30 October 2009

Quality Assurance Programme
Quality Assurance and Safety: Medicines (QSM)
Department of Medicines Policy and Standards (PSM)
World Health Organization
CH-1211 Geneva 27
Switzerland

Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances
QAS/08.256 Rev 1, September 2009

ISPE welcomes the opportunity to comment on the WHO document QAS/08.256 Rev 1: Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances. Our comments are attached.

We have some overarching conceptual comments as listed below.

1. It is important to stress the difference between hazard and risk. The area of concern is high risk so risk should be assessed on a case-by-case basis. Risk should be reduced wherever it is determined to be above acceptable limits. ICH defines risk as the combination of the probability of occurrence of harm and the severity of that harm. All pharmaceutical compounds are hazardous, but when you factor in the manufacturing conditions, equipment, procedures, etc the risk could be quite low. Based on this pretext, Section 4 Risk Assessment should precede Section 3 General to allow the reader to understand risk assessments are suggested and the solutions developed from the risk assessment are allowed. If a company chooses not to do a risk assessment or a solution cannot be found, and then follow the suggestions within this document.
2. There is a lack of clarity regarding the scope and focus of the document. For example in 1.2 it states that the document only deals with criteria which are not covered in other WHO GMP regulations, yet there are several statements included that are basic GMP issues addressed in other GMP documents such as in sections 2 and 8. The document states its primary focus is on the air conditioning and ventilation systems of the facility but it appears the main focus is on operator safety in high risk processing. To help with

clarity we suggest a title change to Guideline to Operator Protection in High Risk Product Manufacturing Facilities.

3. The proposed guidance is too prescriptive and does not allow for appropriate flexibility to meet the goal of reducing risk.

If you have any questions please do not hesitate to contact me.

Thank you for the opportunity to comment.

Yours sincerely,

Robert P. Best
President/CEO

Attachment

Comments on WHO Working Document QAS/08.256 Rev 1 Sept 2009

Title of the document: Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances

Comments submitted by: ISPE
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Date: October 25, 2009

		General comment(s) if any : This document will cause greater and not lesser confusion and make compliance nearly impossible since measurable goals are not stated. The document makes no reference to ICH Q 9, which if applied to this document would greatly improve it. Publishing this document will be a retrograde step and it would be to the WHO's credit if this document were completely re-written by an International committee of experts.			**Originator of the comments**
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General		Be cautious about dictating design details too specifically from this general document, and instead allow individual risk assessments to rationalize the need for selected areas of greater protection and to drive which specific avenues to pursue based on individual operations.		H	ISPE
General		One of the objectives of the WHO is too make affordable, pure and effective medicines, this guide does nothing to reduce costs, and it increases them without added value.		H	ISPE
General		Throughout the document (individual instances are detailed below) risk and hazard are confused. All pharmaceutical compounds are hazardous. Per ISO/IEC Guide 51 and ICH Q9: Hazard is defined as the potential source of harm. Risk is defined as the	Focus the document on risk rather than hazard	H	ISPE

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		combination of the probability of occurrence of harm and the severity of that harm			
General		The guide is very confused as to whether it is a Quality, Occupational or Environmental exposure guide. Instead of stating objectives, such as breathing zone protective equipment will provide protection below the identified safe threshold for the substances handled, actual methods are stated. These may be inappropriate in many scenarios. The material of gowning is restricted to one. But the guide states that a Risk Assessment is required to identify the hazard. Gowning appropriate for a very high hazard compound may be completely inappropriate for a lower hazard.	Refocus document	H	
		This guideline would foment existing disorder regarding hazardous substances in GMP. It is because the definitions of hazardous substances have never been established. dearing to use this guideline, this guideline would be available as engineering check list, in the only case where there is any sever risk that hazardous substances would be exposed into the processing room or suites over the acceptance limit.			
General		This document appears to only be applicable to new construction, not existing facilities.	Clarify what is to be done in existing facilities	M	ISPE
General		Document contains redundant information with other environmental and occupational documents and	Consider if this document is really needed. If so, perhaps it could be issued as a Reference document	H	ISPE

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		Engineering documents (EPA, OSHA, HSE in the UK etc)	that points to where the original information (OSHA, EPA, FDA, ISPE Best Practice Guides for Pharmaceutical Manufacturing etc) can be found.		
General		Confusion between Good Practice and GMP Good manufacturing practice, what is this document? GMP, Occupational and or Environmental safety	Should be separated into GMP's which are enforceable in application to product quality and Guidance on Occupational and Environmental Safety	H	ISPE
Title		While we understand the importance of a document to protect workers and the environment from hazardous materials, this document is not a "GMP" it is primarily focused on personnel and environmental protection, not product and patient protection. Further, many aspects of this document seem more appropriate to a biosafety document, rather than a hazardous compound document, yet no mention is made regarding live organisms.	Suggest it be retitled "Guidance" or "Common Practices". Due to the lack of a rigorous and structured methodology for risk assessment and evaluation of mitigating features we cannot recommend that it be titled "Best Practices"	H	ISPE
Title		All pharmaceutical products contain hazardous substances; some more hazardous than others. The focus of the document should be on RISK not hazard.	Guidance for Processing of High Risk Pharmaceutical Products	H	ISPE
1.1		Including the phrase "such as certain hormones" does not give the user clarity and may add confusion that the only compounds of interest are hormones. In addition "certain hormones" isn't an actionable definition. Focus on high risk not hazard.	Replace with the following: This guideline serves to set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) where hazardous substances are exposed into the processing rooms or suites over the acceptable limits. It does not replace national legislation for	H	ISPE

		General comment(s) if any : This document will cause greater and not lesser confusion and make compliance nearly impossible since measurable goals are not stated. The document makes no reference to ICH Q 9, which if applied to this document would greatly improve it. Publishing this document will be a retrograde step and it would be to the WHO's credit if this document were completely re-written by an International committee of experts.			**Originator of the comments**
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		All substances are hazardous, water is a classic example, to ingest too much water is fatal, as is too little. Therefore this guide applies to every compound no attempt is made to set limits. Leading to even more uncertainty. It is quite possible to set limits for the vast majority of compounds, where it is not possible to achieve the limit than segregation and dedication is an alternative. This subject needs to be addressed in this guide. The EMEA is updating their GMP's to bring clarity by removing the terms "certain" in sections 3.6, 5.18 and 5.19 by adopting a risk based approach as documented in ICH Q9. Suggest WHO follow suit.	environmental and personnel protection.		
1.2		The text is oriented towards operator protection issues rather than product quality and includes extensive text on Personal Protection Equipment and Air Showers. In addition when the text turns to product protection/ quality it refers to other WHO guidance.	Replace with the following: This guideline's primary focus is on operator protection when working in these types of facilities.	H	ISPE
1.2		HVAC systems are only one aspect of an overall systemic approach for containment of hazardous compounds. The document should more explicitly state that, or many of the less experienced readers will infer that WHO is stating that HVAC is the major mechanism of controlling hazardous substances.	Replace with the following: It is recognized that there are many different aspects to achieving effective containment of hazardous substances. This paper focuses primarily on the aspects of effective ventilation and PPE.	H	ISPE

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1.3		This statement leads to confusion as many other areas in the document exclude GMP issues.	Replace with the following: The areas where this document finds application are all zones where the handling of these products could lead to over exposure of personnel, or discharge to the environment. This includes research and development facilities, API manufacturing, storage and finished product manufacturing.	M	ISPE
2.1		Focus should be on risk, not hazard	Replace with the following: The main goals in the design and operation of facility for high risk processing are threefold, as follows.	H	ISPE
2.1.2		If this document is a "GMP", by definition it should focus on product quality. Operator protection is not a GMP concern.	Delete this statement in its entirety	H	ISPE
2.1.2		Focus should be on risk, not hazard	Replace with the following: To protect the operators from possible harmful effects where processing products leads to exposure above acceptable limits.	H	ISPE
2.1.3		If this document is a "GMP", by definition it should focus on product quality. Environmental protection is not a GMP concern.	Delete this statement in its entirety	H	ISPE
2.13		Focus should be on risk, not hazard	Replace with the following: To protect the environment from contamination and thereby protecting the public from possible harmful effects of emission of products above acceptable limits.	H	ISPE
2.2	1	Statement is very vague and provides no clarity. This appears to be more a hazard based rather than a risk based requirement. Handling a "high hazard"	Delete in its entirety	H	ISPE

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		compound does not always equal high risk. Need to factor in processing methods, equipment, etc to determine the exposure paths as exposure will be the factor that determines the actual risk profile. Again, "certain products" isn't actionable			
2.2	1	What constitutes a "separate" Entrance and what are "staff facilities"? Does this include washrooms, locker rooms, cafeteria, credit union, company store, sidewalks?	Delete in its entirety	H	ISPE
2.2	2	This should be listed under the glossary as dedicated, self-contained facilities	Add to Glossary: Dedicated, self contained facilities may be in the same building as another facility but should be separated by a physical barrier and have separate entrances and air handling systems.	M	ISPE
2.2	1	It is of no practical use to set this as guidance, there is no guidance here. What is the definition of certain (Uncertainty?)	Delete in its entirety	H	ISPE
2.2	1	This statement contradicts the statement made in section 4.1. Risk assessments should be required to determine how to control (if necessary) exposure to the product and the operator. This statement does not seem to take into account of closed systems which should protect operator as well as product from exposure.	Delete in its entirety	H	ISPE

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		This statement appears to allow multi-processing of different hormones in the same facility. This does not address/ solve cross contamination issues. Even though cross contamination issues are excluded from this document per Section 5.1, this statement may cause conflict with other guidance documents for cross contamination.			
2.5		What is the definition of a contained facility? With the three pronged approach of this document measurable limits should be set for product, Occupational and Environmental contamination, We would suggest the ADI (Patient population) of the contaminant, The OEL (Occupational Population) for the workers and a limit for Pharmaceuticals in the environment, (the ADI again). Of course a significant percentage of the drug will end up in the environment because of excretion, the percentage escaping the facility is far lower, and should be collected by filtration, inactivation or other relevant means.	Delete in its entirety or provide a proper definition of a contained facility.	H	ISPE
2.2 – 2.5		Missing 2.3 and 2.4	Correct numbering so that it is sequential	L	ISPE
2.5		What is the purpose of this statement? It implies a definition of "containment facility" that may not be warranted. The combination of the definitions for these two words is insufficient to convey the construction practices for such a facility. Without	Delete in its entirety	H	ISPE

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		regard to quantity, frequency, concentration, activity, state, mitigation? If my lab handles 10 micrograms is there a need to construct a containment facility?			
2.5		The use of biosafety cabinets, isolation systems or glove boxes may provide an adequate means for containment and operator protection, obviating the need for a containment facility	Delete in its entirety	H	ISPE
2.6.3		This seems vague – all facilities need HVAC whether they are for hazardous compounds or not	Clarify further, "Properly designed to prevent material migration?"	M	ISPE
2.6.8		Does this also include other procedural controls (besides what is referenced in 2.6.2), for example degowning and decontamination?	Clarify	M	ISPE
3	All	Suggest alphabetizing the list of terms for ease of use		L	ISPE
3.1	5	The definition would make a corridor an airlock. The need to segregate MAL and PAL is total overkill and is not necessarily effective. In many cases it will be very expensive to apply and maintain. There are other controls that are just as effective. Much better to state the objectives, the prevention of the mechanical and airborne transfer of contaminants from an area or zone to another in concentrations that would lead to adulteration.	Replace with the following: An enclosed space that prevents the mechanical and airborne transfer of contaminants from an area or zone to another in concentrations above acceptable limits. An airlock is designed for and used by either people or goods (PAL, Personnel airlock and MAL, Material airlock).	M	ISPE
3.1	6	Alert Limit - term is not used in the body of the document	Delete in its entirety	M	ISPE
3.1	7	Spelling/grammar: Remove the space between the s and y in "system"	Change s ystem to system	L	ISPE

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3.1	7	"Barrier technology", definition could encompass more. You don't really intend to limit the definition to barrier isolators and RABS do you?	Replace with the following: A system designed to segregate (or isolate) product from people and the surrounding environment.	M	ISPE
3.1	7	"Barrier Technology", What is meant by "uncompromised"?	Delete the term. I don't understand what it adds / what is intended by it.	M	ISPE
3.1	10	The word commissioning is not used within the body of the text	Delete in its entirety	M	ISPE
3.1	12	"Contamination": could also affect API	"starting material, intermediate, or API"	M	ISPE
3.1	13	"Cross-contamination": could also affect sampling and packaging	Add "sampling, or packaging" after "production"	M	ISPE
3.1	14	Design Condition – term is not used in the body of the document	Delete in its entirety	M	ISPE
3.1	15	Environmental Control System – the definition adds no more clarity to the term than what is stated within the body of the text. The definitions are misleading and is a repetition of the Glossary entry	Delete in its entirety	M	ISPE
3.1	18	Heating, Ventilating and air-conditioning - the definition adds no more clarity to the term than what is stated within the body of the text. The definitions are misleading and is a repetition of the Glossary entry	Delete in its entirety	M	ISPE
3.1	19	HEPA definition should include the reference to EN1822 on page 11 (then it could be deleted from page 11).	Add: "Where HEPA filters are mentioned in this guideline, they refer to HEPA filters with a minimum rating of H13 according to EN 1822."	M	ISPE
3.1	21	Laminar airflow – term does not appear in the body of the document	Delete in its entirety	M	ISPE

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3.1	21	Laminar airflow "…of a **clean** zone …" whether the zone is "clean" or not is irrelevant.	Change "clean zone" to "defined zone".	M	ISPE
3.1	22	Normal operating range – term does not appear in the body of the document	Delete in its entirety	M	ISPE
3.1	23	Operating range – term does not appear in the body of the document	Delete in its entirety	M	ISPE
3.1	24	Definition of OEL is incorrect.	Replace existing text with the following "Occupational Exposure Limits (OEL)- A health-based airborne concentration limit to which worker exposure levels should be controlled. Limits are usually expressed as eight-hour time weighted averages for exposures for 40 hours a week over a working lifetime."	H	ISPE
3.1	29	UDAF: of a **clean** zone …" whether the zone is actually "clean" or not is irrelevant to the definition.	Change "clean zone" to "defined zone".	M	ISPE
3.1	30	Consider using the definitions provided in ASTM 2500		H	ISPE
3.1		Add definition for risk	Add the following: Risk Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.	H	ISPE
3.1		Add definition for acceptable risk For the encyclopedia of Public health "The term "acceptable risk" describes the likelihood of an event	Add the following: Acceptable risk with respect to operator, product and environmental protection is achieved when the risk assessment (qualitative or quantitative) indicates the	H	ISPE

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		whose probability of occurrence is small, whose consequences are so slight, or whose benefits (perceived or real) are so great, that individuals or groups in society are willing to take or be subjected to the risk that the event might occur. The concept of acceptable risk evolved partly from the realization that absolute safety is generally an unachievable goal, and that even very low exposures to certain toxic substances may confer some level of risk. The notion of virtual safety corresponding to an acceptable level of risk emerged as a risk management objective in cases where such exposures could not be completely or cost-effectively eliminated."	level of risk is below a predetermined level of safety.		
4		This appears to neglect risk assessment for product quality (eg cross-contamination risk) which I would expect to be primary in a GMP. Further, this section should suggest some of the mitigating factors to be considered in a risk assessment (eg process duration, product concentration, frequency of operation, mass handled, energy - dustiness- of the operation and state of the product [powder, granulation, liquid, compressed, coated, encapsulated])			
4		After doing the risk assessment, it appears that the only option is "full implementation" of the guideline or "it is not needed".		H	ISPE
4.1		Focus on risk, not hazard	Replace with the following:	H	ISPE

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		This is so vague and generalized as to be entirely useless, no statement as to the criteria that categories the risk	Not all products have equal risk profiles and risk assessments should be carried out to determine the potential risks to product, operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from API manufacture to finished product distribution, would fall under the requirements of this guideline. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination and solid waste disposal considerations.		
4.1		Could help visualize the process	Consider including a FLOW CHART?	M	ISPE
4.1		This conflicts with the introduction (Section 1.3) to the document states that this guide applies to all phases of manufacture.	Delete the section 1.3 in its entirety	H	ISPE
4.2		Should allow the manufacturer's a choice if the cannot or choose not to do a risk assessment to follow the guideline, should not been seen as precedent setting	If the manufacturer chooses not to assess risk or that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or public and/or the environment, the guidelines to be followed for the facility design and operation should be as detailed in this document.	M	ISPE
4.3		OEL is only one risk to be assessed and only addresses operator protection, not patient protection, and environmental protection.	Reword as follows: Risk assessments should take into account all risk factors such as operator exposure levels (OEL), acceptable daily intakes (ADI), cleaning validation limits, etc when conducting the risk assessment.	H	ISPE

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4.3		OEL's do not apply to cross-contamination. Need to include acceptable daily intakes (ADIs) for assessing cross contamination risk.	Add the following sentence: Acceptable daily intake (ADI) values should be used when assessing the risk of cross contamination as well as applicable environment exposure limits when assessing risk to the environment.	H	ISPE
4.3		No mention is made of the other routes of exposure which may be more significant on a case by case basis.		H	ISPE
4.3		How is the assessment to be conducted? Should reference ICH Q9 , but even so many risk assessment methods are subjective and garbage in will always be garbage out. Each statement in a Risk Assessment should be substantiated by data.		H	ISPE
4.4		Confusion between PEL's and OEL's. OEL's are set by the company handling the compound and normally refer to API's. Governments have no knowledge of these compounds until an INDA or NDA is posted. Government bodies may set PEL's for commonly encountered chemical substances that may be elements in the synthesis of the API. Is WHO suggesting that governmental bodies are going to set OEL's for these compounds?		H	ISPE
5		A significant opportunity to hit the GMP issue is being missed. The risk of cross-contamination increases as product potency and effect or side-effect profiles		H	ISPE

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		become more serious. There is a GMP issue here that bears significant expansion.			
5		Product Protection has no mention of potential for cross contamination to other products from such highly hazardous compounds. An evaluation of other compounds handled in the same area or equipment for the potential impact to the patient of low levels of carryover should be included. We don't believe that equipment should be dedicated, but there should be an evaluation of cleaning and/or inactivation methods to ensure safe levels before further production.		H	ISPE
6	all	Statements such as "Wearing flash-spun, high-density polyethylene fiber material suits or impervious washable protective suits, integral hoods may be required depending on the respirator type used" as the only acceptable form of gowning, unless stated otherwise in the MSDS is completely unacceptable, why is this not a statement of purpose.	Reword as follows: Gowning is required that protects the operator from dermal and mechanical transfer of the hazard and which is removed at strategic locations to prevent contamination by mechanical transfer to other products and areas, means to prevent mechanical and airborne transfer during de-gowning is to be provided and the re-use of the gown once used is to be prevented.	H	ISPE
6	all	PPE is not an appropriate control for employee exposure. It is not permissible in the US, UK and many other countries, The Hierarchy of Controls, with Engineering as priority control is required.	Start this Section with reference to the Hierarchy of Controls showing Engineering as first step, then Administrative and PPE can follow.	H	ISPE
6		Use or personal protective equipment and respirators protection. The MSDS cannot be specific enough for the actual risk that occurs during use	The document should recommend that quantitative industrial hygiene risk assessment be conducted to determine if exposures exceed OELs that would	H	ISPE

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			require the use of PPE and RPE and the level of protection required based on data.		
6.2.1			Replace with the following: There should be a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a double ended shut off (DESO) to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure operator safety and comfort with respect to carbon monoxide, hydrocarbons, temperature and humidity. The air source could be a high pressure regenerative blower or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters and carbon adsorption fitted to the system. Where impermeable full body gowning with supply air is used, accommodation should be made for suit cooling via a vortex tube or similar device.	H	ISPE
6.2.3		Not just lower contamination levels, but perhaps less restrictive OEL's, would warrant a reduction in the type of respirator/PPE needed. Also, the term "contamination" as used here can become confusing. Do you actually mean "emission concentration level", or similar?	Add "or higher OELs" after "levels".	L	ISPE

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6.3		PAS is not defined in this document	Define the acronym	L	ISPE
6.3		The current text does not take account of the Exposure as a result of applying engineering control methods and the reliability of those controls and the ability to alarm excursive events. The objective of all IH is to eliminate the need to PPE, wich is mandated by regulation in many countries.	Reword as follows: The selection of the respirator type is based on the relationship between the performance capability of any control measure and its ability to indicate failure, the accepted OEL, the 8-hour PAS and the respirator certified protection factor (PF).	M	ISPE
6.5.6		Not sure what the rationale is for continual, manned SO2 monitoring. Is this an EU regulatory requirement?	Add annual testing for O_2, CO, CO_2, and hydrocarbons.	L	ISPE
6.6		How does 6.6 relate to 6.4?		L	ISPE
6.7			Replace with the following: Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is often used, but other systems (eg cleaned copper) are acceptable. The final filters should be as close as possible to the operator connection points.	M	ISPE
7.2		Focus on risk rather than hazard	Reword as follows: The external atmosphere and public external to the facility should be protected from possible hard due to unacceptable risk.	H	ISPE
7.3		This statement lies at the core of why this document should never be published in its current form. 1 the statement is made in section 5 that GMP's are dealt with in other documents. Then the statement is	Rewrite document and at the very least delete the italicized note.	H	ISPE

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		made that *This aspect is not specifically related to product quality and, therefore, falls outside the scope of this guideline and should be handled as an environmental protection programme* Scope of the document seems confused; either people protection and environmental protection are in or they're not.			
8	All	The items listed in this section apply all GMP facilities and is stated in other documents. This is unnecessary information.	Remove this section in its entirety.	M	ISPE
8.3		What type of showers for the operators, mist or hygienic or both? If removing a full "moon suit" a hygienic shower may serve both uses, but Tyvek coverings will not protect in a shower of this type. In addition the need for showers will be obviated by containing the powder at the source. Hierarchy of Controls again. This must be the main point of any employee exposure control approach.	Showers may be referenced as needed if there is an emergency. Then this suggestion is fine.	H	ISPE
8.5		You need to contain pre & post-production operations as well.	"…installed to facilitate **contained** cleaning …"	M	ISPE
8.7			Add the following statement to the end: "and developed to potential for an event to occur"	M	ISPE
8.10		Cannot construct facility such that there is no air leakage.	Replace with the following: The facility should be a well-sealed structure to	M	ISPE

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			minimize air leakage through ceilings, cracks or service penetrations.		
8.11		What part of the facility? To say that every location within a facility necessarily needs to be negative to the outdoors is not always warranted, and starts to dictate a rigid, centralized design response over situations where it adds no value. (And anyway, section 9.3.11 contradicts this, so reconcile the two.)	Suggest changing the wording to the following: The facility should be maintained at a negative or neutral air pressure to the environment.	H	ISPE
9		Entirely lopsided, should be part of a facility guide similar to ISPE's Baseline facility guides which would be far more relevant. In other words why are WHO creating something that is not as effective as other guides? Much of the information here is outdated.		H	ISPE
9.3		Focus on risk rather than hazard	Reword as follows: Facilities and premises that have high risk processing should have the following basic air-handling characteristics	H	ISPE
9.3.1		Don't dictate this de facto across the board. Let the risk assessment process drive the appropriate response for each situation.	Delete in its entirety or reword as follows: The outcome of a risk assessment will determine if direct venting of air to the outside is acceptable.	H	ISPE
9.3.2		In other words environmental contaminants are preferable to cross contamination, but the system is closed so the risk of escape by pressure cascade is insignificant and easily dealt with by pressure bubbles at external access points.	Reword as follows: Air-conditioning/ventilation resulting in a negative or neutral pressure, relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the area of exposed product and the external environment. Special attention may be needed	H	ISPE

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		It is not essential that a space be negative for containment. Controlling leakage paths may be sufficient. Please remember that this is a GMP space, so ingress of contaminants presents a hazard to the product.	in aseptic processing to maintain product quality.		
9.3.3			Reword to the following: Appropriate air pressure or airflow direction alarm systems should be provided to warn of loss of design containment. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to containment failure.	H	ISPE
9.3.4			Reword to the following: The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop during when the fans are not running.	H	ISPE
9.3.5			Reword with the following: The air pressure cascade within the facility, even if negative to environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.	H	ISPE
9.3.6			Reword to the following Visual indication of the status of room pressures or	H	ISPE

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			airflow direction should be provided in each room.		
9.3.7		This is common practice, but is not the only way to achieve this goal. Cross-contamination and, in fact, employee protection are related to the arrestance (gravimetric efficiency) of the filtration, not the penetration (particulate efficiency at MPPS). HEPAs are nearly absolute in arrestance, but with a poly-dispersed challenge much lower rated filters in cascade are just as effective a HEPA. Furthermore, when excellent primary containment is provided by the process equipment, leaving air particulate levels orders of magnitude below the OEL one could argue that only protection against spills is needed, this may not be a HEPA.		H	ISPE
9.3.7		This is inconsistent with section 10.2. Don't dictate this de facto across the board. Let the risk assessment process drive the appropriate response for each situation. This is stated correctly in 10.2.	Delete this section in its entirety	H	ISPE
9.3.7		The second sentence really belongs in the definition section	Move to definition (per earlier comment)	M	ISPE
9.3.8		Having permitted single pass in the previous paragraph, this paragraph completely flies in the face of energy conservation a subject that is important world-wide. An impact study between the environmental impact of energy generation versus a	Reword as follows: As determined by a risk assessment, single-pass air-handling systems with no recirculation should be provided.	H	ISPE

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		controlled and monitored re-circulatory system would be interesting. Single pass may be necessary in the case of solvents.			
9.3.9		Again, this is a common practice, but certainly not the only one; arguably it's not even the best. Recommend BI/BO housings when filters are serviced outside the containment by lesser trained personnel. Changing from within the contained space, by appropriately protected personnel is certainly also viable. Especially when contained process equipment is used.	Reword with the following: Exhaust air or return air should be filtered through a filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the system.	H	ISPE
9.3.11			Reword as follows: Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, air lock or pass-through hatch bordering on an external or non-GMP area should be at a positive or negative pressure to prevent the ingress of contaminants into the facility.	H	ISPE
9.3.12		Air showers can very easily be ineffective; if not properly designed, vented, and utilized, they wind up just blowing the dust around and can actually cause more aerosolization / airborne compound than before they are used.	Consider deleting the reference, or add strong language about the need to assure proper design and ongoing procedures regarding their effective use. Rewording should include: Operators leaving the containment area should pass through a decontamination system, e.g. mist dust control system, to assist with removing or controlling	M	ISPE

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			dust particles on operator garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.		
9.5			Reword as follows: Where practical, HEPA filters in the supply air system should be terminally mounted to provide back-flow cross-contamination protection in the event of a supply airflow failure.	H	ISPE
9.7		This is redundant with 8.9? This is a requirement for all GMP facilities.	Delete in its entirety	M	ISPE
9.8		This is redundant with earlier sections. Also, direction of airflow should be the primary requirement, not pressure. A velocity of 200fpm will contain most pharmaceutical dust at door cracks, however a pressure difference of .05"WC is equivalent to 890fpm, much higher than is typically required. Even if we wished to be at a capture velocity around 500fpm we would still be at the limits of reliable pressure measurement.	Delete in its entirety	H	ISPE
10.3		Energy wheels.. might physically carry over residual compound on the wheel from the exhaust side to the supply side, contaminating the fresh air inlet duct.	Delete reference, or at least note that a risk assessment might be warranted to assure that the risk of this is acceptable for the facility, based on the	M	ISPE

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			detail design analysis of the wheel configuration and hardware.		
10.3		Strongly recommend against energy recovery wheels for critical airstream separation. If the air was contaminated enough that the only safe course was to throw it away, why would I run an adsorptive media through it and into my incoming airstream, this is tantamount to recirculation. Static refrigeration devices and run-around loops are better suited.	Reword as follows: Where a full fresh-air or single-pass system is used, an energy recovery means could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the energy recovery device. The relative pressures between supply and exhaust air systems should be such that the exhaust-air system operates at a lower pressure than the supply system. *(Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)*	H	ISPE
10.5		Prefer to keep return filters close to the room, it is certainly viable for them to be remotely mounted, even integral with the AHU. Additionally, as indicated earlier, the decision to use BI/BO should be optional and part of the risk assessment.	Reword as follows: If return air is to be recirculated it should pass through a filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the design of the facility.	H	ISPE
10.6		This is a repeat of section 9.3.4	Delete in its entirety	M	ISPE
10.6,		For aseptic processing, aseptic processing rooms	Rework to address aseptic processing	H	ISPE

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10.7		should not be pressurized at negative.			
10.7		is an interesting idea, since many AHU's are equipped with discharge dampers as required for smoke control; however this sequence is neither common nor, in our opinion, required. Once de-energized, the inertia of the fan wheels provides only a small fraction of the design flow.	Delete section in its entirety	M	ISPE
11.1			Add the following statement: "Filters utilized in controlled areas are to be released by the quality unit prior to use."	M	ISPE
11.3		Focus on risk not hazard This kind of precaution is only common in BSL 4 and some BSL 3 facilities. Redundant HEPA frames are sometimes provided to allow maintained protection during change out of large installations, but this is extraordinary. Simply put, the most significant failure of HEPA filters is from incorrect installation. This is the reason for filter testing as-installed. The failure mode of a tested HEPA, baring abuse by personnel, is a pinhole leak, which has a negligible effect on arrestance of the filter. Again, arrestance is the critical factor in filters employed for cross-contamination control or operator protection.	Delete in its entirety	H	ISPE

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11.3		Let the individual risk assessments drive this kind of decision. Many times (for instance) immediate dilution upon exiting the building will drop concentrations below any standard or threshold that there may be for any given compound. Unless there is an overall emissions compliance standard that a facility can point to which it needs to follow, be careful to not mandate the design details "from afar" when you don't know the specific process or risk that a process will embody. (The document does state "should be considered", however such "soft statements" still have a habit of becoming standards over time due to frequent usage without proper rationalizing on a case-by-case basis.)	Delete in its entirety	H	ISPE
11.5		This is not technically correct. The development of a filter cake improves the filtration efficiency of any filter. Physical failure is sometimes seen, especially with thin, low efficiency filters, but is almost unheard-of in HEPAs. Generally speaking, filter change out pressure is an economic, not a GMP decision.	Delete in its entirety	H	ISPE
11.6		Local monitoring is available. Computer-based monitoring for HEPA condition is not always needed.	This sentence should be deleted.	H	ISPE
11.8		For containment, leak testing (scanning) is not required, an overall filter efficiency is all that is required in this case, as it is the arrestance of the filter	Reword as follows: Installed filter efficiency tests should be performed in accordance with ISO 14644-3. Injection ports	H	ISPE

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		that matters. No single particle is of concern.	(upstream) and access ports (downstream) should, therefore, be provided for this purpose.		
11.9		Use of an efficiency test rather than a scan allows for much simpler testing and a fixed sampling probe (array) may be used without exposing the downstream side of the HEPA	Reword as follows: The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as detailed in Figure 2, so that air can be circulated through the HEPA filters, while testing. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.	H	ISPE
11.10		The circulation of a gaseous sanitizing agent is normally employed to address organisms of concern, not denature compounds in a HEPA filter. Some mention of compatibility of the decontamination agent and the materials of construction might be appropriate.		M	ISPE
11.11			Reword as follows: All exhaust systems from the facility, including dust extract systems, vacuum system exhaust, fluid bed drier exhaust, coating pan exhaust, etc., should be passed through filter housings before being exhausted to the atmosphere.	M	ISPE
11.12		Locating points far from one another is not a guarantee against re-entrainment. If adequate separation is not achievable, location directly over one another, with adequate height is another alternative.	Reword as follows: All exhaust points outside the building should be located to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions	H	ISPE

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		This principle is discussed in the literature.	should be taken into account when positioning exhaust and supply points.		
11.13		Last sentence - watch the wording. Reading the sentence literally, it is saying that the "maintenance staff" will be protecting "the operators". (Was that what was intended to be said?)	1. Rephrase if that was not the intent. 2. Also, add "… decontamination and degowning airlock"	M	ISPE
11.13		If so dusty that bag house is needed, this would need review for Process Safety, powder explosion protection	Consider integrating Process Safety and Explosion Proofing if getting into Dust Collectors an d Bag Houses	M	ISPE
11.14		Indicating that this is a contamination source and staff must wear PPE, is not appropriate when safe change device technology exists for these activities.	Consider replacing reference to PPE with SAFE CHANGE wording.	M	ISPE
12.1		We do not recommend air shower for dust decontamination	A means of preventing contaminants from leaving the facility on personnel garments should be provided. This could be in the form of a mist shower, water shower or appropriate device. Delete section 12.2 in its entirety	H	
12.1		Air showers can very easily be ineffective; if not properly designed, vented, and utilized, they wind up just blowing the dust around and can actually cause more aerosolization / airborne compound than before they are used.	Consider deleting the reference, or add strong language about the need to assure proper design and ongoing procedures regarding their effective use.	M	ISPE
12.4			Reword as follows: Wet mist/fog decontamination systems for operators	H	ISPE

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			can be employed causing contaminants to adhere to the garments so that they are not easily liberated.		
12.5			Reword as follows: A hygienic water shower can be used with personnel changing into clean garments after the shower.	H	ISPE
13.2		Section 7.3 excludes this area from the scope of the document.	Delete in its entirety	M	ISPE