Connecting a World of Pharmaceutical Knowledge

13 July 2011

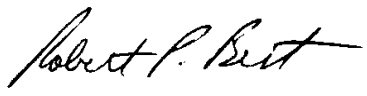
World Health Organization
1211 Geneva 27
Switzerland

SUBMISSION OF COMMENTS ON QAS/08.251/Rev.3: Pharmaceutical Development of Multisource (generic) Finished Pharmaceutical Products – Points to Consider

ISPE is pleased to provide comments using the WHO template for the above document, as requested. While WHO are to be commended on their support for science and risk-based approaches to formulation development, this document lacks consistency with the recent ICH guidelines (Q8 (R2) and Q9). There are major sections which would benefit from a complete rewrite to be consistent with the principles of the ICH guidelines. Specifically, we believe Appendix 2 should be rewritten, as it is not a risk assessment.

ISPE would be pleased to offer the resources of subject matter experts to WHO to assist in any redrafting. Please feel free to contact me if you have any questions.

Yours sincerely,



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Comments on WHO Working Document QAS/08.251/Rev.3
Title of the document: Pharmaceutical Development of Multisource (generic) FPP's – Points to consider

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

Template for comments

General comment(s) if any :	**Originator of the comments**
While WHO are to be commended on their support for science and risk-based approaches to formulation development, this document lacks consistency with the recent ICH guidelines (Q8(R2) and Q9). While detailed comments on some sections are provided below, there are major sections which would benefit from a complete rewrite to be consistent with the principles of the ICH guidelines. For example, the section on quality risk management should be revised to address the risk to the formulation and manufacture of the drug product instead of repeatedly referencing issues related to the API impurity profile. The purity of the API should be demonstrated to be suitable. Particularly Appendix 2 should be rewritten as it is not a risk assessment. ISPE would be pleased to offer the resources of subject matter experts to WHO to assist in redrafting.	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)**
2.1	2	Risks, such as impurities (dimethyl sulphate) have already been assessed as acceptable as the API has	Delete the sentence.	M	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)
		been previously approved. They are not risks for the drug product.			
	6	Again this is dealing with the risk to the purity of the API. This is not truly a risk to the pharmaceutical development plan, even though such impurities should be avoided. There are similar examples in subsequent paragraphs.	Put in a general statement of considerations when selecting the API source rather than highlighting these as risks to the product. Product risks come from polymorphs, stability, hygroscopicity etc.	M	ISPE
2.2.1	3	The scientific rationale for selecting a comparator batch with intermediate dissolution is not obvious. There are concerns as to how one selects the comparators and the number of batches to be tested to find an appropriate range.	Depending on the intended usage, it could be more important to select the slowest (or fastest). The section should be changed to require that the applicant should justify the profile and batche(s) selected.	M	ISPE
2.2.3	All	A QTPP is a prospective summary of characteristics that ideally will be achieved, and as such QTPPs are not available in the public domain. There is an assumption that the optimum formulation is one which has a matching dissolution profile when it has not been established that the dissolution test is indicative of the in-vivo performance. Finally, there is a mis-assumption that the quality of the product is defined by its CQAs. CQAs are not public information, and not all CQAs will form a product's specification. Even where they are common, appropriate limits may not be determinable through stress testing.	This section needs to be rethought and redrafted as it is not scientifically possible to execute as recommended.	H	ISPE
3.2.P.2		The QTPP is not an appropriate quality standard.	Replace QTPP by specification.	H	ISPE
3.2.P.2.3	4	CQAs can only be accurately and reliably predicted if a model is developed which relates all relevant material	Delete line 593	H	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)
		attributes and process parameters to the particular CQA. This is possible only in exceptional circumstances.			
3.2.P. 2.3	Line 596	By definition a CPP should be monitored or controlled so this sentence is not required.	Delete sentence.	M	ISPE
3.2.P. 2.3	Line 609	Critical aspects should be CPPs	".. in particular the CPPs (e.g., rate of addition…..	H	ISPE
3.2.P. 2.3	Line 610	Q8 refers to process robustness, not robustness in relation to a CQA (and there are many CQAs for a given product).	Replace sentence with the sentence on process robustness from Q8(R2).	M	ISPE
4		Lifecycle definition should be aligned with Q8(R2)		M	ISPE
Appe ndix 2		This is not a risk assessment. Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (Q9). What is presented is simply a summary. In line 1128, what is a multi-source company? Line 1132 references Q9 "Risk Management approach to focus on critical attributes". There is no such statement in Q9 and nothing which would relate to the table presented. The table is also misleading in its references to control strategy: good control does not change the risk associated with a CQA.	Replace Appendix 2 with an example of an assessment of risk based on identifying the CQAs of a finished product and how the API may impact upon those CQAs.	H	ISPE
Appe ndix 3 & 4		The examples should be deleted as it should be left to the applicant to decide what experiments should be conducted for their particular product and how the results should be presented.		L	ISPE
		Please add rows as necessary (with "copy and paste" empty rows)			