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World Health Organization
1211 Geneva 27
Switzerland

Ref: WHO Good Practices for Pharmaceutical Microbiology Laboratories,

July 2010, draft

Dear Dr van Zyl:

PDA is grateful to have the opportunity to provide comments on the draft "WHO Good Practices for Pharmaceutical Microbiology Laboratories, July 2010". Our comments were prepared by a group of member experts in this field, and are attached in the requested WHO format. We would like to highlight a few issues that we believe to be of particular concern, as follows:

- 1. The document refers to the EU environmental classifications (Grade A/ B/ C/ D) and in some cases the ISO classification is also provided. PDA recommends that for an international guidance document such as this it is appropriate to use only the ISO denominations.
- 2. Regarding the proposed classifications tables on Pages 9 and 27 respectively, PDA believes that the table in the appendix (p27) should be adopted and remain in the appendices. The table on Page 9 represents a burdensome increase in requirements for micro labs, requiring substantial modifications to existing laboratories, and should be deleted. Specific comments are provided in the comments table.
- 3. Regarding the requirement for growth promotion testing by the user on every batch of media, PDA believes this may be unnecessarily burdensome. Likewise, the addition of antioxidants and free radical scavengers to media which are irradiated is not always necessary. We have proposed alternative wording.

PDA appreciates the opportunity to comment on this important document. If I can be of further assistance, please feel free to contact me 1-301-656-5900 ext. 123 or Johnson@pda.org.

With best regards,

Richard M. Johnson President, PDA

cc: M. Gaspard, WHO (gaspardm@who.int); Robert L. Dana & James C. Lyda, PDA

Comments on WHO Working Document QAS/09.297/Rev.2, Title of the document: WHO GOOD PRACTICES FOR PHARMACEUTICAL MICROBIOLOGY LABORATORIES, July 2010



Comments submitted by : PARENTERAL DRUG ASSOCIATION , Richard M. Johnson, President

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Email : johnson@pda.org Date : 1 October 2010

Template for comments

General comment(s) if any:	Originator of the
	comments
Under Proposed change / suggested text, we have shown deleted text with the strikethrough markings, and when appropriate added text is marked with underlining.	

# section	# Paragra ph If more than one	Comment / Rationale	Proposed change / suggested text	Classification L= low M= medium H= high	Originator of the comments (for WHO use)
Intro		Typographical error	Change yest to "yeast"	L	
General		The document uses classifications that include in some cases both the EU Grade A/B/C/D and ISO and in other instances (referenced specifically in comments below) just the EU Grades. Industry generally is now using ISO classification.	We suggest removing all references to EU Classifications (Grades) and using only ISO denominations throughout the document.	Н	
Glossary		FALSE POSITIVE AND FALSE NEGATIVE.	We recommend these definitions be deleted from the	H-	

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		The definition is unclear and potentially misleading. It appears to apply only where two methods are compared (e.g. a classic method vs a rapid method) but it is very difficult to understand the meaning as written. On the other hand there is a clear definition of false positive and false negative e.g. in USP / Ph.Eur. under sterility testing. In addition, the definitions as provided do not appear to support the use of the terms in the text e.g. refer to section 2.1.6	glossary as these are well known termsor- Alternatively, bring the definitions in line with those in USP and <i>Ph.Eur.</i> with reference to sterility testing.		
1.2		Job descriptions should be maintained but it is not essential that they be maintained in or by the microbiology laboratory. This is more usually a Human Resources function	Revise text to read: "Current job descriptions should be available for all personnel"	L	
2.1.1		For clarity emphasize the importance of separarting the microbiology laboratory from the production areas. Suggest deleting support equipment unless this is restricted to production equipment – it is common to share e.g. between micro and biochemistry laboratories.	Edit to delete strikeout section as follows: "Microbiology laboratories and certain support equipment (e.g. autoclaves, glassware) should be dedicated and separated from other areas especially from production areas."	L	
2.1.2		For clarity add the reason for separate storage, i.e. separation of clean and dirty operations	"Due to the nature of some materials (e.g. sterile media vs reference organisms or incubated cultures) separate storage locations may be necessary. For example, biological indicators and reference organisms should be separated from culture media."	М	
2.1.4		The current wording below is overly prescriptive – see suggested revision "Separate air-handling units and other	Revise current wording to read: "Separate air handling units and other provisions, such as	M	

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		provisions, including temperature and humidity where required, are needed for microbiological laboratories."	temperature and humidity <u>controls if necessary</u> , <u>should</u> <u>be installed in</u> microbiology laboratories."		
2.1.6		Typographical error	Change arras to "areas"	L	
2.1.7	Table	This table is overly prescriptive and will result in most of the industry having to redesign their existing microbiological laboratories. For example, it is unnecessary to require a classified area for loading an autoclave in the microbiology laboratory. On the other hand, the table in the appendices (p 27) appears appropriate for the intended use.	"Consideration should be given to designing appropriately classified areas for the operations to be performed within the microbiology laboratory. Sterility testing should be performed under the same class as used for sterile / aseptic manufacturing operations."	Н	
2.1.8	1 st sente nce	The sentence should be clarified to indicate that it refers to moving ítems (e.g. glassware) between areas of different cleanliness classes.	We recommend to delete this entire sentence -or- clarify as follows: "In general laboratory equipment should not routinely be moved between areas of different cleanliness class, to avoid accidental cross-contamination."	М	
New	New	Add a new sentence to require inclusion of the	Add the following sentence:	М	
2.1.9	line	microbiology laboratory in the pest control program.	"The Microbiology Laboratory should be included in the company's pest control program."		
2.4.2		We suggest deleting terms such as DQ, IQ, OQ, PQ and instead using the general term qualification, or validation which is more inclusive.	Revised text to read: "The premises, services and equipment should be subject to the qualification/ validation process."	M	

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2.4.3		This paragraph refers to Grade A and Grade B air quality. Consistent with our comment above (General), we recommend all EU classification terminology be deleted, and only ISO classifications be used in this document.	Revised text – replace Grade A and Grade B with relevant ISO classes.	Н	
2.4.4		Clean room classification and air handling equipment are usually requalified twice a year for grade A areas and surrounding environment.	Revise text to require twice yearly requalification.	М	
2.4.12		For clarity (because already addressed more specifically in 2.4.4) delete requirement for "periodic requalification.	Delete: "The sterility test environment should be periodically requalified and" And revise to read: Requalification of the sterility test environment should include at a minimum	L	
3.2		Sentence 1. The terms "formal endorsement" and "peer reviewed validation" have no accepted definitions. Sentence 2. We suggest deletion of the this sentence as it is not necessary. If kept, it should reference the definition of validation in the ICH Q2 guidance.	Delete 1st sentence and replace with, <u>"Test methods not based on compendia or other recognized references should be validated before use."</u> -and- Delete 2 nd sentence, or change to include validation definition consistent with ICH Q2.	M	
4.0		The second sentence is redundant as it is addressed in section 4.3.2	Revise text as shown: Delete second sentence of introduction to this section.	М	
5.2.1		The sentence, "Growth promotion should be done on all media on every batch by the user," is highly prescriptive, costly and is not justified by experience. Where the manufacturer of the media is qualified, has provided certification of growth promotion and the user has validated transportation conditions, a periodic verification	Revise to read: "where the supplier of media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of their results."	Н	

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		of the manufacturer's growth promotion test should suffice Refer also to 5.2.10 which appears to support PDA's recommendation.			
5.2.2		This appears to be an open-ended paragraph which could be interpreted to mean that qualification studies are needed on every batch of media / reagents.	Revise to read: "Consideration should be given to qualifying culture media, diluents and other suspension fluids where relevant, with regard to"	М	
5.2.7		The sentence, "Plated media which is to be irradiated requires the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process," is not true in all cases. Revise to read "may require" the addition of	Revised text: "Plated media which is to be irradiated <u>may require</u> the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process."	Н	
5.4 and 5.4.2		Consistency and clarity of text	Change from "media resuscitation" to "organism resuscitation" (two appearances).	L	
6.2.3		It is not usual practice to subculture working stock. Normally the reference strains are prepared as working stock and used for as long as the culture lasts (refrigerated). The reference stock is passaged once a month and a new working stock prepared from that.	Delete section 6.2.3 Add the following at the end of section 6.2.2: "Working stocks should not normally be subcultured. Commercial derivatives of reference strains may only be used as working cultures."	М	
8.5		The sentence, "It may be appropriate that it is performed according to national or international standards, where they exist, or by validated in-house methods" is ambiguous. It is not clear which national or international standards pertaining to subsampling are the subject of this recommendation.	Delete the subject sentenceor- Define what standards are being referenced.	L	

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11.1.2		The following text is problematic, "Typical standards applied by the pharmaceutical industry are as follows: — microbial limit testing/total bioburden — 1000 g for bacteria and 100 g for yeasts and moulds; and — environmental monitoring — 15 organisms for TVC on Tryptone Soy Agar (TSA) and 5 organisms for yeasts and moulds on Schwartz Differential Agar (SDA)." Additional clarification is required: — If intended to refer to sterility testing microbial limits are not relevant and environmental monitoring limits provided are very high. — In the case of microbial limit testing the limits are meaningless without referring to a sample weight or volume. — For environmental monitoring it is not clear to which type of environment they refer. Also, "Schwartz Differential Agar" is usually referred to as Saboraud Dextrose Agar	We suggest deleting section 11.1.2 -or- Rewrite this section with more clarity about what activities are covered, reference to recognized standards, and appropriate placement in the text.	Н	
	1	End of	comments.	l .	l .