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World Health Organization
1211 Geneva 27
Switzerland

SUBMISSION OF COMMENTS ON QAS/10.342: WHO Supplementary guidelines on good manufacturing practices for heating ventilation and air conditioning systems for non-sterile pharmaceutical dosage forms.

ISPE is pleased to provide comments using the supplied WHO template on the above document, as requested.

Our comments reflect our concerns that the ISPE subject matter experts believe that this document is not a technically competent and current representation of the state of technology or practices within the target subject (e.g. the inappropriate reference to sterile practices and classification and only casual reference to risk management as envisioned under ICH Q9). A thorough revision is recommended.

We also pleased to offer any assistance we may in revising the document to reflect current practices, and form more of a technical guide for the user group.

Yours sincerely,

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Comments on WHO Working Document QAS/0.342/Rev.1

Title of the document: SUPPLEMENTARY GUIDELINES ON GOOD MANUFACTURING PRACTICES FOR HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

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Template for comments

Kindly complete the table without modifying the format of the document - thank you.

General comment(s) if any :	**Originator of the comments**
• Below are a representative, though not complete, sample of the comments from a group of 10 SME's from across operations, engineering, consulting, construction, quality, sustainability and maintenance; with a collective industry experience of over 200 years. • These comments are limited in quantity due to the general consensus that the document requires restructuring and major revision, which limits the value of detailed commentary.	ISPE
• ISPE would like to volunteer the services of industry SME's to assist WHO in a rapid re-write of this critical document.	ISPE
• The ISPE subject matter experts believe that this document is not a technically competent and current representation of the state of technology or practices within the target subject (e.g. the inappropriate reference to sterile practices and classification and only casual reference to risk management as envisioned under ICH Q9). A thorough revision is recommended.	ISPE
• ISPE recommends that the scope and applicability of this document be reinforced and clarified. A clear statement at the beginning of the document giving the authority and intended applicability of this document is needed. Clarify that this is a guide, not a regulation, that it does not supersede applicable cGMP and safety regulations. Clarity is required to separate topic areas, avoiding confusion.	ISPE
• Maintenance of HVAC is not adequately covered in the document. This is a critical area of compliance.	ISPE
• The definitions used in this document are not aligned with industry standards (e.g. ASHRAE, ISPE, ICH, PIC/S, ISO, etc.) • As written, this document would serve to confuse the target audience.	ISPE

• We believe that many of the requirements and suggestions herein are excessive for non-sterile dosage forms. • In compliance with prevalent cGMP regulations, solid dose forms are often manufactured in Unclassified, Controlled Unclassified (CNC), Grade D or Grade E environments. Due to their non-sterile status, many manufacturers don't formally classify their environments for OSD type products, using internal references or ISPE baseline guide reference of LPP1-3 & CNC. • HVAC energy use in these facilities is dominated by the number of airchanges flowing around the facility, these are often selected based on tradition rather than actual requirement and as a result are invariably over-specified and hence facilities use excess energy. This document does not serve to eliminate this practice, but in our opinion, should do so.					ISPE
# section	**# Pararaph If more than one**	**Comment / Rationale**	**Proposed change / suggested text**	**Classification** **L**= low **M**= medium **H**= high	**Originator of the comments (for WHO use)**
Pg 5		The definition given is for *SUPPLY air changes per hour*, not for *air changes per hour*	May also want to consider adding the definition of *TOTAL air changes per hour* which is the greater of the supply air rate or the extract air rate divided by the room volume. Total is more appropriate in rooms under negative pressure where the inflow of transfer air also contributes to the dilution ventilation of room airborne contaminants.	H	ISPE
Pg 5		The *at-rest* definition says equipment is operating however figure 3 on page 10 shows the at rest condition to be with the equipment installed but not operating. We are more accustomed to the at-rest condition being as Figure 3 shows, i.e. the equipment not operating.	Revise to match Eudralex	H	ISPE
Pg 7		Unidirectional airflow (UDAF) like that shown in Figure 7 on page 12 implies laminar airflow, high airflow/high air change rates, and continuous/nearly continuous ceiling coverage with supply air terminals. The application of UDAF is excessive in most areas of OSD facilities.	Recommend adding a definition for "General Directional Airflow" like that which is shown in figures 10 and 11 on page 13.	H	ISPE

Pg10	4.1.5	Often the decision on classification is made based on industry norms. Future designs should be based on a risk assessment of the specific requirements of the product / process and people.	The air change rates should be determined by the manufacturer and designer taking into the various critical parameters using a risk based approach and with due consideration of capital cost, running cost and energy use. Primarily the air-change rate should be set to a level which will achieve the required cleanliness classification without excessive over capacity.	H	ISPE
Pg10	4.1.6	At design stage – key inputs such as particle emissions (people and process) and heat gains are not known. Maybe we should have some typical particle emissions for common processes and people to use as a basis for airflow design. It must also be reiterated that many non-cleanrooms would achieve Grade D "at-rest", without the benefits of HEPA supply, high airchange rates etc	Air-change rates normally vary between 5-20 achr, but could be greater than 20, and are normally determined by the product / process and people critical requirements. Steps should be taken to ensure over-design is avoided and facilities and air-change rates are selected based on need rather than tradition.	H	ISPE
	Fig 6	This suggests that good practice is to have low level extract. In my view – in grades C – important, but in grade D – ideal but not essential. Also, often non-sterile dosage products are produced in unclassified environments – hence more likely to be high level than low level.	**Perhaps include a statement;** • Grade C = low level extract recommended • Grade D = low level extract is ideal but not essential • Unclassified = low or high level	H	ISPE
	Fig 7	This should include a health warning regarding the width – high ratio as low level sidewall grilles on wide rooms can result in airflow shear and hence a cone of up-drafting turbulence	Not sure why Grade A type UDAF's are in this document as they are not used in the manufacturer of non-sterile dosage forms for cleanliness reasons.	H	ISPE
Pg 10	4.1.6	Air change rates of 4 and lower have been used successfully. Air distribution and extraction are more important than air change rate. If the heat load on the room is less than 6 air changes per hour and the room contaminants can be adequately controlled, then why not use less than 6 air changes per hour.	After "but could be greater than 20 ACH" add "or less than 6 ACH"	H	ISPE
Pg 11	4.1.9	The *at-rest* definition says equipment is operating however figure 3 on page 10 shows the at rest condition to be with the equipment installed but not		H	ISPE

		operating. We are more accustomed to the at-rest condition being as Figure 3 shows, i.e. the equipment not operating.			
Pg 11	4.1.10	Recovery Testing is not a cGMP requirement for non-sterile facilities. It may be used as a commissioning activity to prove room performance. Recommend this clarification so that the readers are clear that the 20 minutes doesn't start until all activities in the room such as cleaning have ceased.	Clarify applicability of the use of this test At the end of the paragraph add "after the room has been cleaned, the personnel are gone, and the equipment has stopped operating".		ISPE
Pg 12	4.2.2	Obsolete ASHRAE efficiency figures used and MERVE used in lieu of the correct MERV	Consider adding ASHRAE Standard 52.2 (the MERV rating system) to the EN references.		ISPE
Pg 13	Figure 8	Consider adding ASHRAE Standard 52.2 (the MERV rating system) to the table. The Dust spot efficiency ASHRAE 52/76 is out of date but may want to be kept for reference.			ISPE
Pg 13	4.2.5	Soften this requirement for ventilation dampers, filters and other devices should be designed and positioned to that they are accessible from outside the manufacturing area.	This can be a costly nice to have but is not a requirement in an OSD facility.		ISPE
Pg 13	4.2.10		Change the word "exhausted" to " extracted" or add the words "or returned" after "exhausted"		ISPE
Pg 13	Figure 9	Induction diffusers are fine for Level 1 spaces and Level 2 spaces that do not have airborne product particulates. This type of system does a great job of eliminating "dead" spots within a space with a relatively low amount of supply air.	Deleted words "(not recommended)" A more complete discussion of types of diffusers and their application is recommended		ISPE

Pg 17	4.5.15	Do not agree that 15 Pa (0.06" wg) is the most widely accepted pressure differential for achieving containment between two adjacent zones. 12.5 Pa(0.05" wg) is the recommended design value for US aseptic facilities and 10 to 15 Pa(0.04 to 0.06" wg) is cited for EU aseptic facilities. Note that OSD production requirements are far less critical to the patient than for Aseptic production. Also in the US, the requirement for Hospital isolation rooms is greater than 0.25 Pa (0.001 " wg) which equates to a door crack velocity of approximately 0.5 M/sec (100 FPM) which is the generally accepted standard for conventional fume hood containment velocity. For reference, 15 Pa (0.06" wg) yields a door crack velocity of approximately 4.1 M/sec (800 FPM) and 10 Pa (0.04" wg) is approximately 3.3 M/sec (650 FPM) crack velocity which are much higher than needed to keep airborne particulates from passing the wrong way through the cracks.	Concentrate on direction of airflow, cite pressurization control as a means to achieve this control. Unclassified spaces do not require pressurization control. Recommend to change the paragraph to suggest that the generally accepted dP design is between 5 Pa and 20 Pa however lower and higher values have also been used successfully.		ISPE
Pg 18	4.5.23	Why are sliding doors not recommended. Virtually every OSD plant I have been in utilizes several to many sliding doors. These types of doors are less disruptive to room air currents than swing type doors when opened and closed.	This is an aseptic plant recommendation; not applicable here.		ISPE
Pg 18	Figure 18 And 4.5.27	The figure and associated text indicates that differential pressure is measured to a common reference point. That is great for control but the containment or protection requirement is the actual dP across the doors between adjoining spaces. The local Magnehelics should read pressure between adjoining spaces and have their normal, alert, and action indications based on room to room dP instead of room to reference dP. Also the diagram and text implies minus and ***plus*** limits. What's wrong if the dP goes high. Low room to room dP is the main concern. If the room to room dP	Re-write this section to properly address control and monitoring of pressure as well as setting of Critical Process Parameters in alignment with product requirements		ISPE

		gets a little high, and the facility construction can handle it and the doors can be readily opened, and they don't stand open, then we don't see a problem.			
Pg 18	Figure 19	For this type of airlock what generally is important is the dP between both sides of the airlock. In this example, what is important is 15 Pa dP between the high room and the low room and the 22.5 Pa inside the MAL doesn't matter. If it did matter, then someone would have to keep fine tuning the door cracks until 22.5 Pa was achieved. This is not practical and the 22.5 Pa is not important to space segregation..	Recommend that the internal pressure criteria of 22.5 Pa be deleted from the cascading type airlock.		ISPE
Pg 21	5.4	The low velocity end of 15 M/sec seem a little high, is noisy, and energy consuming. Many pharmaceutical dusts are light and can be handled with a low end of 12.5 and even as low as 10 M/sec.	Include a proper description of the relationship between capture velocity and particle size/mass. This is not generally a cGMP issue, but rather a safety issue in this application(clarify this).		ISPE
Pg 21	5.6	The term "general directional airflow" is useful and should appear throughout	We recommend that it be put into the definitions section as indicated in our comments for page 7.		ISPE
Pg 21	5.11	We find that the trend is to get away from air compressor type breathing air systems to Powered Air Personal Respirator (PAPR) systems. The breathing air cord tends to be a tripping hazard and are quite cumbersome in moving from room the room.	This topic is outside the document scope as defined		ISPE
Pg 24	7.1.1	Don't agree with implying that OSD facilities should be designed to Class 8. Where does that requirement come from? Our experience is that Class 8 generally is excessive for OSD facilities.	As discussed in our general notes: Unclassified space is often an appropriate and compliant solution. Discussion of the application of classified space in line with risks is recommended		ISPE

Pg 26	7.3.2	In some cases the better place to put the HEPA filter is in the return to better protect the facility, ductwork, AHU, and HVAC maintenance personnel from product particulates.	Delete word "supply". This topic is not a simple one, no single recommendation is appropriate	H	ISPE
Pg 26	7.3.5	Why is flexible ducting not recommended for connection to terminal HEPA filters. There are plenty of manufacturers of high pressure insulated flexible ductwork that are quite suitable for this application. Just don't use the cheap office grade flex.	HEPA filters can be connected with flex duct, depending on the quality of flexible ductwork available.	M	ISPE
Pg 26	Figures 26 and 27	Three in series filters in the exhaust air handling unit seems excessive and yields high pressure drop and higher first cost and operating cost.	Revise the graphic	M	ISPE
Pg 27	Figure 23	Recommend moving reactivation air fan to downstream of the desiccant wheel. If installed at the shown location, there is risk of the pressure on the reactivation side of the wheel being higher than the pressure on the process air side which will cause hot humid air to enter the process air stream and increased the cooling and dehumidification load on the facility. May also want to consider moving it to upstream of the desiccant wheel to keep it cleaner.		M	ISPE
	Table 1&2	The discussion of Sterile process grades and micro limits is inappropriate.	These classifications are not common for non-sterile and are not tied to regulation	H	ISPE
Pg 13	4.2.9	• Four way blow – WHO not recommended • Swirl & perforated plate – WHO recommended Four-way blow diffusers are used pretty widely in cleanrooms currently, as are swirls and perforated plate diffusers. Some may suggest that induction / high mixing devices are helpful in dilution of particles in turbulently ventilated – lower grade cleanrooms. Some may also suggest that swirls themselves provide a high induction / mixing pattern of supply. A risk exists using perforated plate diffusers and low	Supply diffusers may be selected to provide high dilution / mixing of the clean supply airstream with room air, or for displacement. The room design can employ a number of techniques for contaminant control. No single answer exists.	M	ISPE

		level extract that plumes of clean air result which doesn't dilute emissions outside the plume. At lower flow rates, diffuser selection is important to ensure adequate ventilation effectiveness. Also, terminal selections twinned with terminal HEPA's need thought, as HEPA's only come in certain sizes and as a result, grille selections may be sub-optimised.			
Pg 14	4.3.7	Strange velocity quoted – 0.36 to 0.45 m/s equates to 0.405 +/-11% - not as other guidance documents = 0.45+/-20%. Proves the point that this document is not particularly relevant to grade A / sterile areas.	Not sure why Grade A type UDAF's are in this document as they are not used in the manufacturer of non-sterile dosage forms for cleanliness reasons.	M	ISPE
Pg 18	4.5.23	I have seen many examples of good quality sliding doors in operation within high specification cleanroom facilities.	Not appropriate for this guide, not an HVAC issue	L	ISPE
Pg 24	7.1.1	This is good news, as it provides a citable reference for customers who are not sure about their own OSD facility classification / filtration requirements	The applicability of HEPA filters is a risk based decision, even recirculated air may not need HEPA filtration (e.g. single product or campaign production)	L	ISPE
Pg 28	Fig 29	This is another key to successful facility design and joined up understanding of critical requirements – product / process / people Narrowing the gaps will reduce energy use and reduce facility capital and running costs.		L	ISPE
Pg3	1	The user requirements are based on product requirements – single or multiple products. AHow can a guide to HVAC systems for non sterile pharmaceutical focus mainly on OSD – it should cover-clean liquids, creams and ointments as well. These dosage forms also create demand on the utility	Clarify the exact scope of the document, and align the content with the scope.		ISPE

		systems – should those be defined in this document, as they may impact product quality?			
Pg4	1	This document aims to give guidance to pharmaceutical manufacturers and inspectors of pharmaceutical manufacturing facilities on the design, installation, qualification and maintenance of the HVAC systems. These guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products (1)* and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements set out in the parent guide.	This guideline has been developed to complement "Good Manufacturing Practices for Pharmaceutical Products" providing specific technical guidance related to the HVAC systems used for non sterile product manufacturing.		ISPE
Pg 4	2	What is a "GMP inspector"? Does Many Manufacturers mean pharmaceutical manufacturer – design parameters is not an industry standard term in this context, user requirements is. The scope described here is beyond GMP, covering EH&S – yet the latter is not really addressed, nor is the requirement to identify and comply witl local/National standards described.	The content of the document should be revised to match the defined scope.		ISPE
Page 5	Fig 1	Qualification and Validation are generally related to process equipment/manufacturing processes, with EH&S activities not in their scope – not as depicted in the figure	Correct the figure		ISPE
Page 5	Glossary	Many of the definitions here are not aligned with industry standards – or practices, eg action limit, as built – a term used to define a drawing /specification status, at rest does not agree with the Eudralex definition etc– none of the definitions give the source	Revise this section to align with relevant regulations/industry standards.		ISPE
Pg 4	4.1	The approach defined here does not follow industry practice – it is normal to ; Define the product/process requirements Define the products and any specific requirements in terms of exposure limits/special cleaning requirements Define any specific risks – product contamination/cross contamination The facility design is usually developed based on these requirements – with the HVAC requirements developed with the facility layout The designer view process – led by engineering with	Revise the document to reflect best industry practice	M	ISPE

		quality involvement is what "qualifies" the design as fit for its intended purpose – in this context you have to look at the layout/finishes/HVAC as an integrated package. An discussion of at rest and operational conditions is completely irrelevant in a non sterile context.			
Page 13	4.2.4	What are the options for the MoC – what are the potential issues with each?	Content needs to be added		ISPE
Page 13	4.2.6	People are the major source of contamination			ISPE
Page 13	4.2.10	Low level extract is more costly than high level, and is not always warranted – the guide should explain the issues	Content needs to be added		ISPE
Page 13	Figures 9,10,11	How can you recommend one component when you have no other information about the basis of a system design? Swirl diffusers are an expensive solution – much more commonly seen in a sterile environment where complete mixing of the room and supply air is a design objective.	Inappropriate content – either provide full text or delete		ISPE
Page 15	Figures 12, 13	These drawings are not clear or helpful – downflow units typically have a bleed to allow some inward movement of outside air – designing the equipment for a specific use is critical to obtain the operator protection that this type of equipment is usually specified for – to provide product protection a cheaper simpler in room device is more commonly used – this is a key decision to make when selecting the equipment to be used.	nappropriate content – either provide full descriptive text and drawing or delete		ISPE
Page 17	4.5.13	The design concept commonly used is controlled airflow direction for an OSD facility, as shown by a differential pressure – the guidance figures here are really not correct within the context of the document.			ISPE
Page 4	1	Sentence "The guidelines also refer to other systems or components which are not relevant to solid dosage manufacturing plants…." Does NOT belong in this	Delete this sentence as well as the content within the guideline that does not apply to OSD or non-sterile API facilities.		ISPE

		document, not does that content which doesn't apply. This causes much confusion among the audience.			
Page 5	2	w.r.t – What does this mean?	State "with respect to"		ISPE
Page 5	Figure 1	"Environment Protection"?	State that this refers to the external environment, not the manufacturing environment. These are non-GMP issues, separate from the cleanroom/manufacturing environment.		ISPE
Page 7	3	Clean Room – should be one word vs. 4.1.5.	Be consistent throughout the document (as per ISO 14644) of the use of "clean zone" or "cleanroom".		ISPE
Page 7	3	"Commissioning" – definition is misleading	Commissioning planning actually needs to begin during design. It is a plan for failure when approached only as an end-of-construction activity on a GMP project.		ISPE
Page 7	3	Critical Parameter or Component – CQA?	Text of document needs to be written in current terminology of Risk Based approach, ie, parameters which affect Critical Quality Attributes (CQAs) per ICH Q9.		ISPE
Page 9	3	Qualification vs. Verification?	Text of document needs to be written in current terminology of Risk Based approach (ie, verification vs. qualification… including DQ/IQ/OQ.		ISPE
Page 10	3	Relative Humidity vs. Absolute Humidity? In the design of HVAC for facilities RH can be very misleading, so we need to talk about absolute humidity also in terms of dewpoint or grains/pound.	Define "absolute humidity" and "dewpoint" and then be clear throughout the document which of these three is really important for the specific application referenced.		ISPE
Page 10	4	Last sentence in UDAF definition … why talk about the "used to be" laminar flow?	Remove last sentence (Modern standards no longer refer to laminar flow but have adopted the term unidirectional airflow).		ISPE
Page 10	4.1.1	"Controlled Areas" – term is used but not defined??	Define "controlled areas" in the glossary.		ISPE
Page 11	4.1.3& 4.1.4	Air change rate or flushing rate **vs. air flow rate?**	Air change rate is not necessarily a parameter that affects CQA in a non-sterile facility. We do need to design the airflow rate to adequately cleanup after an event and to avoid cross contamination, but do not want to set a minimum required air change rate.		ISPE
Page	4.1.3	Other important criteria to be considered include	Add "Cleaning" and "Gowning"		ISPE

11		"Cleaning" and "Gowning"			
Page 11	4.1.7	This is problematic in that it implies an OSD or non-sterile API facility should be classified. This is a problem throughout the document, especially when mentioning an "in operation" classification for OSD facilities.	Change this wording to remove the confusion regarding classification of OSD and non-sterile API facilities. Some users might choose to set a minimum design criteria that the room meets (for example) ISO 8 in as-built or at-rest conditions at 0.5 micron particles and make that a commissioning, not qualification, test of room performance.		ISPE
Page 16	Figure 6	(Low level extract is essential for grade A, B & C areas.) See previous comment on section 4.1.7. This does not belong in an HVAC guide for OSD and non-sterile API facilities.	See comment on section 4.1.7		ISPE
Page 17	4.1.16	"People should not be a source of contamination"????	People WILL BE the major source of contamination. That is why we pay so much attention to gowning, cleaning, airflow direction and work locations, and minimizing the cross-flow of people, product and equipment.		ISPE
Page 18	Table 1	The entire section of this table below the description of Level 3 has no place in this guide. Same issue as previous comment on section 4.1.7	Delete the portion of Table 1 below the Level 3 description.		ISPE
Page 19	Table 2 and 4.2.2	Return Air or Exhaust HEPA Filters? ASHRAE MERV ratings?	State where you are referring to supply or to exhaust/return filters. Include the appropriate ASHRAE MERV rating.		ISPE
Page 20	Figure 8	**Confirm vs. HVAC GPG**	This is pretty close to the comparative tables in the ISPE HVAC Good Practice Guide. Suggest that you add the corresponding IEST filter class to the table as included in the ISPE HVAV GPG.		ISPE
Page 21	4.2.5	This is a matter of preference. Many users prefer room-side HEPA filter changes for exactly the reason stated in section 4.2.8 (containment within the room)	Make this a point of consideration by the user, not a requirement.		ISPE
Page 24	4.3.1	This section has been misapplied by inspectors to require the same level of air flow pattern testing (AFPT) as that required in Grade A (sterile manufacturing) environments.	State that this testing, where used is for containment/safety/ cross contamination control purposes and not the same requirements –(if the scope includes EH&S then content needs to be added re monitoring of staff) as AFPT is for aseptic operations.		ISPE

Page 25	4.3.7	As mentioned previously in section 4.1.7, discussion of Grade A requirements has no place in this document and confuses, rather than enlightens the audience.	Revise this entire paragraph to remove references to Grade A criteria.		ISPE
Page 30	4.4.1	"Air infiltration of unfiltered air…should not be the source of contamination." Similar to section 4.1.16, it WILL BE a source of contamination.	Change to "Infiltration of unfiltered air…should be minimized."		ISPE
Page 30	4.4.2	OSD facilities are rarely maintained at a positive pressure relative to surrounding rooms due to containment issues.	Not true – correct this statement.		ISPE
Page 31	4.5.1	Cross contamination via people and equipment movement poses a much greater risk than does HVAC.	State importance of consideration of the flow of people/product/equipment and their decontamination in addition to the correct HVAC design.		ISPE
Page 31	4.5.3	Manufacturing cubicles/suites for OSD are rarely designed with a positive pressure to atmosphere due to containment issues. See previous comments on section 4.4.2.	Incorrect - state correctly.		ISPE
Page 32	4.7.4 & 4.7.5	The pressure differentials stated are appropriate for EU Grades where microbial control is of great importance, but are not required nor appropriate for OSD and non-aseptic API manufacturing. Airflow direction in important, but does not require the pressure differentials used in sterile manufacture.	Incorrect - State correctly.		ISPE
Page 33-36	Figure 18 thru 21	The concepts in the diagrams are pretty much correct, although it is more normal to make the airlock a pressure bubble. However, the pressure differentials shown (as high as 30 Pa) are not required per comment on sections 4.7.4 & 4.7.5	Incorrect - State correctly.		ISPE
Page 37	4.7.16	"OOS" Assume you mean "out of specification"?	State correctly.		ISPE
Page 37	4.9.1	Temperature and RH (or absolute humidity) are not always parameters which affect product CQA.	State that when these parameters are determined to impact CQA they must be controlled, monitored, and recorded…..		ISPE
Page 38	4.9.10	Should be added to the boiler system.	**Shall** be added to the boiler system.		ISPE
Page 38	4.9.16	See previous comment on Section 3 re. RH vs. absolute humidity.	"…. the associated temperature should also be specified. Often instead of relative humidity, the		ISPE

			moisture limits may be specified in terms of absolute humidity as determined by dewpoint or grains/pound of dry air."		
Page 39	5.5	There are many more requirements which need to be stated regarding if the intent of this HVAC guideline is to address the issues of dust control, LEV systems and preventing dust explosions. Once again, these are primarily safety, not GMP issues.	Clarify whether these issues should be a part of this guideline. Either delete or address comprehensively.		ISPE
Page 41	7.1.1	See comment from section 4.1.7	See response from section 4.1.7		ISPE
Page 41	7.1.2	Why wait to mention of this on page 41? In addition to specific technical issues with Section 7, it seems out of place to finally address the design of HVAC systems 41 pages into the guideline.	Reorganize and correct the technical content.		ISPE
Page 43	Figures 22 & 23	Neither diagram shows a HEPA filter in the return, which is a very common design in multi-purpose and potent compound OSD facilities for containment and to protect the return/exhaust ductwork and downstream equipment for maintenance personnel.	Show optional HEPA filter in the return/exhaust either at the room or at the inlet to the AHU/exhaust fan.		ISPE
Page 43	7.3.5 "Note"	Same issue as previous comment in section 4.1.7. Why continue to mention requirements which do not apply to OSD and non-sterile API facilities?	Same response as section 4.1.7		ISPE
Page 46	7.5.2	The preferred location (most economical) of a dehumidifier could be either in the return duct, the outside air duct or the mixed air supply duct depending on the application.	Locations for drying wheel – for your application perform an economic evaluation to determine which of these three locations is most economical.		ISPE
Page 47	8	The entire discussion of C&Q is written in outdated language. Need to define C&Q plan early in the project (see comment from section 3 re. "commissioning"). Need to include discussion of CQAs which drive design and verification requirements.	Rewrite this section in current language.		ISPE
Page 48	8.2.16	Room recovery test is not a GMP requirement for OSD and non-sterile API facilities but is sometimes used as a commissioning (not qualification) test of room performance in the as-built or at-rest state.	State as such. This applies to Table 3, Part B also.		ISPE
Page	Table 3	Same issues as mentioned previously for "particle	Revise to be technically correct, discussing the issues		ISPE

51	Section A	count testing" (classification) and "air pressure differential" (15 Pa differential should not be mentioned as the standard).	around defining requirements/acceptance criteria.		
Page 52	Table 3 Section B	Frequency of HEPA filters tests must be determined by a risk assessment of that application. Airflow visualization for containment purposes in OSD facilities (as opposed to the AFPT in sterile areas) is not required to be done every 24 months.	The information from ISP-14644 is not given appropriately here. See proposal above		ISPE
Page 53	Ref. # 6 & 7	ASHRAE handbooks for applications and systems referenced (1999 and 2000) are at least two editions out of date. Were the most current versions referenced in developing this guideline?	Correct or delete references if you did not use them.		ISPE
Page 53	Ref. 11& 15	ISPE Volume 12 is pending (Risk Based approach to replace Vol. 5). ISPE is developing a "bridging document" to transition from the Vol. 5 to the Vol. 12 approach. ICH Q9 is referenced, but the "old language" remains in this document.	Revise the document to bring "C&Q language and methods" into current "Quality Risk Management" approach.		ISPE