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QUALIFICATION DOCUMENTATION FOR HVAC IN DRY FORMULATION PLANT NO. 1...7, TERAPIA

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Abstract: the paper is a result of the author's experience of more than 7 years in the field of pharmaceutical equipment maintenance. He has worked in Qualification documentation and realized it for 7 HVAC (Heating, Ventilating and Air Conditioning) plants, documentation which is part of the Validation documentation, that involve also Validation Protocol and Report. The last two chapters are not part of this paper. The Qualification documentation is a very important document of the validation process. The complexity of equipment, utility systems (plant steam, cooling water) involved and their relationship to the quality of the production will dictate content of qualification documentation.

Key words: validation documentation, IQ-installation qualification, OQ-operational qualification, PQ-performance qualification, GMP-good manufacturing production

1. INTRODUCTION

The heating, ventilating and air conditioning (HVAC) system is used to supply environmental air to manufacturing areas and to maintain appropriate air flow direction, temperature and humidity. Process areas are pressurized negatively with respect to adjoining non-process areas in order to ensure containment. The HVAC system consists of air handlers, ductwork, fans, pre-filters, filters, heating steam/electrical and cooling coils, gauges and controls. HEPA filtration units are used against airborne cross-contamination and air showers are employed to separate areas of differing classifications.

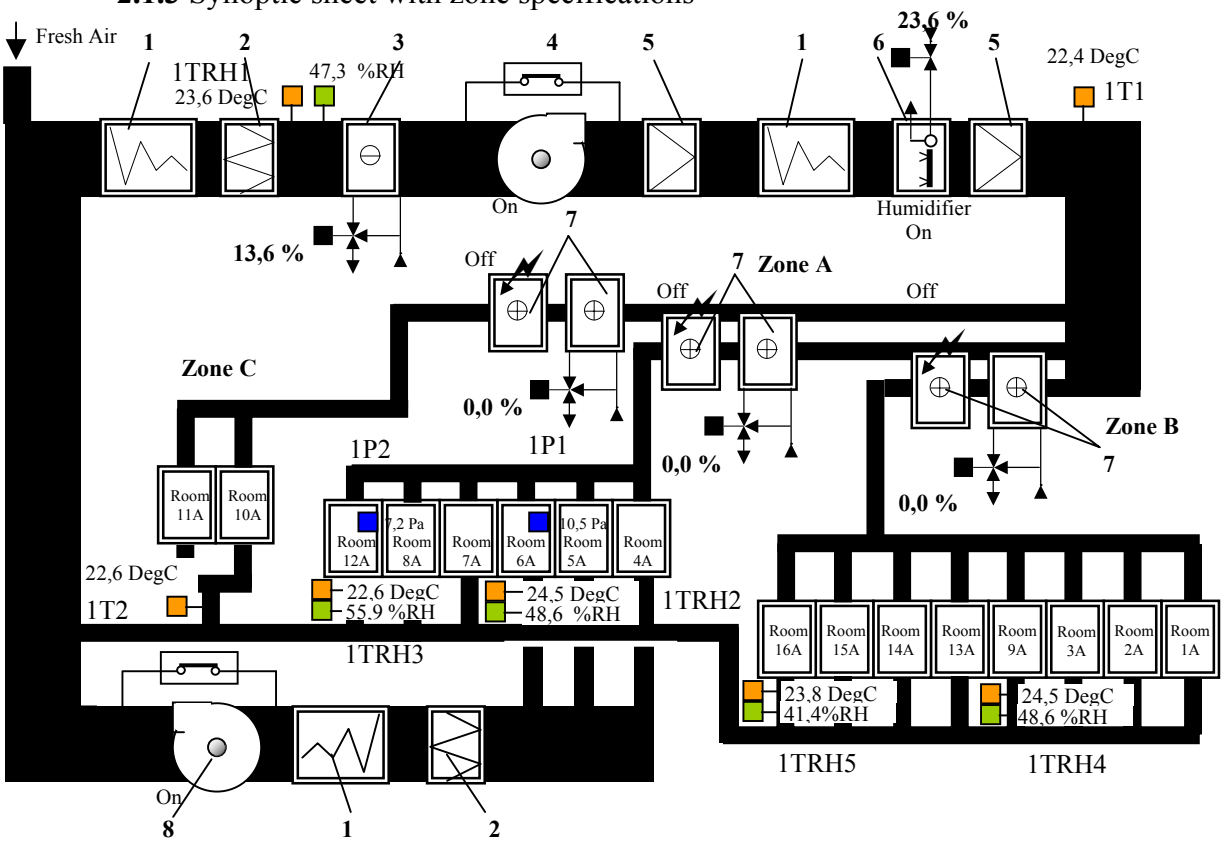
The validation process of HVAC lasts one year and has two stages. The first stage lasted 4 weeks. The results obtained in this stage, provided optimal maintenance procedures to establish the best functioning parameters of the plant. The second stage, have evolve until the end of the year and have prove that the system works as intended, that is reproducible and that meets the established specifications and quality attributes.

The development of validation documentation is an essential part of any successful validation program. In this paper, we want to state by examples, the major components of qualification documentation.

2. INSTALATION QUALIFICATION

Sheets 2.1.1 Rooms laying [1]

2.1.2 Synoptic sheet with airflow diagrams [1]
2.1.3 Synoptic sheet with zone specifications



Legend:1-silencer, 2-prefilter, 3-cooling battery, 4-centrifugal fan, 5-filter, 6-humidifier, 7-heating battery, 8-centrifugal fan, 9-inlet air ductwork, 10-outlet air ductwork

2.1.4 Piping drawings Diagrams in technical floor with diameter specification[1]
2.1.5 Electrical drawings [1]

2.1 Points of test laying

Piping airflow, Air suppliers/diffusers and air exhausts/grills, Differential pressure instruments (supplementary), Temperature, Relative Humidity, and airborne particles.

2.2 Sensor list (e.g.)

Senzor code	*Senzor name (ENVAIR)*	*Senzor type*	*Map pos.*	*ENVAIR Drawings*	*Cable No.*
1T1	*Sup. Air Temp. sensor, (A1)*	*Therm TT 522*	*HI 78*	*1171-V1*	*47*
1TRH1	*Rtn. Air Temp. sensor, (A2)*	*Therm RH 521, 4 - 20 mA*	*JK 89*	*1171-V1*	*48*
	Rtn. Air Hum. Sensor, (A3)		*JK 89*	*1171-V1*	*49*
1T2	*Zone C , Extract Air Temp. sensor, (A4)*	*Therm TT 522*	*JK 78*	*1171-850,3/13*	*50*

This table contents informations also about: *1TRH2, 1P1, 1TRH3, 1P2, 1TRH4 , 1TRH5*

2.3 Filters - Technical Specifications

Type, manufacturer, model, efficiency, area, dimensions, quantity, air flow.(e.g.Type HEPA (H16), CAMFIL, efficiency 99,997%, area: 6,5m^2 , dimensions: 592x592x630, quantity: 4, airflow: 6550m^3/hour). ENVAIR – *In situ test* of HEPA filters, which

includes: Method of test for the determination of filter installation leaks, Location, Test details, equipment used, results, accepted by…, test carried out by…, and others details.

2.5 Fans

Location, Technical details fan, Technical details motor, Flow (design/ measured), Statically pressure after and before fan, Fan and motor rpm, Connection star/delta, Carry out by…, verified by…, and others detail.

2.6 Steam/ Electrical heating coils and Cooling coils

Plant pos.	*Designation*	*Dimensions [mm]*	*Power [kW]*	*Actuator type**	*Landis Valve type*	D_N *[mm]*	K_V
P1.1	*Steam heater*	*1154x995*	*36,2*	*SKB62*	*VVF 52.15-2,5G*	*15*	*2,5*
P1.2	*Steam heater*	*1304x1156*	*51,1*	*SKB62*	*VVF 52.15-3,2G*	*15*	*3,2*
P1.3	*Steam heater*	*904x752*	*19,5*	*SKB62*	*VVF 52.15-1,25G*	*15*	*1,25*
PC.1	*CHW bat.*	*2520x1580*	*167*	*SQX61*	*VXF31.65*	*65*	*49*

*)Landis. For steam heater are specified steam flow [kg/sec], for chilled water battery: water [l/sec] and for all coils, air flow [mc/h], *Air inlet temp.= 14˚C, air outlet temp.= 24˚C.*

2.6.1 Electrical drawings for heating suppliers.

2.6.2 Control panel inspection and test certificate.

2.6.3 Room thermostats 2-3-4 stages and low differential pressure switches.

2.7 Dampers/ Silencers/Humidifiers

Type. Technical data and position on the drawings. Maintenance program and periodic inspection. Function, free movement, periodic is testing.

2.8 Programmable Logic Computer and Network server

Outstation 11 (plant 1): Trend IQ131+. Technical documentation. Outstation 15 (Chiller Water Plant): Trend IQ92e. Technical documentation.

Network interface for modem: Trend NETB/AND. Modem: US robotics sportster 33.6. Technical performances. Server technical specification.

3. OPERATIONAL QUALIFICATION

3.1 Operator Workstation

ON/OFF all installations, setup parameters, view and print all graphics/alarms-procedures. (e.g. *Ref. Temperature room 4A, 5A, 6A, 7A, 8A, 12A*, *Tolerance heating/ cooling, Ref Temperature electrical bat.,Ref. Relative humidity exhaust air, Tolerance drying/humidifying, Plant 1 run time, Cancel Plant 1 run time).*

3.2 PLC Software validation

Digital inputs list, Knobs and switches list, Drivers list, Sequence table, Time zones, Nodes table, Modules Used, IC comms/plots list, Connectivities list.

SENSORS

Channel no.	*Description*	*Interface*	*Signal type*	*Cal. Instru*	*Syst. Value*	*Diff*
A1	*Supply Air Temp*	*TT522*	*Therm*	*17.6*	*18*	*0.4*

This table contents informations about channel no: A2...A14.

UNIVERSAL OUTPUTS

Channel no.	*Description*	*Inter-face**	*Signal type*	*Chked. Oper*	*Date*	*Action req.*
A19	*Supply fan air flow DP switch*	*Paks*	*VFC*	*OK*		

**)single relay module.*

This table contents informations about channel no: A19,A20,B1...B8.

3.3 Acceptance criteria: temperatures and humidity for zones. Setup.

Setpoints Plant 1: ZoneA (6A,12A) = 22,0±1°C, ZoneB (9A, 16A) = 22,0±1°C, ZoneC (10A, 11A) = 22,0±1°C, Humidity (16A,12A, 9A, 6A) = 50,0 ±15%.

3.4 Acceptance criteria: differential pressure

Standard requirements are for rooms to be pressurized in discrete steps from cleanest rooms down to the surrounding base, but in Solid Oral Dosage Forms manufacturing, containment of process materials is contrary to room pressurization. This principle is named negative pressure cascade. Negative pressure cascade work in an equal and opposite manner with areas of highest sensitive protected by lowest negative pressure. The entrance sequence to a containment suite is protected by a positive pressure zone to prevent a net inflow of dirty air. [2]

Acceptance criteria for **process** differential pressure: min. 5 Pa.

Accuracy for differential pressure transmitter SONTAY PA-267-50, (**control system**), full-scale deviation: range 0…50Pa, ±3.00%fsd.

Accuracy for **supplementary indication** instruments MAGNEHELIC 0…60 Pa: 2 Pa.

Accuracy for Fluke 700 P01, S/N 75000101 Differential pressure module 2.5 kPa (**parallel measurement)**: accuracy specifications apply for 0 … 100% of full scale, 0 … 50°C, 0.1% FS typical

Note: More important than "acceptance criteria for differential pressure" is the real air flow sense. This was tested with smoke candle, but until yet, we haven't evaluate all cases "in worst case" (doors completely open).
Manometer localization: 1M1- room 4A, 1M2- room 5A, 1M3- room 6A.

3.5 Acceptance criteria: air changes per hour

The quantity result by design is necessary to displace particles from the environment, pressurize the space and control the temperature and humidity. Federal standard 209D recommend > 20, but not impose it. The most of manufacturing rooms, have 20±10% or more (until 50-realised value), but in offices only 5…10 air changes. In this cases, HVAC provide all parameters, in conformity with Federal standard 209D (class of rooms for Solid Oral Dosage Forms Manufactory, is 100.000 particles of 0.5μm per cubic feet).

Accuracy for air velocity:

- Range 5…25m/s, ±1% reading/±0,05m/s
- Range 0,25…5m/s, ±1% reading/±0,002m/s

3.6 Acceptance criteria: particle number

Air in controlled areas is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100.000 in a size range of 0,5 micron and larger (class 100.000) when measured in the vicinity of the exposed articles during periods of activity. [3]

3.7 Acceptance criteria: clogged filters

Each filter unit has "U" glass manometer, which points clogged filters. Accuracy 10 Pa.
$\Delta P \leq 120$ Pa, EU3, pre-filter supply air
$\Delta P \leq 300$ Pa, EU9, supply air
$\Delta P \leq 120$ Pa, EU3, return

$\Delta P \leq 400$ Pa, EU14 (HEPA-high efficiency particulate air filters), return

3.8 Acceptance criteria: filters integrity

Using a test aerosol with a defined number of particles is the basis for checking the integrity of the filter. We utilize DEHS (di ethil hexil sebacate) test aerosol.

3.9 Acceptance criteria: temperature and relative humidity sensors

Temperature and temperature and relative humidity sensors - Technical specifications.

Acceptance criteria for **process** temperature: 22 ± 3°C.

Accuracy for temp. sensors (**control system**): ±2°C, range 0…70°C.

Accuracy for temp.&RH sensors (**control system**):

- Temp.: ±1%, range –20…+50°C,
- RH: ±3%, range 10…90%.

Accuracy for temperature and relative humidity sensor Rotronic HYGROLOG-D, S/N14336 027, (**parallel measurement**):

- Temp.: ±0,3°C, range –10…+50°C,
- RH: ±1%, range 10…90%.

3.10 Parallel measurement

Control system is considered in drugs manufacturing a "black box"and is considered necessary to have proved that the system continuously produces conditioned air of the required quality (**G**ood **M**anufacturing **P**roduction). This parallel measurement is documented and is realized before beginning of process validation and along it, to assure a good start/control of validation process.

3.11 Calibration procedures

Objective and scope of the calibration. Responsibility of each functional group (lab and quality) relating to the calibration activities. Calibration frequency. Manufacturer recommendations (frequency, tolerances). Environmental conditions required during calibration. Measurements to be made and the accuracy required. Acceptance criteria and action to take when results are unsatisfactory. Calibration records (documentation).

3.12 Instruments. Conformity certificates

Calibration standard or certifying equipment to be used, for:

- differential pressure: Fluke 743B S/N 7095809 Documenting process instrument with Fluke 700 P01, S/N 75000101 Differential pressures module 2.5 kPa
- temperature and relative humidity: Rotronic HYGROLOG-D, S/N14336 027
- number of particles/ cf.: Model 3313-.3-1-SS Laser particle counter, P/N 2083993-03, S/N 010100536
- filter integrity: Met One Laser particle counter, Model 3313-.3-1-SS, TOPAS aerosol generator ATM, TOPAS dilution system DIL 550.
- number of air changes: AIRFLOW Edra 6 Anemometer, S/N 091246.
- Micro Cal 1000, S/N 0008451

4. PERFORMANCE QUALIFICATION

4.1 Air changes per hour before starting validation process [1]

4.2 Duct traverse test sheet before starting validation process [1]
4.3 Particle number before starting validation process [1]

4.4 Stage 1

4.4.1 Parallel measurement: differential pressure, temp.&RH-diagrams.
4.4.2 Control system: differential pressure, temp.&RH in monitoring rooms, set and real values-diagrams.

4.5 Stage 2

4.5.1 Air changes per hour

Room	*Denomination*	*Volume M^3*	*Design flow m^3/h*	*Real Flow m^3/h*	*%*	*Adjusted Air changes ±10%*	*Air changes*
16A	*Granulare umeda*	*256*	*4200*	*4263.7*	*101.5*	*16*	*16.66*

4.5.2 Parallel measurement (Only sensors which are in controlled loops)
4.5.3 Control system: differential pressure, temp.&RH in monitoring rooms, set values and real values-diagrams (only in interests rooms)
4.5.4 Clogged filters, Change control

5. ANNEX (TREND software and technical specifications for control system parts)

6. CONCLUSIONS AND PERSPECTIVE

In our opinion, the biggest problem is to define what are the conditions necessary and sufficiently to prove that the system works as intended, that is reproducible and that meets the established specifications and quality attributes. We believe the documentation is concise, unambiguous, and detailed.

Normally, the documentation can be improved, modified or completed. Our documentation isn't perfect but we consider that our goal was attaint. After second stage of validation process, all parameters are in tolerance- with a high degree of confidence. However, we have installed indicators for temperature, differential pressure or temperature and humidity recorders in some prerequisite rooms.

Design documentation for pharmaceutical HVAC must be more rigorous than for other types of projects. Generally, system testing must include methodologies to prove system operation. In most cases, in pharmaceutical industry, is necessary to have an Validation compartment with an validation team leader which should approved all new machines and should be prepared to incorporate unusual testing requirements in the project specifications.

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