	
High	High chance that existing controls will detect a failure.	1 in 15000	3	
Moderately High	Moderately high chance that existing controls will detect a failure. Failure would be detected early allowing corrective actions to be taken.	1 in 2000	4	Medium
Moderate	Moderate chance that existing controls will detect a failure. Failure would be evident to experienced personnel	1 in 400	5	
Low	Low chance that existing controls will detect a failure. Failure would be evident to a technical expert or a subject matter expert.	1in 80	6	
Very Low	Very low chance that existing controls will detect failure. Failure would be detected when data is being reviewed but possibly after execution.	1 in 20	7	Low
Remote	Remote chance that existing controls will detect a failure. Failure would not be detected without further analysis and/or testing.	1 in 8	8	
Very Remote	Very remote chance that existing controls will detect a failure.	1 in 3	9	
Almost Impossible	Almost impossible chance that existing controls will detect failure. Failure would not be detected by data review or testing.	≥1 in 2	10	

Table 4

Risk Acceptability Definitions Used In This Assessment

Risk Level	Risk Acceptability
Intolerable	Unacceptable risk for which risk reduction measures are required. Individual risks may only be accepted on a case by case basis by proving that the risk/benefit ratio is favorable, once all feasible risk reduction measures have been taken.
ALARP	This level of risk is considered acceptable if further reduction is not practicable or feasible and the benefits outweigh the residual risk.
Broadly Acceptable	These are acceptable risks. No further risk control measures needed. No risk/benefit rationale required for acceptance

Table 5

Risk Acceptability Table

	Severity			
RPN	Negligible	Marginal	Critical	Catastrophic
501-1000	Cannot achieve this rating	Intolerable	Intolerable	Intolerable
100-500	ALARP	ALARP	Intolerable	Intolerable
51-99	Broadly Acceptable	ALARP	ALARP	ALARP
1-50	Broadly Acceptable	Broadly Acceptable	ALARP	ALARP

NOTE: ALARP = "AS LOW AS REASONABLY PRACTICABLE"

METHODOLOGY (QRM) PROCESS INITIATION

An evaluation to assess the risk associated to the impact of using Potable Water during the final rinse process used to clean the exhaust cloth filter bags of the Fluid Bed Granulators at the Plant Y, facility was requested. A QRM approach was followed to evaluate risks associated to cleaning process, product and patient safety.

Exhaust Cloth Filter Bags in Fluid Bed Granulation Processes

In the fluid bed granulators, the exhaust cloth filter bags are used on top of the fluidization zone/expansion chamber to prevent air-borne or fine granulation particles to reach the exhaust blower or process exhaust air to the environment, refer to Figure 1. The exhaust cloth filter bags are attached to a filter frame assembly and during the granulation process shaking periods are used to prevent clogging of the filters with material. In the fluid bed granulation process, inlet air flow is controlled and flows into the fluid bed granulator from the bottom, where the granulation is contained in the bowl to fluidize the materials while binder solution is sprayed down opposite to the flow of air to granulate the mixture of excipients and API within the fluidization zone/expansion chamber. The exhaust cloth filter bags are not in constant direct contact with the granulated drug product. Also the process air is pulled by the exhaust fan from the fluid bed granulator through the filters and out to the environment, there is no blow back of process air from the exhaust filters into the expansion chamber or granulated material. The granulation process is designed to control the air flow levels and material within the expansion chamber during granulation and bed moisture pick up to prevent excessive material to reach the exhaust filters. Exhaust filter pressure differential is monitored and process air flow ramp up levels with respect to granulation bed movement is controlled to prevent material to reach the exhaust filters. This prevents exhaust filter clogging and stagnant granulation bed due to lack of air flow/fluidization through the granulator. If the exhaust cloth filter clogs with material there will not be material flow through the granulator and process will stop. Thus the granulation process is designed and controlled to prevent excessive material contact with exhaust filters.

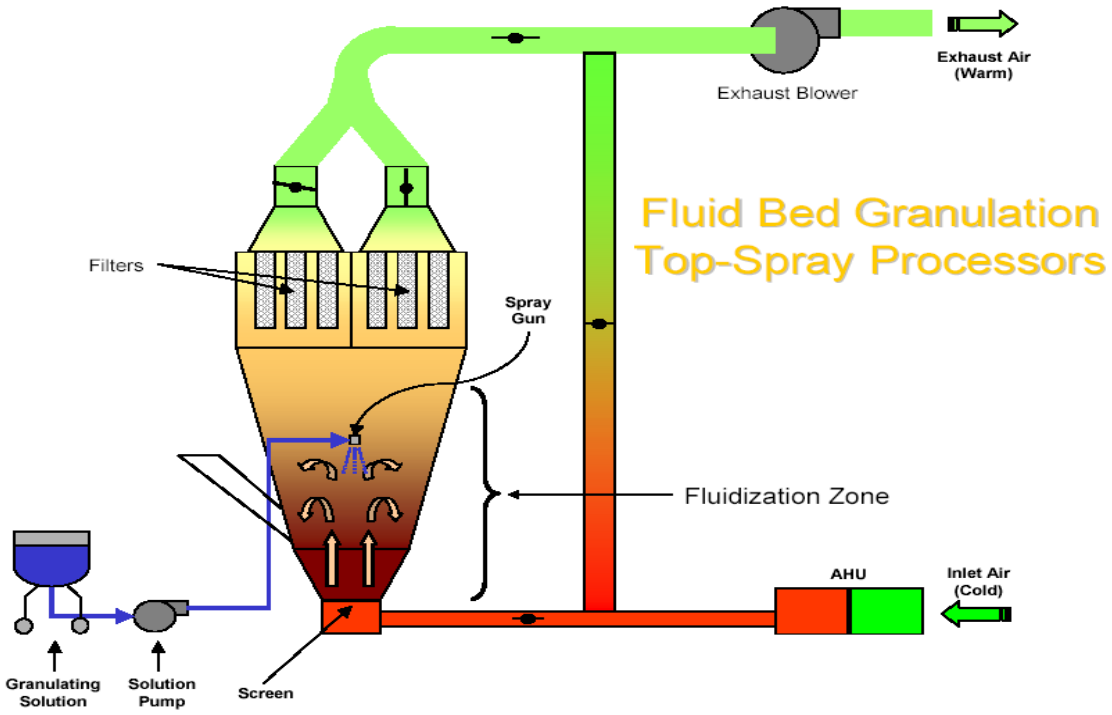

Figure 1
Exhaust Cloth Filters in Fluid Bed

Exhaust Cloth Filter Bags Cleaning Process

The cleaning process for the exhaust cloth filter bags is controlled and performed as per SIPOC diagram presented in Figure 2. The cleaning process for the exhaust cloth filter bags was previously validated under protocol showing that the cleaning process performance is validated and complied with the following acceptance criteria:

- Visual Cleanliness: No visible residues, odors or moisture.
- Microbial Bioburden: The results met the acceptance criteria, (TAMC = NMT 23 CFU/2in; Yeast & Molds = NMT 27 CFU/2in).
- Cleaning Agent (Chematic 99) Residues: No cleaning agent residues were detected.
- Active Pharmaceutical Ingredient (API): Although filters are dedicated per drug product, API was tested and results met the protocol acceptance criteria.

The validated cleaning process for the exhaust cloth filter bags suggests that the cleaning process and cleaning materials, including potable water, do not affect the cleaning process performance. The SIPOC diagram was developed to provide a high level view of the process and the relationship between cleaning process, materials, product and patient/customer, refer to Figure 2.

The SIPOC diagram presented in Figure 2 shows that the cleaning process performance to obtain cleaned and dry filters in compliance with cleaning validation visual, microbial and detergent acceptance criteria is effective using the established process and cleaning materials, (e.g., Potable Water and Chematic 99).

Therefore, the critical output quality attributes from the filter cleaning process are not affected with the use of Potable Water as evidenced by the executed cleaning validation study results. Potable water is completely removed from the cloth filters during the validated drying cycle.

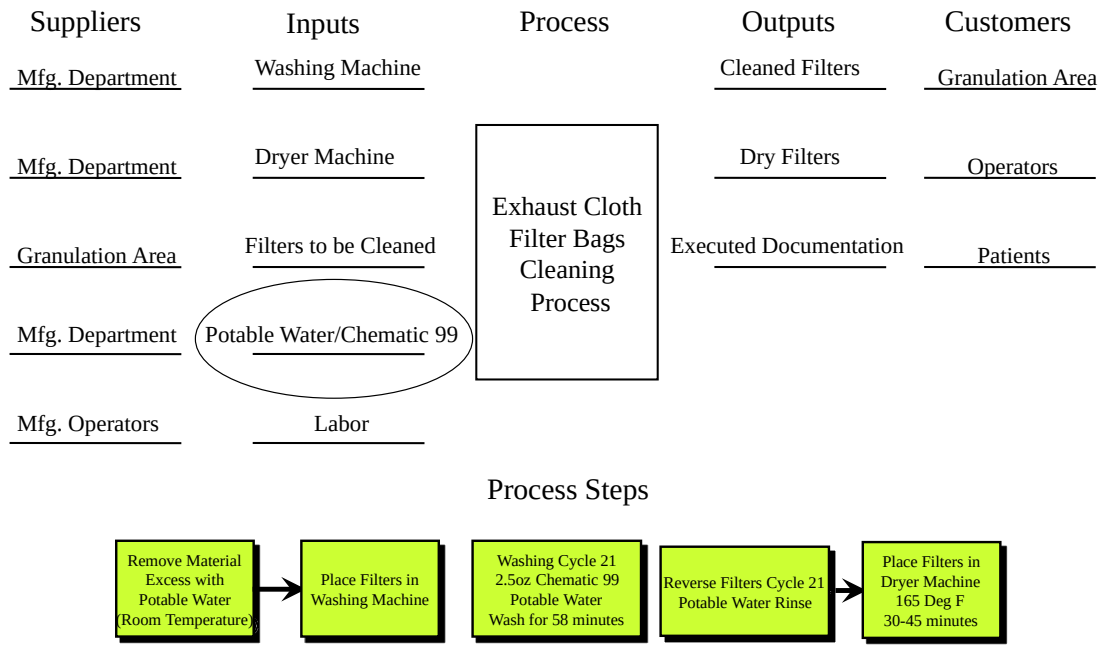

Figure 2
General SIPOC Diagram for Exhaust Cloth Filter Bags Cleaning Process

The suggested relationship between the exhaust filters cleaning validation results and Potable Water critical to quality characteristics is presented below:

- Visual Cleanliness: No visible residues, odors or moisture. These results suggest that there are no visible white residues on filter surface that could be indicative of potential water hardness suspended or un-dissolved residues that might have precipitated.
- Microbial Bioburden: The results met the acceptance criteria, (TAMC = NMT 23 CFU/2in; Yeast & Molds = NMT 27 CFU/2in). These results suggest that the water quality does not promote unacceptable levels of microbial bioburden.
- Cleaning Agent (Chematic 99) Residues: No cleaning agent residues were detected. These results suggest that there are no potential water hardness suspended or un-dissolved residues that could have affected the cleaning solution efficacy.
- Active Pharmaceutical Ingredient (API): Although filters are dedicated per drug product, API was tested and results met the protocol acceptance criteria.

Although data suggests that the use of potable water does not affect the cleaning process performance for the filters, a risk assessment was performed to assess potable water quality impact.

RISK ASSESSMENT /CONTROL /ACCEPTABILITY

Risk management is a complex problem and is to be solved with understanding of all relations and circumstances. Substantial part of risk management is risk assessment. It is necessary to clearly define which part of risk assessment is solved, because complex risk assessment is composed from many partial tasks.

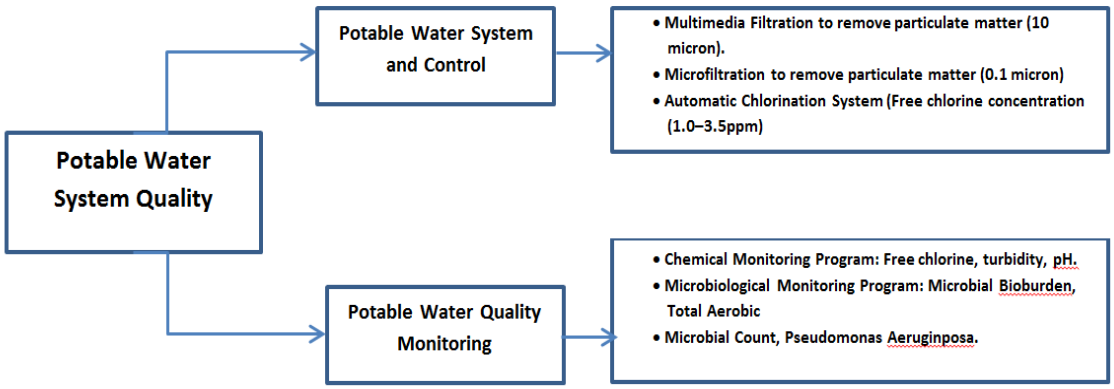

Figure 3:
Potable Water System Critical to Quality (CTQ) Diagram.

Risk Assessment Potable Water System

Critical to Quality Diagram (CTQ) was used to assess the potable water system quality [3]. Refer to Figure 3 for the Potable Water System critical to quality evaluation.

- **Risk Control Potable Water System:** Based on the CTQ diagram presented in Figure 3, for the potable water system the following can be stated:
  - Potable Water System and Controls: Potable water at the Plant Y, facility is pre-treated and controlled beyond regular potable water requirements. Multimedia filtration, microfiltration and automatic chlorination system ensures that there are internal processes, systems and controls for potable water quality.
  - Potable Water Quality Monitoring Program: In order to ensure Potable Water system consistency and quality, Plant Y, implemented a monitoring program that includes chemical and microbiological periodic sampling.
- **Risk Acceptability Potable Water System:** Refer to Table 6 for the Potable Water System Quality FMECA (Failure mode, effects and criticality analysis) analysis for actual process.

Table 6
FMECA for Potable Water System Quality

Risk Scenario	Risk Factor			Risk Priority Number (RPN)
	Severity	Occurrence	Detection	
Visually Clean (Turbidity)	3 Negligible	3 Low	5 Moderate	45
Chemical Monitoring	3 Negligible	3 Low	5 Moderate	45
Microbiological Monitoring	3 Negligible	3 Low	5 Moderate	45

RESULTS

The actual resulting RPN of 45 for a "negligible" severity, according to Tables 4 & 5, has a "Broadly acceptable" acceptability. "Broadly acceptable" criteria mean that these would be acceptable risks, no further risk control measures needed. No risk/benefit rationale required for acceptance.

Impact on Customer/Patient Safety

As it can be noticed from Table 6, the severity rating was 3 or negligible for the evaluation. Water is the base for many biological forms, and its safety is unquestioned provided it meets standards of quality for potability and microbial content [6].

CONCLUSION

This report presents the use of QRM approach to evaluate the risk factors related to the use of Potable Water rinse to clean the exhaust cloth filters used in the fluid bed granulation process.

Cleaning validation and potable water system controls & chemical/microbiological monitoring data at the Plant Y facility, supports and suggest that the use of potable water rinse to clean the exhaust cloth filters used in the fluid bed granulation process will not impact cleaning performance and will not cause an adverse drug product impact that could negatively affect the patient. Potable water is pre-treated using multimedia (10 micron) filtration and microfiltration (0.1 micron) to remove particulate matter. Therefore it is not likely that potable water suspended or un-dissolved residues will be adhered or retained in the fluid bed granulators exhaust cloth filters, provided that the porosity/retention of the exhaust filters is greater, (e.g., Polyester Fiber: 15-25 micron for all fluidized bed granulations; Polyester Fiber: 3-5 micron for Motrin drying process), when compared to the 0.1 micron restriction level for particulate matter.

The evaluated factors and quality risk management suggest that there is no potential impact on safety, efficacy and quality.

REFERENCES

[1] Viornery, L., "Quality Risk Management (QRM)", *Implementation of ICH Q9 in the pharmaceutical field an example of methodology from PIC/S,* Version r1 A0, Jan 2010, pages 2-3

[2] Bris, R., Guedes, C., Martorell, S., "Risk management – Selection of adequate tools, P. Fuchs", *Reliability, Risk and Safety, Theory and Application*, Vol. , SEPTEMBER 2009, page 1149-1150

[3] Dyadem Press, "Overview of Failure Mode, Effects and Criticality Analysis (FMECA)", *Guidelines for Failure Mode and Effects Analysis for Automotive, Aerospace and General Manufacturing Industries*, lst Edition, March 2004, page 19.1

[4] Hyatt, N., "Failure Mode and Effects Analysis, Risk Priority Number (RPN)",*Guidelines for Process Hazards Analysis, Hazards Identification & Risk Analysis*, 1 Edition, March 2004, page 9.7

[5] Brassard, M., Finn, L., Ginn, D. & Ritter, D., "Critical To Quality (CTQ) Tree", *The Six Sigma Memory Jogger™ II*, 1st Ed., 2002, page 91-94

[6] Wade, A., Weller, P. Handbook of Pharmaceutical Excipients 2nd Edition (1994), American Pharmaceutical Association, page 548