11 September, 2013

Dr Sabine Kopp
Manager, Medicines Quality Assurance Programme
Quality Assurance and Safety: Medicines
World Health Organization
1211 Geneva 27
Switzerland

Subject: Submission of comments for WHO Working Document QAS/13.521/Rev.1, General Guidance for Inspectors on "Hold-Time" Studies

Dear Dr. Kopp,

ISPE welcomes the opportunity to comment on the *"WHO General Guidance for Inspectors on Hold-Time Studies".* ISPE welcomes this guidance document; the intent to provide manufacturers/ inspectors with a harmonized approach to "Hold- Time" studies is fully supported. Our comments are attached.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Thank you again for the opportunity to provide feedback on this draft guidance. Please feel free to contact me if you have any questions.

Yours sincerely,

President/CEO, ISPE

cc: Ms. Marie Gaspard

Comments on WHO Working Document QAS/13.521/Rev.1
Title of the document:
General Guidance for Inspectors on "Hold-Time" Studies

Comments submitted by : ISPE – International Society for Pharmaceutical Engineering
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Template for comments

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

General comment(s) if any	**Originator of the comments**
ISPE welcomes this guidance document. The intent to provide manufacturers/ inspectors with a harmonized approach to "Hold- Time" studies is fully supported.	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification L= low M= medium H= high	Originator of the comments
Introduction	71	Storage should be extended by the term "staging".	Storage and staging should not have any negative …	L	
Introduction	76	It is essential for temperature sensitive material that the hold time incorporates temperature limits. The hold time must be connected to the temperature.	These time periods must be supported by adequate data to demonstrate that the product subject to the allowed hold time conditions will be stable throughout the approved shelf-life.	M	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification L= low M= medium H= high	Originator of the comments
Scope	107	It will be difficult for third world countries to develop a hold time study prior to marketing. The approach on determining hold times must be risk based e.g.use as a default the longest duration during the first validation batch.	Hold times should normally be determined prior to marketing of the product and following any significant change in processes, equipment, starting and packaging material, using a scientific risk based approach.	H	
Scope	107	Re "hold times should normally be determined prior to marketing of a product…" For sensitive material a hold time may be provided by the transferring site or R&D lab.	Insert "Especially for sensitive products tentative hold times for each stage of the process may be provided by the transferring or R&D site and these can be utilised to confirm and document hold time specific to the production site."	L	
Scope	110	Determination of hold-time studies of existing product should be on a similar risk based approach basis.	For products already marketed retrospective risk based hold time studies should be performed.	M	
Scope	127	The statement, "Generally, as an example for oral tablets, the following stages should be considered" - does not include hold time for the equipment before it could be taken up for cleaning. Guidance in this section is considered appropriate.	Insert "Note: A hold time for equipment before it should be cleaned should be established especially for microbiological aspects."	M	
Scope	127	Oral liquid hold time studies are equally important. Hence an example for oral liquid manufacturing should also be included particularly as oral liquids might have a greater risk of microbial growth if the hold time is exceeded.	Insert an example for Oral Liquids. The following stages should be considered: - Sugar Syrup manufacturing to addition in bulk - Bulk solution (after filtration: ready for packing to filling and sealing - Maximum filling period (covering worst case conditions)	M	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification L= low M= medium H= high	Originator of the comments
Scope	147	If head space becomes an issue, the head space proportion should consider worst case scenario with high head space	Insert “Where head space is important the hold-time samples should represent the maximum possible head space (worse-case scenario) to bulk stored in manufacturing/quarantine”	M	
Scope	171	The risk assessment should also cover the hold time conditions, particularly temperature.	Risk assessment (product specific) may further assist manufacturers to determine which stage, tests, intervals and storage periods and storage conditions should be considered for a hold time study	M	
Table 2	178	Dispensed material storage: It is not always possible to meet the same conditions/pack used by the manufacturer. In addition to microbial tests other factors as appropriate for the materials should be considered. For example, some materials would degrade / absorb moisture/ decolorise if required conditions are not met with.	Microbial test: Other specific tests depending on the material and packaging used may need to be considered.	M	
		Please add rows as necessary (with "copy and paste" empty rows)			