Comments on WHO Working Document QAS/18.759
Good Manufacturing Practices for Heating, Ventilation and Air-Conditioning Systems for Non-Sterile Pharmaceutical Dosage Forms: Part 2

Comments submitted by International Society for Pharmaceutical Engineering (ISPE)
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*Kindly complete the table **without modifying the format** of the document - thank you.*

Template for comments

General comment(s) if any:	**Originator of the comments**
Many of the statements in this document are written as design guidelines instead of regulatory guidelines. To that point, regulatory guidelines should define required results, not the specific method of achieving them because, in many cases, there is more than one method of achieving the desired result. If it is desired to leave in these diagrams and specific designs for developmental or educational purposes, the document should very clearly state there are other methods to achieve the desired results.	
The majority of countries do not require a classified area for manufacturing a product that is taken orally. Implying that one is required could increase costs and may not improve quality; the risk is higher in the process equipment that uses a large volume of air for the process, e.g. granulation or coating, where high quality air filtration may be beneficial.	
The document should include the concept that the level of classification and segregation be based on risk (see comments on Lines 152 and 161).	
The document opens with relying on risk management principles and it would be much improved if those principles according to Q9 were emphasized throughout the document. This would be very important with respect to the types, numbers and potency of products produced in a particular facility.	
The document would benefit from additional editorial review. Examples of such edits are below: Line 201 (Figure 2): What does “Brocken” mean? Line 216: “…production areas where there is ~~**then**~~ a higher pressure…” Line 384: “In these room**s**…”	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
1 and 2	105-107	1.) number of air handling units: area separation is important and will affect the number of air handling units, but the number of AHUs itself is not necessarily important; 2.) room air distribution is a very important aspect of maintaining a suitable environment for the manufacture of quality pharmaceutical products and should not be overlooked.	"…for example, ~~the number of air handling units (AHUs)~~, components in AHUs, room pressure, pressure differentials, pressure cascades, levels of filtration, humidification, dehumidification, heating and cooling of air."		
4	159	The term "…special precautions should be taken." is ambiguous and needs to be clearer.	Reword the phrase to increase clarity in requirements / "…pressure, special precautions should be taken, for example, the use of pressure "bubbles" and/or "sinks" ~~should be used~~ to provide containment and protection from infiltration to production areas."	M	
4	161	The sentence "Where necessary, air locks, change rooms and pass-through hatches…" is not clear. The use of air locks (PAL, MAL) is always necessary to support personnel and material movement into and out of the classified production area(s).	Rewrite as follows: "Include the use of personnel air locks (PAL) and material air locks (MAL) to support the transition of personnel and material into and out of the classified production area. A pass-through may also be utilized to move material between classified production areas and non-production areas."	H	
4	162-164	The sentence "Special attention…" as it seems to speak to door construction and doors used to define an air lock (MAL or PAL). The use of the work "changes" is used incorrectly in regard to the effect of doors on room differential pressure between areas.	Change the sentence to read "Special attention should be given to door design as door seals, gap between the door and floor, door type (e.g. sliding door), egress doors with high differential pressure can adversely affect area differential pressure stability."	M	
4	175	"…see ISO 14644." The definitions should be provided in this document for reference.	Recommend adding the definition to this document.		
4	185	: "…appropriate number of AHUs" is unclear.	Delete "appropriate number of AHUs".		

	256	The number of AHUs is not defined criteria and should not be addressed as such; however, the outcome of space segregation requirements will be System Zoning Plans that define each zone, the sum of which will determine the number of AHUs required.	"Other aspects such as ~~the number of AHUs~~ **AHU system zoning**,"		
6	352 (Figure 8)	"Degree of filtration required" implies that filtration is always required; however, exhaust filtration is not always required, so it should be "whether and to what degree" instead of "degree".	"~~Degree of~~ **Whether** filtration required depends on exhaust air contaminants"		
7	371	The number of air change rates per hour should be only as many as needed to meet classification limits and comfort requirements AND/OR to meet recovery times. No other guidance should be given - it should be science based.	Remove guidance values for air changes per hour and describe above methodology. Unclear whether the document is citing another source.	H	
7	375	The majority of countries do not require a classified area for manufacturing a product that is taken orally – implying that one is required will increase costs, and may not improve quality; the risk is higher in the process equipment that uses a large volume of air for the process, e.g. granulation or coating, where high quality air filtration may be beneficial. If a classified space is being requested – then clarify which room/area classification needs a 15-20 minutes recovery time; is this for Grade C and/or Grade D? If the guidance recovery time varies per classification then note such and define what the time should be. Please also clarify why this is suggesting use of the classified area for manufacturing.			
7	394	Suggested pressure differentials of 5-20 Pa contradict with Row 287 which states 5-15 Pa	Resolve contradiction. We recommend that a reference for source of the pressure differential is provided.		

7	422-423	Convert to regular text (not a note) - this is an important point often interpreted incorrectly.			
8	461	Design consideration – velocity at dehumidification coil to prevent condensate carryover. Many of the statements in this document are written as design guidelines instead of regulatory guidelines. To that point, regulatory guidelines should define required results, not the specific method of achieving them because, in many cases, there is more than one method of achieving the desired result.	Include recommendation stated.	H	
12	501-512	These requirements relate more to the classified room as opposed to the HVAC or air handler. Consider an approach that prevents unnecessary validation and requirements around the air handler and its components but rather focuses on end results - similar to environmental characterization - limit the air handler itself to minimal validation such as installation qualification and commissioning.	The approach used to qualify the HVAC should be aligned with ASTM E2500, and use Good Engineering Practice to generate the documented evidence that the system is designed, installed and operates to suit the user requirements Typically the critical items are the HEPA filter, and the monitoring system. ISPE would be pleased to facilitate a conversation between the section author and the ISPE members who are developing an update to the ISPE Baseline Guide for Commissioning and Qualification.	H	
12	505	Minor changes such filter replacements should not require qualification. In fact, as long as the conditioned space qualified monitoring system indicates after changes that the space is maintained at its design airflow rate, temp, RH% (when necessary), and differential pressure, then qualification should not be required.	Recommend removing “Qualification to be done over the life cycle of the HVAC system should be described and executed including, e.g. when changes are made to the system.”	H	

12	515	Most of the items below should be monitored on an ongoing basis; therefore, they do not require qualification tests at defined intervals.	Recommend removing "~~**Some of the typical HVAC system parameters that should be included in the tests during qualification are listed below. It is recommended that the tests be done at defined intervals.**~~" Recommend adding: **''System parameters monitored by a qualified monitoring system do not require qualification re-testing at defined intervals.**"	H	
		Please add rows as necessary (with "copy and paste" empty rows)			