12 April 2013

Medicines Quality Assurance Programme
Quality Assurance and Safety: Medicines
World Health Organization
1211 Geneva 27
Switzerland

Attention: Dr Sabine Kopp
Email: kopps@who.int

cc: Ms Marie Gaspard
Email: gaspardm@who.int

Subject: Submission of comments for WHO Working Document QAS/13.52, General Guidance for Inspectors on "Hold-Time" Studies

Dear Sir/Madam:

ISPE welcomes the opportunity to comment on the *"WHO General Guidance for Inspectors on Hold-Time Studies".* We support the requirement that maximum allowable hold times should be established to ensure that in-process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material. We also support that these time periods must be supported by adequate data to demonstrate that the product will be stable throughout the approved shelf-life.

Thank you again for the opportunity to provide feedback on this draft guidance.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

Our comments are attached.

Yours sincerely,

President/CEO, ISPE

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

Comments submitted by: Nancy Berg, President/CEO, ISPE
Telephone number: +1- 813-960-2105
Address: 600 N. Westshore Blvd. | Suite 900 | Tampa, Florida 33609 | USA
Email: nberg@ispe.org
Date: 12 April 2013
Kindly complete the table without modifying the format of the document - thank you.

World Health Organization

Template for comments

General comment(s) if any :	**Originator of the comments**

# 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)**
Page 8	Para # 2	Justification for additional storage time must be specified as an exception	Interim storage of the dosage form in bulk containers should generally not exceed 6 months, **unless otherwise justified by the hold time study data.**	M	
Scope	Page 3: Para #3 Page 6: table 1 Page 8: last line	Could be read as conflicting information regarding acceptable holding time: is it 25% of shelf life (page 3), the period indicated in Table 1 (page 6) or less than six month (page 8)?	Clarify.	H	
Introduction and	Para # 3	25% of approved shelf-life, even for a product with 24 months shelf life, leads to bulk storage of no more than 6 months, which is very high, even as a general rule.	Normally bulk solid oral dosage forms should not be stored for more than 30 days and bulk sterile products for more than one day (prior to packing into the final	M	

# 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)
backg round		The proposed change refers to EMA Q&A on quality (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0#section10)	containers) unless these are tested, with stability-indicating methods, prior to packaging.		
Scope Page 2	Para # 5	"A written protocol, procedure…." Too much detail on report format for document scope	Remove rest of paragraph after first sentence	M	
Scope Page 6	Para # 1	Last sentence "Statistical calculations should be done..: Intent could be misinterpreted	Remove sentence as previous sentence is sufficient	M	
Scope Page 6	Para # 2	"Batches of products subjected to a hold-time study should also be subjected to long term stability testing." As only a representative sample is subjected to the hold-time study and is not progressed further, it is not posible to subject the tested sample to a long term stability study. Doing a study on the remainder of the batch is irrelevant.	Delete the sentence.	H	
Scope	Table 1	Very good table with reasonable suggested examples	Remain as is	H	
Scope	Table 2	Examples of tests too detailed and not all appropriate for purpose. The tests should be stability indicating and several proposed are not (eg dose uniformity, friability of coated tablets).	Delete the table and replace with text that states the tests should be suitably stability indicating	M	
Scope	Table 2 footnote	"manufacturers have to identify…..or excluded from a hold time study" Unclear the expectation for justification required for exclusion criteria, especially if example tests are not modified	"Manufacturers have to identify and justify the selection of stages and parameters selected ~~or excluded from a hold-time study~~." (remove the portion with strike through)	H	

# 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)
		Please add rows as necessary (with "copy and paste" empty rows)			