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RESEARCH OF THE SCOPE OF TESTING REQUIRED FOR QUALIFICATION OF THE HVAC SYSTEM

Abstract: *In the pharmaceutical industry, HVAC system qualification is carried out by applying a risk management model in accordance to relevant GMP requirements. Qualification of these systems is an integral part of quality assurance and represents a systemic approach of data collection and data analysis that will provide documentary evidence that the system works properly and continuously gives the expected results. GMP requires identifying the extent of the qualification required to ensure reliability and compliance with GMP principles based on the outcome of the risk assessment. This paper provides an example of risk assessment approach using the FMEA method. Potential risks were identified, it was estimated which risks were considered acceptable, and risk reduction actions were proposed, from their impact on the HVAC system*

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Keywords: *Qualification, FMEA, HVAC.*

1. INTRODUCTION

Qualification is an integral part of quality assurance. In order to determine the extent of the necessary testing, certain risk management models should be used. The FMEA method represents a reliable and proven method for determining the extent of testing during the qualification of the HVAC system. Any changes on the system should be followed and documented, as will be shown below.

HVAC (heating, ventilation and air conditioning systems) represent an indispensable part, and the best technical solution that achieves maintenance of an acceptable environment for production needs in pharmaceutical plants. These systems consist of several components integrated into a reliable process, which carried out automatically, adapting to the changing effects of the external climate, providing the required ambient conditions. The aforementioned engineering set includes knowledge of fluid mechanics, construction, mechanical design, as well as control of instruments. (Todorović, 2009)

One of the basic requirements for the production of drugs is the pharmaceutical quality system, which implies the application of GMP (Good Manufacturing Practice) in all phases of the life cycle of the drug. GMP requires from the pharmaceutical industry to implement a program of control, qualification and validation of the HVAC system. The qualification implies a documented procedure that demonstrates that all equipment and systems function properly and consistently provide the appropriate expected results. Qualification of the HVAC system is carried out using risk-based methods, where the most frequent is the FMEA (Failure Mode and Effects Analysis) method.

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GMP Annex 15 (2015) describes the principles of qualifications applied to the premises, equipment, auxiliary systems and processes used to produce drugs. Any planned changes to the HVAC system, which
may affect on the product quality, must be formally documented, and an assessed impact on the principles of qualification or an assessed control strategy. Whenever changes are initiated on the product, equipment / system, installations, production procedures or any other parameters affecting the quality, integrity and efficiency of the product, it is obligatory to carry out the qualification. The extent of testing in conditioned qualifications depends on the type and extent of the initiated change. In order to determine the extent and ratio of the qualification, it is necessary to carry out a risk assessment. Through risk assessment, it is necessary to analyze the potential risks / failures related to unwinding of process, system functionality, as well as the functionality of critical components of the system. Within the framework of the risk analysis, the scope of the testing that need to be carried out during the qualification of the HVAC system is proposed. The selection of tests during the qualification of the HVAC system must be at least in line with risk analysis, and tests that are not prescribed by risk analysis can be added. It is necessary to perceive of all tests and to carried out the ones on which change has influence.

The initial document for changes to the HVAC system is URS (User requirements specifications). The URS needs to write as correctly and precisely as possible, that is the key document that often represents the basis of the contract - a definitive statement about what the system must do. It should not be designed by saying how to do it, but what should the system do? After properly written URS, according to Annex 15, it is necessary to follow the steps: URS – DQ – RA - FAT/SAT - IQ – OQ – PQ.

DQ (*Design qualification*) – is the first element in the validation of new spaces, equipment or systems and proves that the design is appropriate to the needs of users and GMP requirements.

RA (*Risk analysis*) – Defines the scope of testing which needs to be performed on the equipment and system.

FAT (*Factory Acceptance Test) / SAT (Site Acceptance Test*) – System Acceptance Test before Delivery / System Acceptance Test after Delivery and Receipt of the System.

IQ (*Installation qualification*) – the correct installation and configuration of software and hardware is proven. Installation qualification is the establishment of documented evidence that the equipment and related systems are properly installed. IQ should include at least the following: checking the correctness of the installation of components, instruments, equipment, pipelines and works on them in relation to technical schemes and specifications; checking the correctness of the installation in relation to the previously defined criteria; collecting and verifying the supplier's operating instructions, handling with equipment and requirements for maintenance; calibration of instruments; and verification of construction materials.

OQ (*Operational Qualification*) – documentation of evidence that the whole system really works in the proper way. OQ should include at least the following: tests that have been developed based on knowledge of processes, systems and equipment, to ensure that the system functions as it is designed; tests that confirm the upper and lower operating limits, and / or the conditions of the "worst case".

Successfully completed OQ should enable the finalization of standard operational procedures of work and cleaning, training of operators and defining preventive maintenance requirements.

PQ (*Performance Qualification*) – documentation of evidence, with a high level of security that the system will continuously work in accordance with the predefined

specifications.

The essence of the problem is to assess the extent of the testing in detail, depending on the initiated change on the system. Efficient risk analysis should be carried out by an expert team that has sufficient knowledge about design and application of the system, and as such, a testing evaluation should be given, after which the system with high reliability will continuously deliver the expected results.

Previous works with a similar approach are listed below. Tabasevic et al., (2018) give an overview of the qualification of the control system (BMS), Shukla1 et al., (2011) give an overview of the qualification of the HVAC system, while Kamakshi et al., (2015) presents the management of the HVAC system risk. In practice, the qualification of HVAC and BMS are rarely analyzed together, although they are inseparable entities. Therefore, in the continuation of the work, the qualification of the HVAC system will be demonstrated, using the FMEA method for determining the scope of testing necessary for properly qualify the system and in accordance with the regulations.

2. METHODOLOGY

GMP requirements prescribe that manufacturers identify the qualifications that need to be carried out in order to prove it that critical points in production processes are under control. It is necessary to qualify space, equipment and production processes changes that affect on the quality of the product. It is necessary for any changes in the HVAC system, or a change affecting the HVAC system (installation of additional components, changes in the software, defining new alarms, changing room dimensions, changing the number of air changes, etc.) to make a risk assessment in order to determine the extent of necessary qualification.

After changing on the HVAC system, it is necessary to identify all possible FM (Failure Modes) modes relevant to each process phase, as shown in Table 1. Where S (Severity) can be estimated with 1 - Low, 3 - Medium, 5 - High; P (Probability of Occurrence) can be rated with 1 - Low, 2 - Medium, 3 - High, and D (Detectability) can be rated with 1 - Low (detected automatically), 2 - Medium (detected following manual check), 5 - High (not detected).

Table 1. Risk ranking

Qualitative ranking	Risk factor		
	Severity (S)	**Probability (P)**	**Detectability (D)**
Low	FM does not affect on the functionality of the process and does not affect on the quality of the product.	Rare occurrence of potential risk / failure.	There are no additional checks and / or subsequent procedural controls, which have a goal to detecting a **potential cause of cancellation** or cancellation.
Medium	FM has a moderate effect on process functionality and on product quality, but alternative methods can be applied to ensure process execution.	Risk / cancellation is likely to occur during the life cycle.	Additional checks and / or subsequent procedural checks whose goal is to detect the **cancellation** exist.
High	FM has a direct impact on the functionality of the process and on product quality, and there are no alternative methods for performing operations.	The risk will occur during the life cycle.	Additional checks and / or subsequent procedural checks whose goal is to detect a **potential cause of cancellation** exist.

In Table 2 is presented a risk analysis for the selection of tests due to the qualification of the HVAC system. A quantitative risk assessment has been assigned to each identified potential risk. Evaluating of the severity level (S) assigned to each of the potential risks, identifying potential causes (P), as well as evaluating the relevant levels of detection (D) the final score for each of the potential risks is ranged.

Table 2. Risk Assasment for HVAC system

Risk Scenario	Risk Cause / Comments	S	P	D	Risk Score	Qualification Testing Required	Routine Controls Required
Installed equipment does not meet customers requirements.	Installed wrong equipment that can affect on the entire working of the HVAC system.	**5**	**1**	**2**	**10**	Verify that the received equipment corresponds to the ordered equipment. URS and DQ should be available. Check the system components. IQ - Orders. IQ - System Components.	No.
	The air humidifier is not connected to the appropriate auxiliary systems, it will not work properly and give the required ambient conditions.	**5**	**1**	**2**	**10**	Verify that the power systems meet the required specifications and that are properly installed. Check drawings. IQ - Power Systems - Steam. IQ - Drawings.	No.
	The information about relative air humidity in the room is not accurate. Incorrect reading from the control system / incorrectly installed sensor. It can lead to a direct impact on the product in the room.	**5**	**2**	**2**	**20**	Check system design, Critical instruments, sensor calibration and RH test in the room. IQ - Calibration test. OQ - A critical instrument. OQ - Test alarm, OQ - Test verification RH	YES (Calibration test and test verification RH)
Channels are not installed according to user requirements.	Air leakage in the channel can lead to contamination and increased energy consumption	**3**	**2**	**2**	**12**	It is necessary to check the leakage of the channel, through the smoke test. IQ - leak test.	No.

Table 2. Risk Assasment for HVAC system

Risk Scenario	Risk Cause / Comments	S	P	D	Risk Score	Qualification Testing Required	Routine Controls Required
	Filthiness of the channel can lead to faster filter contamination and bringing impurities.	**3**	**2**	**2**	**12**	It is necessary to visually check the newly installed channels. Make a purification test. IQ - Purification test.	No.
HEPA filters are not installed properly. The pressure switchs are not installed.	Contamination of the filter can lead to an insufficient number of air changes, it can affect on the maintenance of the cleanness class..	**5**	**2**	**2**	**20**	Check the HEPA filter certificates, perform the integrity test, and check that the pressure switchs generate an alarm. IQ - Filters, OQ - Electromechanical test and PQ - Filter integrity test.	Yes (Test integrity of the filter).
Measuring instruments do not function according to user requirements.	Sensors are not calibrated / IBM was not assigned to them. They can influence on the monitoring and on control of ambient conditions.	**5**	**1**	**2**	**10**	Check all built-in sensors and calibration certificates for all sensors. IQ - Critical instruments. IQ - Non-critical instruments. OQ - Calibration verification test.	YES (Calibration test)
Documents and drawings are not upgraded. Drawings do not conform to GMP during DQ.	The drawings are not adequate / available. Insufficient number of air changes due to room volume increase..	**5**	**2**	**2**	**20**	Check all available drawings. It is necessary to revised all documents affected by the change of drawings. IQ - Drawings.	No.
The personnel are not trained to use the system, and the equipment is not in the maintenance plan.	Technical literature, instructions and maintenance plan are not verified / available. The personnel are not trained for work and maintenance according to SOP, new equipment is not in the maintenance plan.	**5**	**1**	**2**	**10**	Check additional documentation, technical literature and maintenance plan in IQ. Verify SOP during OQ. IQ - Additional documentation. IQ - Technical literature and instructions. IQ - Maintenance plan. OQ - Checking the documentation.	YES (Test documentation checks)

Table 2. Risk Assasment for HVAC system

Risk Scenario	Risk Cause / Comments	S	P	D	Risk Score	Qualification Testing Required	Routine Controls Required
The number of air changes in the room does not meet the needs of the users.	Class D is not satisfied. The number of air changes is less than 20 / h. It can also affect on the heat loading and contamination.	**5**	**2**	**2**	**20**	Measure the air inlet into the room with a balometer and calculate the number of air changes. PQ - Number of air changes.	YES.
Differential pressure between rooms does not meet users requirements.	Class D is not satisfied. Crocontamination of the clean room is not prevented. It can affect on the number of air changes.	**5**	**2**	**1**	**10**	Measure the differential pressure between adjacent rooms and make visualization of air flow and attach trends from the control system. PQ - Differential pressure.	YES.
Leaking HEPA filter is not within the allowed limits.	Filter leak is greater than 0.01%. Class D can fall.	**3**	**2**	**2**	**12**	Measure the leakage of the filter through the absolute filter integrity test using the smoke generator and photometer. PQ - Absolute filter integrity test.	YES.
The number of particles goes out of the specified limits.	Class D is not satisfied.	**5**	**2**	**2**	**20**	By particles counter at a recommended number of locations, measure the number of particles. PQ – Particles number verification test.	YES.
Temperature and RH are output from specified limits.	The clean room does not meet the required ambient conditions. Values from the control system do not match with the measured values.	**5**	**2**	**2**	**20**	Using a thermohygrometer measure T and RH in the room and compare them with the values from the control system. PQ - T and RH.	YES.

The HVAC system belongs to systems with a direct impact on the quality of the product, therefore the "severity" in most cases is rated with mark "5". Therefore, the overall risk will depend on the probability of occurrence and detection capabilities. Priority should be given to reducing the likelihood of occurrence rather than increasing the level of detection. Based on a comparison of the quantitative risk assessment with Table 3. - Nominal marks during risk analysis,

guidelines were obtained for the minimum scope of testing required for each risk. The listed risk minimization actions in Table 3 have been formed using the ISPE Good Practice Guide, but the approach needs to be adapted to the considered equipment / system and complement with the previous knowledge or experiences related to similar equipment / system.

Table 3. Risk Analysis score

Level	Risk score	Risk Reduction Actions
1	1-5	Testing is not necessary. Relevant SOP. Training of users.
2	6-19	Nominal testing required - Nominal testing is performed to prove that the functions are working properly. Relevant SOP. Training of users.
3	20-31	Required extensive testing - Extensive testing that includes testing in the zone of alarm activation limit values. Relevant SOP. Training of users.
4	32-49	Required extensive testing – Predict extensive testing and possible additional routine checks/controls. Relevant SOP. Training of users. Consider the level of the system redesign.
5	50-75	Required extensive testing–Predict extensive testing and possible additional routine checks/controls. Relevant SOP. Training of users. System redesign.

Table 4 shows the results of the performance qualification. All performance tests resulting from the risk analysis have been carried out, according to the appropriate guidelines. Procedures and instructions for carrying out tests, as well as the recommended equipment that were used, are found in each of listed standards. All results meet the acceptnace criteria.

Table 4 . Performance qualification of HVAC system

Test	According to:	Acceptance criteria		Results	
Number of air change per hour	FDA guide	min 20 1/h		32.35	
Air pressure difference test	ISO 14644-3 Annex B5	15 ± 4 Pa		14 – 16 Pa	
Air flow visualization test	ISO 14644-3 Annex B7	from +ve to –ve pressurized zone		Meets acceptance criteria	
HEPA filter leakage test	ISO 14644-3 Annex B6	less than 0.01%		<0.01%	
Particle count test	ISO 14644-1 Annex B / EU GMP Annex 1	**0.5 µm**	**5 µm**	**0.5 µm**	**5µm**
		3 520 000	29 000	112 545	9 586
Temperature uniformity test	ISO 14644-3 Annex B8	22 ± 3 °C		21.8 °C	
Humidity uniformity test	ISO 14644-3 Annex B9	<25%		21 %	

3. Conclusion

The aim of this paper is to demonstrate how it is possible to qualify the HVAC system after the initiated change, using the FMEA risk analysis. By using the risk analysis the criticality of system components has assessed, an assessment of the scope of testing was made and focus of the qualification was given. Qualification is a mandatory activity where prevention is carried out, as well as a mandatory follower of all projects. Plant construction costs, as well as changes to them are constantly escalating, therefore, pharmaceutical companies are struggling with new challenges to meeting GMP demands and managing a profitable business. Knowing the systems and processes, as well as continuous improvement, it is possible to eliminate unnecessary efforts for qualification. This paper presents an example and a recommendation how critical systems can be qualified. The reader so far should have an insight into the problem of qualification, as well as the possibility of discussing about your own individual experiences during the qualification of the HVAC system.

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