Quality Risk Management in the Pharmaceutical Air Compressed Equipment Qualification Process

Juliemar Meléndez Alvarado
Master of Engineering in Manufacturing Engineering
Rafael Nieves, Pharm D
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract *— In the pharmaceutical industry every product and every process associated with risks. To maintain product quality throughout the product life cycle, too much time and resources are allocated. Risk is described in recent project as a combination of the probability of occurrence of harm and the severity of that harm. The Quality Risk Management (QRM) approach initiated by regulatory agencies with recognized management tools along with support of statistical tools in combination allows for a risk-based approach to quality management, thus ensuring that resources are deployed in a timely and expeditious manner to areas that need them most. QRM improves risk awareness and accelerates detection of potential issues by analyzing and comparing existing data from a quality perspective to manage product quality, manufacturing processes, validation and compliance within a risk based Quality Management System. This project describes practical ways to analyze the risks to compressed air quality system, providing guidance along the way to achieving effective and efficient quality management and compliance through QRM.*

Key Terms *— GMP, ISO 8573-1:2010 class two (2), Quality Risk Management, Risk assessment.*

PROJECT STATEMENT

The Food and Drug Administration (FDA) Regulated Pharmaceutical Industry requires updated documentation every three (3) years through a qualification process. Periodically evaluate Good Manufacturing Practices (GMP) Manufacturing System (equipment, system and utilities) to verify that they are still operating in a qualified manner in compliance. It is important to perform a risk management by identifying defects in any pharmaceutical process. Quality Risk Management (QRM) principles require the evaluation of risk to quality based on scientific knowledge and the protection of the patient. QRM tools are used to evaluate risks producing by defects and also the potential drug product impact that these defects could cause on the patient or customer. 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 purpose of this project is to offer a systematic and very comprehensive approach to quality risk management. Will be assessed the risk level to detect if the compressed air has a direct or indirect contact with the drug product. The appropriate use of quality risk management can facilitate compliance with regulatory requirements, such as good manufacturing practices.

Research Description

This project perform a risk management associated to the impact of using compressed air during the quenching, cleaning and drying process used in packaging area, wash room and United State Pharmacopeia (USP) water room at pharmaceutical utility. A risk management is performed to evaluate in point of use where the compressed air has contact or non-contact with the drug product. This project will evaluate the pressure, specification, analytical air quality contamination and microbiological contamination of the product.

Quality Risk Management is accomplished to estimate risk associated with the identified

deficiencies. The intention is to provide a risk evaluation in order to provide decision-making information to mitigate and remediate based on risk level.

Research Objectives

The objective of this project is to document the application of Quality Risk Management (QRM) approach to assess and manage the risk associated to the drug product impact of using air compressed equipment during the packaging, wash and USP water process in pharmaceutical industry. The QRM focused on critical to quality output indicators from the drug product impact with compressed air (e.g., pressure specification, microbiological content, analytical air quality) and their relationship to product quality and patient safety.

Research Contributions

With the project implementation, pharmaceutical industries identify possible risks in air-compressed equipment that can affect the product and performance process. Implement actions of findings during assessment to mitigate and remediate. Maintain high qualification of the equipment. To decrease variability of quality attributes: reduce product and material defects and reduce manufacturing defects.

LITERATURE REVIEW

Risk management principles are effectively utilized in many areas of business and government, including finance, insurance, occupational safety, and public health, and by agencies regulating these industries. Although there are some examples of the use of quality risk management in the FDA-regulated industry today, they are limited and do not represent the full contribution that risks management has to offer. The present FDA focus on risk-based determination is requiring that the regulated industries improve dramatically their understanding and capability of hazard control concepts. In addition, the importance of quality systems has been recognized in the life sciences industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1).

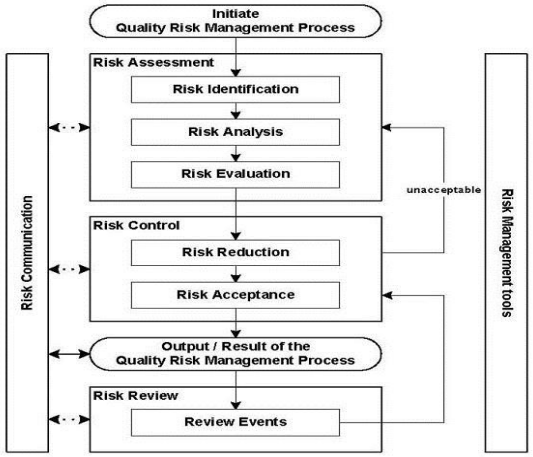

Figure 1
Overview of a Typical Quality Risk Management Process

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessments begin with a well-defined problem description or risk question. *Risk control* includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. *Risk communication* is the sharing of

information about risk and risk management between the decision makers and others.

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience.dd

Testing and monitoring of compressed air and other process gases that come into direct contact with pharmaceutical products is vital to assuring the quality and safety of those products.

The pharmaceutical industry does not have a clear-cut guideline or regulation that specifically addresses compressed air quality requirements, testing frequency, or number of samples. The individual manufacturer is responsible for assessing the risk and affect that a contaminated compressed air supply could have on the final product. An important international standard, ISO 8573-1, provides a variety of Purity Classes that can be incorporated into a robust quality assurance plan for this critical utility.

The major components of the Primary, Secondary Packaging, Wash Room, USP Room and Warehouse Compress Air system include:

- Two (2) Ingersoll Rand Air Compressor units that have an output capacity of 400cfm (±10%) each at working pressure of 125 psig.
- Two (2) desiccant air dryer unit.
- One (1) receiver storage vessel.

The system supplies oil free compressed air to minimize the possibility of hydrocarbons in contact with the product and the system has a desiccant air to provide a compressed air low in moisture. The low moisture content minimizes the possibility of bacterial growth in the point of use. Ingersoll Rand Heatless Desiccant Dryer is constructed with two towers, each containing desiccant beads that alternate between online (drying) and offline (regenerating) modes, yielding a continuous stream of dry air at the dryer's outlet.

The system nominal capacity 400 cfm (±10%) flow rate complies with the air pressure requirements for the proper operation of the manufacturing machinery. Compressed air is provided for product contact and non-product contact applications for the equipment functioning.

The compressed air system equipment and operation description is included in Table 1 below:

Table 1
Compressed Air System for Packaging Area

Equipment Description	Operation Description
Air Compressor	An oil free rotary screw type compressor that provide compressed air. Air from the environment is taken and compressed.
Desiccant Air Dryer	A heatless type desiccant air dryer to remove moisture by adsorption with a dual desiccant chamber.
Air Receiver Tank	A tank use to store the compressed air generated by the Air Compressor, which will be delivered to the Desiccant Air Dryer.
Coalescing Filter	Filters for the removal of moisture and oil particles.
Particle Filter	Filter for the removal of particles.

The area has ten (10) filtered (process air) product contact and non-product contact compressed air point of use (POU) described in Table 2 and one (1) non-filtered (instrument air) non-product contact compressed air point of use (POU) described in Table 3. All these points are installed in single loops.

Table 2
Filtered Compressed Air POU in the Packaging Area

POU 1	Thin Film Packaging Line 1 (Primary Area Room)
POU 2	Thin Film Packaging Line 2 (Primary Area Room)
POU 3	Thin Film Packaging Line 3 (Primary Area Room)
POU 4	IMA Packaging Line 1 (Primary Area Room)
POU 5	IMA Packaging Line 2 (Primary Area Room)
POU 6	IMA Packaging Line 3 (Primary Area Room)
POU 7	Secondary Packaging (Secondary Area Room)
POU 8	Packaging Line (Primary Area Room and Secondary Area Room)
POU 9	Chocolate Packaging Line (Primary Area Room and Secondary Area Room)
POU 10	Wash Room

Table 3
Non-Filtered, not GMP Product Compressed Air POU in the Packaging Area

POU 11	USP Water System Room

Preventive maintenance procedure is complete, approved and scheduled in the maintenance tracking system. This includes equipment maintenance and filter replacement program. This may include: air filter change, oil filter change, oil change, re-greasing of motor, sensor error verification, if applicable, and other applicable items. System Standard Operating Procedure (SOP) includes three (3) forms "Compressed Air

System Daily Checklists", will be completed by utilities operators on all working days. Maintenance supervisor or designee will verify forms once every week. Any discrepancies or deviations found will be reported immediately to the maintenance supervisor or designee.

METHODOLOGY

Quality risk management (QRM) supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk.

The QRM process, methodology and tools that applied in this project included the following:

I. QRM Process initiation:
   a. Risk assessment started with a scope and well defined problem description.
   b. 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, process performance and customers/patient, coming from Six Sigma principles.

II. Risk Assessment/Control/Acceptability:
   a. Risk Assessment:
      1. Critical to Quality Diagram (CTQ) was used to assess the product impact using compressed air. Also the compressed air impact on drug product and patient/customer during the packaging process.
      2. Risks were estimated quantitatively by using Failure Mode Effects and Criticality Analysis (FMECA) and relative ranking/risk indexing.
      3. Drug Product Impact Assessment.
   b. Risk Control:
      1. Risk control involves decision making for risk reduction and/or risk acceptance.
      2. The risk associated should be evaluated based on the assessment of severity, occurrence and detectability.
   c. Risk Acceptability:
      1. Risk priority number (RPN) will be used to characterize risk.

      RPN = Severity X Occurrence X Detection.

The analysis is completed according to these steps:

a. The impact of the risk in terms of severity was rated according to the Table 4.

Table 4
Severity Rating

Rate	Description
0	No impact to quality
1	Low risk for impact to quality
2	Risk for impact to quality
3	Probable impact to quality
4	Risk for customer or product outside regulatory file

b. The probability that the risk will occur was rated according to the Table 5.

Table 5
Probability of Occurrence Rating

Rate	Description
0	Risk will probably not occur again
1	Risk may occur again – Seldom
2	Risk could occur again – From time to time
3	Risk is likely to occur – Often

c. The probability that the risk will be detected was rated according to the Table 6.

Table 6
Detectability Ranking

Rate	Description
0	Risk event will definitely be detected Failure is very obvious and readily detected
2	Risk event will probably be detected again Controls in place may detect the failure
4	Risk event is at risk of not being detected
6	Risk will almost certainly escape detection

d. The probability that the risk will occur again and the probability that the risk will be detected were added. This was called "Total Probability Rank".

e. The Risk Ranking and Filtering Tool shown in Figure 2 was used to determine the risk level of the event based on the severity and "Total Probability Rank". The definition of each risk level is shown in Table 7.

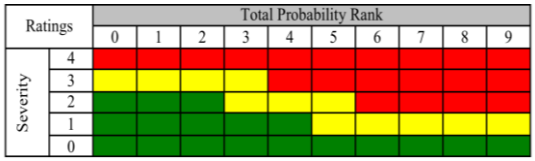

Figure 2
Risk Ranking and Filtering Tool

The risks are to be evaluated and categorized into 3 risk ranking levels using the following risk acceptability definitions. A risk criterion is described in Table 7 "Risk Acceptability Definitions". Final risk is expressed by qualitative descriptors such as "High", "Medium", and "Low". Function risk assessment criteria used is as follows:

Table 7
Risk Acceptability Definitions

Risk Level	Description
Level 3 Critical	**High Risk** – Risk event might create immediate and significant risk to product quality, user safety or data integrity. Risk reduction measures are essential, whatever the cost.
Level 2 Serious	**Medium to High Risk** – Risk event might potentially create a significant risk to product quality, user safety or data integrity. Risk could potentially results in significant observations from a regulatory agency.
Level 1 Standard	**Low Risk** – Risk related to a less serious or isolated nature that is not deemed critical or major but requires correction or suggestions given on how to improve systems or procedures that may be compliant but would benefit from improvement.

Table 8
Risk Acceptability Definitions Used In This Assessment

Risk Level	Risk Acceptability
Intolerable	Unacceptable risk for which risk reduction measures are required. Individual risk 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 it 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 9
Risk Acceptability Table

RPN	Severity			
	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"

RESULTS AND DISCUSSION

This section presents the problem analysis and improvement results using the Six Sigma Methodology and FMECA tools.

Risk Management and Identification

Each requirement is designated as critical or non-critical is based on an evaluation of the impact the requirements has on direct product quality, production needs or safety of personnel. Critical product quality (High critically system) is defined as having a direct impact. Each type of critical requirement includes a descriptor as to reason it is critical. Non-critical (Low critically system) is defined as operationally import but does not directly impact product or safety.

The risk assessed was used in evaluating levels of testing required for each requirement as well as for establishing acceptance criteria to validate the system. All CPQ requirements must be met in order to verify the system will perform with a high degree of assurance in the product quality. Safety and Project Critical Requirements must also be met. A risk assessment was performed to evaluate the drug product impact with air compressed in process Packaging Room, USP Room and Wash Room from pharmaceutical industry facility.

Three different risk scenarios were evaluated per product per compressed air condition: pressure, microbiological content and analytical air quality. This three risk scenarios parameters are describe in the followings Figures 3, 4 and 5. The pressure, microbiological content and analytical air quality specifications or parameters described in SOP's and ISO 8573-1:2010 class two (2) respectively.

Analytical Air quality is analyzed in three different parameters of sampling, Water Dew Point, Oil and Solid Particulate; these parameters are evaluated in samples port of point of use, with requisite of ISO 858573-1:2010 class two (2).

Microbiological Content has a two limit, these are alert and alarm; under these limits there are two specifications, microbial and mold count. These are analyzed on the sample port of each point of use. Pressure of the compressed air supplied must remain in $\geq$ 90 psig for the process to work stable and does not affect the operation of the equipment.

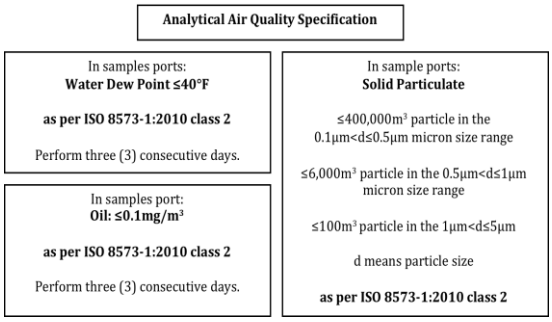

Figure 3
Parameters of Risk Scenarios in Analytical Air Quality Specification

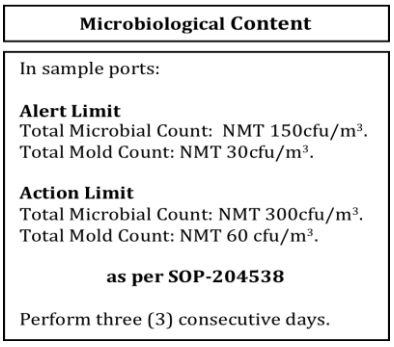

Figure 4
Parameters of Risk Scenarios in Microbiological Content Specification

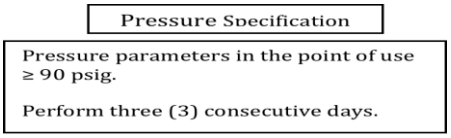

Figure 5
Parameters of Risk Scenarios in Pressure Specification

The SIPOC diagram was developed to provide a high level view of the process and the relationship between air process, materials, product and patient/customer, refer to Figure 6.

Risk Assessment/Control/Acceptability

A Critical to Quality (CTQ) diagram, shown in Figure 7, is used to assess the impact of air compressed with drug product process and resulting critical to quality factors. A Risk Assessment is performed to estimate risk associated with the identified deficiencies. The intention is to provide a risk evaluation in order to provide decision-making information to mitigate and remediate based on risk level. All deficiencies that are identified as a result of investigation and evaluation of the system in the packaging, USP water room and wash room are tabulated in the next section; refer Figures 8, 9, 10, 11, 12, 13, 14, 15 and 16.

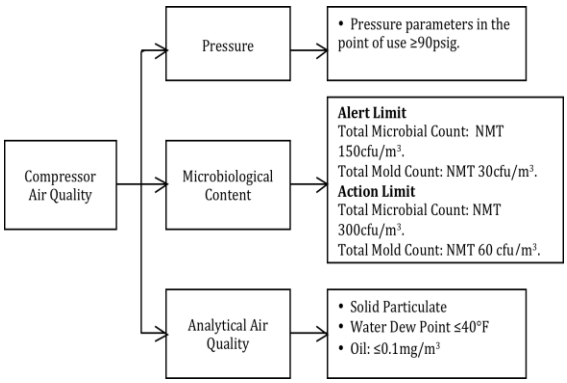

Figure 7
Compressed Air System Critical to Quality Diagram

Based on the CTQ diagram presented in Figure 7, for the compressed air system the following can be stated:

- Pressure - Compressed air at pharmaceutical industry on Packaging Area, USP Room and Wash Room utility is controlled beyond regular pressure parameters in the point of use ≥ 90 psig. If pressure is below in each point of use can affect the functionally or operations of the equipment.
- Microbiological Content - To ensure compressed air consistency and quality on Packaging Area; monitoring packaging, washroom and USP water room includes microbial and mold quarterly sampling. Microbiological Content monitors alert and action limits, of microbial and mold total to avoid possible contaminants if compressed air is in contact with product.
- Analytical Air Quality - Analytical Air Quality includes solid particulate, water dew point and oil periodic sampling.

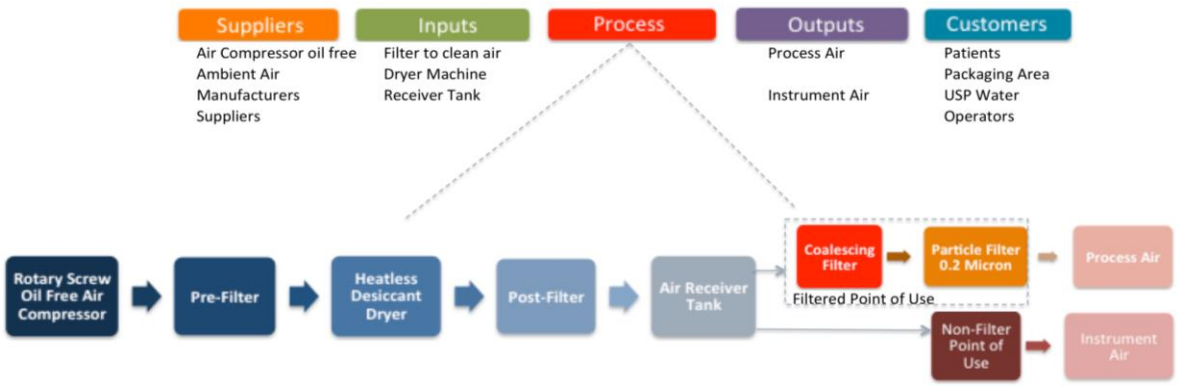

Figure 6
General SIPOC Diagram for Compressed Air Process

Make this assessment for establishing acceptance criteria to evaluate in point of use (refer Tables 2 and 3) where the compressed air has contact or non-contact with the drug product and mitigate risk. The following Figure 8 show the criteria to determine risk level of pressure specification for product and non-product contact. The specification data of pressure is ≥ 90 psig.

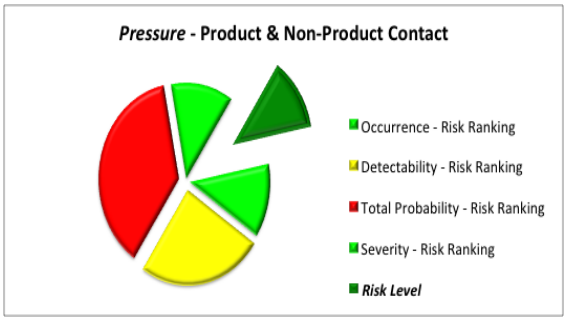

Figure 8
Risk Level of Pressure Specification – Product & Non-Product Contact

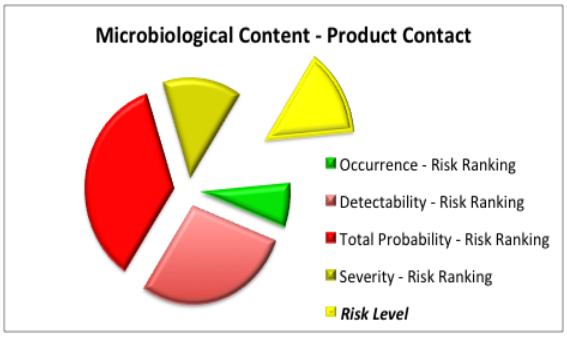

Figure 9
Risk Level of Microbiological Content - Product Contact

The Risk Scenario evaluation is if pressure is below can affect the functionality or operations of the equipment and valve. Can affect the equipment operation and delay in production.

Figure 9 determines risk level of microbiological content specification for product contact. The specifications data of microbiological content for microbial and mold are Alert Limit: NMT 30cfu/m^3 Action Limit: NMT 60cfu/m^3. The Risk Scenario for this evaluation no contact with the product but if the quality of the compressed air is not as per requirements, can affect the products that have direct contact with compressed air.

The risk level is determined in Figure 10 of microbiological content non-product contact. The specifications data of microbiological content for microbial and mold are Alert Limit: NMT 30 cfu/m^3 Action Limit: NMT 60 cfu/m^3. Possible contamination if compressed air is in contact with product. Microbial Content if not as per specification can affect the product are the risk scenario for non-product contact.

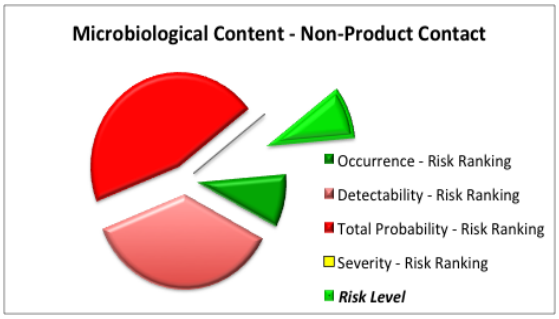

Figure 10
Risk Level of Microbiological Content – Non-Product Contact

For the followings Figures 11 and 12 shown the criteria to determine risk level of Analytical Air Quality (Water Dew Point) specification for non-product and product contact, respectively. The specification data of Water Dew Point is ≤ 40°F.

Risk Scenario:

Figure 11 no contact with the product. There is no dryer in the packing line; if the air filter in the main line fails the product could be affected with water. Risk scenario (Figure 12) reports possible contamination, if compressed air with water is in contact with product. Every valve in the packaging line has not individual dryer and can be a possible water contact with the product.

Figures 13 and 14 represent the criteria to determine risk level of Analytical Air Quality (Oil) specification for product and non-product contact respectively. The specification data of Oil is ≤ 0.1mg/m^3.

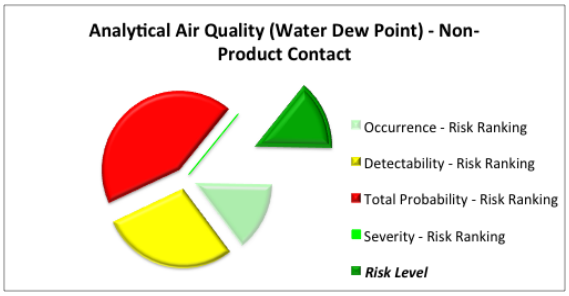

Figure 11
Risk Level of Analytical Air Quality (Water Dew Point) – Non-Product Contact

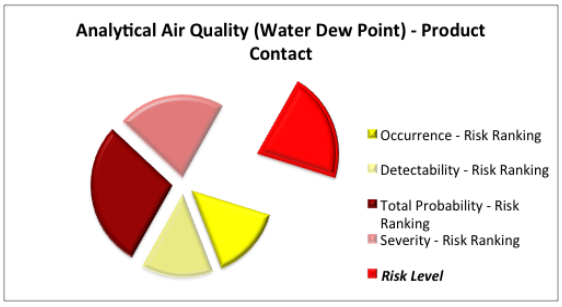

Figure 12
Risk Level of Analytical Air Quality (Water Dew Point) – Product Contact

Risk Scenario:

Figure 13, possible contamination if compressed air with oil is in contact with product. If the filter (at the point of use of the main compressed air line) not absorbs oil can affect the product. The compressed air unit is oil free. In Figure 14 no contact with the product. There is no dryer in the packing line; if the air filter in the main line fails the product could be affected with oil.

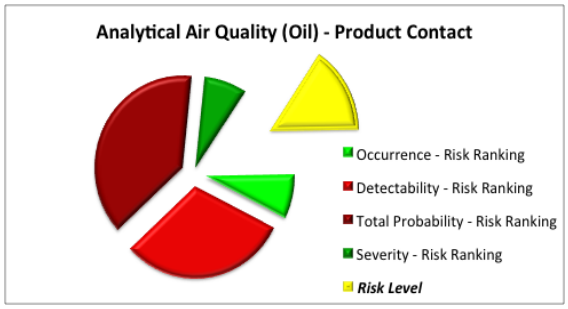

Figure 13
Risk Level of Analytical Air Quality (Oil) – Product Contact

Risk level for Analytical Air Quality (Solid Particulate) specification for product and non-product contact are demonstrated in Figures 15 and 16, respectively.

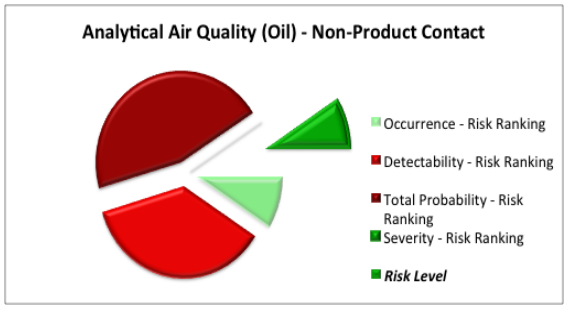

Figure 14
Risk Level of Analytical Air Quality (Oil) – Non-Product Contact

The specifications data of solid particulate are ≤400,000 m^3 particle in the 0.1µm<d≤0.5µm; ≤6,000 m^3 particle in the 0.5µm<d≤1µm; ≤100m^3 particle in the 1µm<d≤5µm.

Risk Scenario:

For product contact graph (see Figure 15) possible contamination if compressed air with solid particulate is in contact with product. If the filter at the point of use of the main compressed air line not capture solid particulate can affect the product. In Figure 16 no contact with the product but if the quality of the compressed air is not as per

requirements, can affect the products that have direct contact with compressed air.

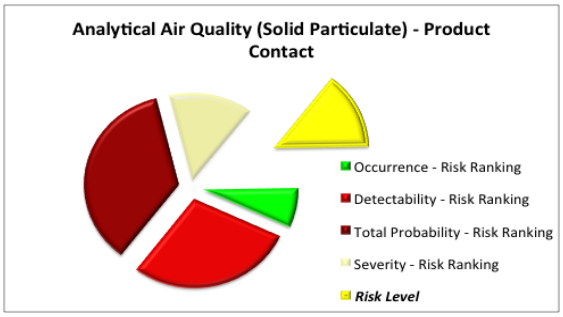

Figure 15
Risk Level of Analytical Air Quality (Solid Particulate) – Product Contact

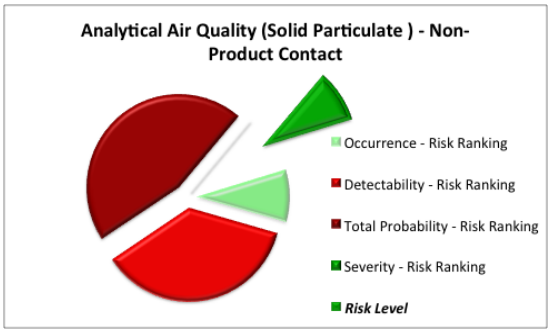

Figure 16
Risk Level of Analytical Air Quality (Solid Particulate) – Non-Product Contact

Risk Control / Acceptance

Risk mitigation and remediation controls were identified for each function on a case-by-case basis. Resulting risk outcome consider both mitigation and remediation efforts that combined will reduce the risk to an acceptance level. Risk Assessment results are detailed in Table 11. For low risk levels is not necessary to make the recommended change. Refer to Table 10 for the Compressed Air System Quality FMECA analysis for actual process.

The actual resulting RPN of 15 and 63 for a "negligible" severity, according to Tables 8 & 9, 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. Resulting 135 RPN for a "critical" severity, according the same tables has an "Intolerable" unacceptable. "Intolerable" criteria mean that these would be unacceptable risk. Individual risk 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. For which risk reduction measure as required, the mitigation and remediation are described in the Table 10 for water dew point risk scenario.

Table 10
FMECA for Compressed Air System Quality

Risk Scenario		Risk Factor			Risk Priority Number (RPN)
		Severity	Occurrence	Detection	
Pressure		1 Negligible	3 Low	5 Moderate	15
Microbiological Content		1 Negligible	3 Low	5 Moderate	15
Analytical Air Quality	Water Dew Point	9 Critical	3 Low	5 Moderate	135
	Oil	3 Negligible	3 Low	7 Very Low	63
	Solid Particulate	3 Negligible	3 Low	7 Very Low	63

Table 11
Assessment Results in Each of Point of Use for Drug Product Impact

Risk Scenario		Occurrence	Detectability	Total Probability Rank	Severity	Risk Level	Risk Mitigation, Remediation and Recommendation
Pressure		1	2	3	0	1	Install pressure regulators in the principal point of use to adjust and verify the pressure of compressed air use. If the requirement of pressure parameter needs to be below or steady certain value, regulators need to be installed.
Microbiological Content		1	2	3	0	1	Install filters in the principal point of use to minimize possible contamination if compressed air has contact with drug product. Continue monitoring and evaluated any count of microbial and mold, quarterly.
Analytical Air Quality	Water Dew Point	1	2	3	4	3	Identify all the filters associated to the compressed air system and install filters in the principal point of use to minimize possible water dew point in compressed air when has contact with drug product. Change the filters at a frequency based on usage and service life.
	Oil	1	4	5	1	2	Identify all the filters associated to the compressed air system and install filters in the principal point of use to minimize possible oil in compressed air when has contact with drug product. The compressed air unit is oil free can't affect the drug product, if functionality of compressor is correct. Change the filters at a frequency based on usage and service life.
	Solid Particulate	1	4	5	2	2	Identify all the filters associated to the compressed air system and install filters in the principal point of use to minimize possible solid particulate in compressed air when has contact with drug product. Change the filters at a frequency based on usage and service life.

CONCLUSIONS

A risk assessment was completed for each validation finding based on a specific equipment operation risk scenario. Recommended Validation Activities and Validation Requirements were demonstrated in the Table 12. Although the actual drug product impact risk assessment documents demonstrate that the utility was qualified and validated, the implementation of actions to mitigate and remediate the findings noted were required. These actions will improve and assure the equipment / system remains within established operational parameters and reduces any potential patient, regulatory and, or business impact.

The resulting risk was evaluated by analyzing against given criteria and considering implemented controls. The purpose of this risk is to assist in making decisions, based on the outcomes of the risk analysis.

Table 12
Final Assessment Results in Each of Point of Use for Drug Product Impact

Risk Scenario		Occurrence	Detectability	Total Probability Rank	Severity	Risk Level	Validation Required YES/NO
Pressure		0	2	2	0	1	YES/ OQ
Microbiological Content		0	2	2	0	1	YES/ PQ
Analytical Air Quality	Water Dew Point	0	2	2	0	1	YES/ PQ
	Oil	0	2	2	0	1	
	Solid Particulate	0	2	2	0	1	

REFERENCES

[1] Rockville, MD., *Implementation of Risk Management Principles and Activities within a Quality Management System*. FDA Global Harmonization Task Force, 2000.

[2] FDA, *A risk-based approach.* Pharmaceutical CGMPS for the 21st century, 2004.

[3] FSE Guide. *Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment*. ISPE Guide.

[4] Applied Risk Management Guide. *Applied Risk Management in Commissioning and Qualification*. ISPE Good Practice Guide.

[5] Dyadem Press, *Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices*, 2003 ISBN 0849319102.

[6] Rodriguez-Perez., J., *Quality Risk Management in the FDA – Regulated Industry*, 2012. ISBN-13: 9780873898348. Publisher: ASQ Quality Press.

[7] Wang, J. X., *Lean Manufacturing: Business Bottom-Line Based*. Five Stages of Lean Manufacturing, 2010. DOI:10.1201/9781420086034-2.