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

Guideline to the Inspection of Hormone Product Manufacturing Facilities
QAS/08.256, February 2008

ISPE welcomes the opportunity to comment on the WHO document QAS/08.256: Guideline to the Inspection of Hormone Product Manufacturing Facilities. Our comments are attached and should be read in conjunction with the attached line-numbered .pdf document.

In addition to the comments on specific sections of the document, ISPE has some overarching conceptual comments that apply to the entire document and are listed below.

1. Lack of Clarity regarding the document scope and focus
    a. Section1.2 states that the document only deals with criteria which are not covered in other WHO GMP regulations. However, there are several statements included that are basic GMP issues addressed in other GMP documents (e.g., section 3.6.) The document clearly excludes GMP issues in several places. See detailed comments for specific areas of overlap.
    b. 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.
    c. The document is currently titled as applying to hormone manufacturing facilities. However, the concepts should be applicable for all high risk manufacturing facilities as indicated by a risk assessment.
    d. To help with clarity we suggest a title change to “Guideline to Operator Protection in High Risk product Manufacturing Facilities.” The document states the provisions within the text are also applicable to other “hazardous compounds” and this title expands the scope to include all High Risk situations as well as the operator protection aspects of the document.

2. Hazard vs. Risk
    a. It is important to stress the difference between hazard and risk. The document fails to distinguish between these concepts.
    b. The document should focus on the areas of greatest risk and the risk should be 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.
    c. By nature of their activity, all pharmaceutical compounds are hazardous at some level. However, when manufacturing conditions, equipment, procedures, etc., are evaluated the risk could be quite low.
    d. Based on this pretext, Section 4 Risk Assessment should precede Section 3 General to allow the reader to understand risk assessments are suggested and that solutions developed from the risk assessment are allowed.
    e. If a company chooses not to do a risk assessment or a solution cannot be found, and then the guidelines as listed in this document should be followed.
    f. By focusing on risk and risk assessment and risk mitigation, sufficient flexibility will be included to allow for the development and deployment of new and innovative solutions.
3. Parenteral Facilities not considered
    a. The document does not take into consideration the manufacturing of parenteral products. Some of the requirements listed are in conflict with the requirements for parenteral facilities.
4. Guidance is too prescriptive
    a. The proposed guidance is too prescriptive and does not allow for appropriate flexibility to meet the goal of reducing risk. This guidance should reflect the need for appropriate control and state the ultimate goal of such control measures (i.e., Operator protection, external environment protection and/or product protection) not specify the means to achieve this control and reducing risk.
    b. Similar to our comment above, the document should focus on risk and mitigating risk. It should not preclude the use of new and innovative solutions for achieving this goal.

Again, ISPE appreciates the opportunity to comment.

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

Yours sincerely,

Robert P. Best
President/CEO

Attachments: ISPE Comments QAS/08.256
Line-numbered QAS/08.256

ISPE Regulatory Comment Form
Proposed Regulation/Guidance Document: ___

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No.	LINE NUMBER	CURRENT WORDING	PROPOSED CHANGE	RATIONALE
1.	General		All risk assessment statements should be first in the section so the reader understands that a risk assessment may lead them to a different solution and that is acceptable.	The logical order is to first let the reader know that risk assessments are suggested and solutions developed from the risk assessment are allowed. If no risk assessment or a solution cannot be found, then follow the suggestions within the document.
2.	General	Definitions add	Routes of Exposure for operator safety – Inhalation, Ingestion, Dermal, mucous membranes and accidental exposure through skin penetration.	Inhalation is not the only route of exposure for operators
3.	General	The document is focused on hormones with additional wording that indicates that all hormones are not the same and has a passing mention that other hazardous compounds should follow this document.	Consider all compounds based on the level of risk they pose	Decisions should be made on the level of risk.
4.	4	Guideline to the inspection of hormone product manufacturing facilities	Guideline to Operator Protection in High Risk Product Manufacturing Facilities	This document excludes product cross-contamination and environmental issues in lines 213 -214. The proposed title would more accurately portray the purpose of the document. This guideline should be applied in the case engineering controls for risk reduction is required as determined by a risk assessment for operators and environment. This guideline should not be limited only for 'hormone'

5.	92-93	This guideline's primary focus is on the air-conditioning and ventilation systems of the facility.	This guideline's primary focus is on operator protection when working in these types of facilities.	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.
6.	99		Add definition of zones	Define zones for the context of this document.
7.	99-103	Where the handling of hormone products could lead to high risk.	Where the exposure level of pharmaceutical products could be evaluated to exceed an acceptable risk by risk assessment based on ICH Q9.	If "hazard situation" not be defined, this guide would be applied for all of the hormone products. But there are some hormone products would not lead to a hazard situation, that is, application of this guide would be confused.
8.	100	…hormone products could lead to a hazardous situation.	…hormone production would lead to high risk situations.	All hormones are a hazard, what the guide needs to focus on is high risk situations. If processing hormones in closed systems the risk is much lower of operator exposure than if processing in open systems.
9.	104-105	Although this document relates to hormone products, the principles contained herein could be applied to other hazardous products where containment is required.	Delete sentence in its entirety	Confusing risk and hazard. If general comments are accepted, then there is no need for this statement as the guide will cover all high risk situations. See comment in cover letter regarding scope

10.	108-197	Glossary	Add these definitions In the risk assessment for exposure, the following definition would be appropriate, **Exposure** = Contact with a compound. **Hazard** = the potential for a chemical to produce harm because of the potential for exposure to a compound that can cause toxicity. **Risk** = the probability that a substance will produce harm under specified conditions of exposure.	Confusing hazard and risk
11.	121		Add definition of Action Limit	
12.	135	Commissioning	Delete definition	Term not used within the body of the document
13.	157	Drug Substance	Delete definition	Term not used within the body of the document
14.	161	ECS	Delete definition	Term not used within the body of the document
15.	173	Laminar airflow (LAF)	Delete definition	Term not used within the body of the document
16.	178		Add definition of OEL	
17.	178		Add definition of PAS	

18.	190	Unidirectional airflow (UDAF)	Delete definition	Term not used within the body of the document
19.	211-212	Other hormone delivery methods not covered above, including delivery methods, will be developed in future.	Other hormone delivery methods not covered above.	Since future delivery methods are unknown, the level of control cannot be defined at this time.
20.	213-214	Facility environmental parameters such as temperature, humidity, cross-contamination control, contamination control, etc are covered in other GMP guidelines.	Delete in its entirety.	Redundant to section 5 and 9.2
21.	215-218	Hormone facilities should be separate, dedicated facilities and should not form part of any other non-hormone facility. They may be in the same building as another facility but should be separated by a physical barrier and have separate entrances, staff facilities, air handling systems, etc	Delete in its entirety in this section.	This statement contradicts the statement made in section 4.1 (line numbers 234-239). 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. 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 3.3, this statement may cause conflict with other guidance documents for cross contamination.
22.	219	In general hormone facilities should be classified….	Hormone facilities should be considered containment facilities. Also suggest moving this statement into section 8 Facility Layout	The term “general” is too vague and needs qualification. The word “classified” implies validated
23.	220-230	The effective operation of a hormone facility……	Delete in its entirety	Redundant since it is covered in other WHO and GMP documents.

24.	235	…determine the potential hazards to operators and to the environment.	….determine the potential risks to operators, the product and to the environment.	Confusing hazard and risk. The risk assessment should make sure that operator safety doesn't impact patient safety and vice versa.
25.	235-239	Not all hormone products are equally potent and risk assessment should be carried out to….	This section should come before all design and operational requirements in this document. This section should be Section 3	This section contradicts Section 3.4. To allow the manufacturer's the opportunity to do a proper risk assessment and determine how to keep hormone facilities in control.
26.	240-242	Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the facility design and operation should be as detailed in this document	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.	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
27.	243-244	Permissible operator exposure levels (OEL) for the relative product should be taken into account when conducting the risk assessment	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.	OEL is only one risk to be assessed and only addresses operator protection, not patient protection, and environmental protection.
28.	245-247	Results of the personal ambient sample (PAS) tests should be provided. These tests should be taken in the proximity of the operator's head and indicate the 8-hour time weighted average level of contamination in the operator's breathing zone.	Delete in its entirety	This should not be required unless a risk assessment suggests there is a concern. The way it is presented makes it mandatory for all situations. Other concerns are: 1. No method given or suggested to perform PAS tests. 2. 8-hour time-weighted average level can be misleading or misinterpreted to show false sense of control 3. This only indicates one potential route of risk (inhalation) and does not address product contamination

29.	248	A recognized risk assessment method should be used and documented	Move to 4.2	The logical flow of information presented is to state risk assessments are needed (4.1) and then state a recognized method should be used currently at 4.5. Details as stated in 4.2, 4.3 and 4.4 should follow the high level statements.
30.	257	Personal Protection Equipment and Breathing Air Systems	The operator is to be afforded appropriate means to exposure protection against inhalation, dermal, ingestion and needle stick exposure routes	Addresses the need rather than the remedy.
31.	263	Wearing single use, disposable latex gloves	Wearing single use, disposable gloves	Latex is a known allergen to many
32.	266	Wearing respirator eye and face protection with associated breathing air system	Wearing eye and face protection and if the risk assessments indicates a need for a breathing air system	This statement leads one to believe breathing air is always necessary. Not all processing will have a need for breathing air, need should be determined by risk assessment and contradicts line 267.
33.	269-270	The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit	PPE should be appropriate to the Routes Exposure and the Hazard	This should be determined by a risk assessment. Also Integral implies that it is attached to the suit. They are not they are a separate element.
34.	271-277	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 one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure operator comfort with respect to temperature and humidity. The air source could be air pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted to the system.	Delete in its entirety	This is too prescriptive; there are other ways that will achieve the same goal. Flexibility should be allowed.

35.	283	For zones with lower contamination levels, a half mask HEPA cartridge respirator of N95-type paper filter mask may be acceptable	Delete statement in its entirety	1. No definition of lower contamination levels 2. This statement makes all “low” levels of risk require this type of respirator regardless of the risk assessment. Many systems can be designed to not require respirators. 3. Contamination has been excluded from this document per statements in line 213
36.	285-286	The selection of the respirator type is based on the relationship between the accepted OEL, the 8 – hour PAS and the respirator-certified protection factor (PF)	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).	The proposed text takes into 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.
37.	313	Due to the hazardous nature of the products being handled in the facility, they should not be allowed to escape into the atmosphere or to be discharged down drains.	Due to the high risk nature of the products being handled in the facility, they should not be allowed to be discharged down drains without suitable treatment to render the molecule inactive or to escape into the atmosphere without suitable treatment	Added consideration for allowed for inactivation to happen prior to discharge to drain
38.	315-316	The external atmosphere and public external to the facility should be protected from possible harm from hormones	Delete	This is covered in other GMP documents and guidelines
39.	317-320	If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.	If liquid effluent or air exhaust poses a safety or contamination risk, the effluent or air should be treated before being discharge to air or municipal drain.	This is not unique to Section 7.3 and applies equally to 7.1 and 7.2 The note in this section excludes this item from the scope of the document and if that is truly the case, this statement should just state “Liquid effluent and air exhaust do not affect product quality and therefore fall out of the scope of this document”.
40.	326-327	The premises should be designed and constructed to prevent ingress or egress of contaminants	Delete in its entirety	This is covered in other GMP documents and guidelines

41.	328-331	The link between the premises' interior and exterior should be through airlocks (PAL and MAL) change rooms, pass boxes, pass through hatches, etc. These entry and exit doors, for materials and personnel, should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.	The link between the premises' interior and exterior should be through airlocks (PAL and MAL) change rooms, pass boxes, pass through hatches, etc. These entry and exit doors, for materials and personnel, should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time and protocols for the effective decontamination of material, equipment and personnel.	The section is strengthened to include decontamination procedures to enhance protection
42.	332-333	The change rooms should have an arrangement with step-over bench. The ablutions on the exit side should incorporate showers for the operators.	The Changing rooms should have a transition zone such as a step over bench to indicate the clean and dirty side. Appropriate gowning should utilized to ensure mechanical transfer does not occur	Added wording so that mechanical transfer of any fugitive material between clean and dirty side is minimized
43.	338-340	The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly shown.	Delete in its entirety	This is covered in other GMP documents and guidelines
44.	341	The flow of people and products should be clearly marked on the layouts and plans.	Delete in its entirety	This is covered in other GMP documents and guidelines
45.	342	The activities carried out in the vicinity of the site should be indicated	Delete in its entirety	This is covered in other GMP documents and guidelines
46.	343-344	Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.	Delete in its entirety	This is covered in other GMP documents and guidelines
47.	345-346	The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service penetrations	Delete in its entirety	This is covered in other GMP documents and guidelines

48.	347	The facility should be maintained at a negative air pressure to the environment.	The facility should be maintained at appropriate pressures with respect to the environment protective of both the product and the environment.	This takes into account contamination of the product from the environment and contamination of the environment by the product. We need to consider parenteral manufacturing.
49.	351-352	The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment	Delete in its entirety	This is covered in other GMP documents and guidelines
50.	357-358	Hormone facilities and premises should have the following basic air-handling characteristics.	Hormone facilities and premises should have the following basic air-handling characteristics. Safe change HEPA filtration and routine performance monitoring and verification.	Should be standard practice to monitor HEPA filters.
51.	359	The absence of direct venting of air to the outside	Delete in its entirety	Sect 9.3.7 addresses this issue with more detail
52.	360-362	Air-conditioning/ ventilation resulting in a negative pressure relative to the outside. Air pressure differentials should be such that there is no flow of air between the work area and the external environment.	Delete in its enitety	Redundant to line 347.
53.	367	The stating	The starting	Correction of typographical error.
54.	378-379	Where possible, single-pass air-handling system with no recirculation should be provided.	"The decision to use return air or recirculated air should be determined by a risk assessment study"	Not all situations require single-pass air-handling. Should be based on a risk assessment.
55.	389 - 392	Operators leaving the containment area should pass through air showers to assist with removing dust particles from their garments. Operators should follow this route before degowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged.	If risk assessment shows a need, operators leaving the containment area should pass through decontamination area to assist with removing dust particles from their garments. Operators should follow this route before degowning to access the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged.	Appropriate risk assessment should be done Air showers can cause more operator exposure. There are many other means to meet this requirement. Added protection for the laundry workers

56.	405-406	In some cases, consideration can be given to the use of biosafety cabinets or glove boxes as a means for containment and operator protection.	In some cases, consideration can be given to the use of biosafety cabinets, glove boxes as well as closed processing and transfer systems as a means for containment and operator protection.	Adds additional options for engineering controls
57.	407-409	There should be a system description including schematic drawings detailing the filters and their specifications, number of air changes per hour, pressure gradients, cleanroom classes and related specification. These should be available for inspection.	Delete in its entirety	This is covered in other GMP documents and guidelines Redundant to section 8.9
58.	410-411	There should be an indication of pressure gradients that are monitored by pressure indicators.	The pressure gradients should be monitored and controlled.	Improved readability and added specific requirement of control.
59.	412	Consideration should be given to providing emergency power systems, e.g. diesel	Consideration should be given to providing emergency power systems	The example is too specific. A more generic reference is preferred. If an example is needed, add the example “e.g. backup generators”
60.	417	Air-Handling Units	Delete	This section should be a continuation or subset of the HVAC section
61.	421	And the filtration should be consistent with the zone concepts and product protection required.	And the filtration should be consistent with the zone concepts.	Lines 213-241 clearly exclude product protection from this document.
62.	422-423	The decision to use return air or recirculated air should be determined by a risk assessment study.	Move to section 378-379	This statement contradicts the statement on lines 378-379. This statement is preferred to the statement on lines 378-379

63.	424-429	Where a full fresh-air or single-pass system is used, an energy recovery wheel 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 wheel. 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 and water coil heat exchangers, may be used).	If energy recovery systems are used, protection should be provided to prevent leakage between the supply and exhaust air streams.	Do not give specific methods, this covers all types of energy recovery systems not just energy wheels.
64.	430-431	A risk analysis for potential cross-contamination through an energy wheel should be carried out.	Delete in its entirety	Lines 213-214 clearly exclude product cross-contamination from this document
65.	432-438		Delete lines 378-379	Contradicts lines 378-379, but prefer the wording here.
66.	439-440	When recirculated air is used, fresh air should be introduced into the system, at a rate of 15% of the supply air or three air changes per hour, whichever is greatest.	When recirculated air is used, fresh air should be introduced into the system, in appropriate amount to maintain the conditions for protection of the worker, the product and the environment	Local building codes in many areas address the minimum requirement for fresh air and the system design in order to maintain the pressure differentials, will determine the need for fresh air. What is the basis for 3 air changes?
67.	441-442	All ventilation, AHU and exhaust fans should be started and stopped in the correct sequence to ensure that a negative pressure is maintained during power up and power down	Delete in its entirety	Redundant to lines 367-368
68.	441-442	All ventilation, . . . that a negative pressure is maintained . . .	All ventilation, . . . that a specified pressure is maintained . . .	Need to consider parenteral manufacturing.
69.	456-458	For exhaust systems where the discharge contaminant is considered particularly hazardous, …	For exhaust systems where the discharge is considered high risk.	Confusing hazard and risk See cover letter

70.	462	Contamination hazard	Risk of contamination	Confusing hazard and risk See cover letter
71.	470-482	Installed filter leakage test……	Delete in its entirety	Too prescriptive there are other ways to achieve the same goal.
72.	486-489	All exhaust points outside the building should be located as far as possible from air entry…..	All exhaust points outside the building should take into account local airflow characteristics and building configuration and should be located…..	The distance is not the only factor in ensuring cross flow of supply and exhaust air.
73.	501	Air Showers	Decontamination Devices Delete in its entirety this section….add all rationale from below. (Air shower, Mist/Fog)	Adding additional options for decontamination protection.
74.	503-504	Air at high velocity should be supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles.	Delete in its entirety use of air showers is not appropriate in this application.	High velocity air causes turbulence and can re-aerosolize the dust particles where the operator can be exposed to the particles.
75.	515-516	Flushing devices similar to air showers for personnel could be used at material exits to assist with removing contaminants	Appropriate procedures to clean equipment and materials should be in place. The procedures should include methods to clean wheels and any other portion of the equipment/ material that may transfer contaminants by their movement.	Strengthened section to include the minimization of mechanical transfer of contaminants
76.	519-	Air showers should be subjected to qualification and validation	Delete in its entirety	Product cross-contamination is excluded from this document per line 213-214. Qualification and validation is not required for items that do not affect the product. If proper risk assessments are conducted the amount of cross-contamination or contamination that would come from properly decontaminated gowning /personnel will not affect patient safety.
77.	523-524	Liquid and solid waste effluent should be handled in a manner so as not to present a product, personnel or environmental contamination risk.	Delete in its entirety	This is covered in other GMP documents and guidelines