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May 12, 2015

Dr. S. Kopp
Medicines Quality Assurance Programme
World Health Organization
1211 Geneva 27, Switzerland
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Reference: QAS/15.611 PROPOSAL FOR REVISION OF GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS

Dear Dr. Kopp,

PDA appreciates the opportunity to offer comments on this proposed guidance and wishes to thank WHO for the opportunity to do so. I realize this is being submitted after the requested date of April 30th but it was important to PDA to reach a strong consensus position prior to making this submission and respectfully requests that WHO incorporate these comments in the revision process.

It is PDA's opinion that Section 7, Repackaging and Relabeling be edited to remove all references to "combining materials of different batches". A distributor should not be combining materials to form a new batch. That is a manufacturing activity requiring appropriate filing, license and inspection. By performing this type of operation a distributor becomes a manufacturer and is subject to the respective WHO guidelines regarding Good Manufacturing Practices.

In addition, PDA believes the intention in this guidance was to address excipients (inactive ingredients) and is recommending changing the title of the document accordingly and adding a scope section for clarification. At present, the scope is unclear. PDA believes that details concerning trade and distribution of APIs used as starting material are already covered in TRS 957, Annex 2, 2010, 130-189 and that the 'GMP for API' document covers the GDP elements as described in this draft too (please see discussions in the ICH Q7 Implementation Working Group and the ICH Q7-IWG Q&A).

The use of the term "starting material" is inappropriate if the intention of the document is to address excipient standards. Starting material is defined in ICH Q7 as *raw material, intermediate or API incorporated as a*

significant structural component in the API itself. PDA uses the IPEC definition of excipient which is: *substances other than the API which are intentionally included in a drug delivery system*.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

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

Sincerely,

Richard M. Johnson

Richard Johnson
President, PDA

Cc: Denyse Baker, PDA; Richard Levy, PDA

Comments on WHO Working Document QAS/15.611
Title of the document: Proposal for Revision of Good Trade and Distribution Practices for Pharmaceutical Starting Materials

Comments submitted by : Parenteral Drug Association (PDA) Inc.
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Date : 14 APR 2015

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

Template for comments

General comment(s) if any : PDA notes that excipient standards have already been developed by IPEC and recommends efforts be made to align with these standards.	**Originator of the comments**
Critical comment: PDA recommends changing the title and adding a section defining the scope of the document. At present, the title and the scope of the document is unclear. PDA believes that details concerning trade and distribution of APIs used as starting material are already covered in TRS 957, Annex 2, 2010, 130-189 and that the 'GMP for API' document covers the GDP elements as described in this draft too (please see discussions in the ICH Q7 Implementation Working Group and the ICH Q7-IWG Q&A). If this draft guidance is intended to be applicable for API's too there would be two guidance documents addressing the same topic which is liable to cause confusion and even conflicting requirements. PDA believes the intention was to address excipients (inactive ingredients) used as in pharmaceutical formulation or compounding and we have recommended (in the line by line comments) changing the title of the document accordingly and adding a scope section for clarification. PDA uses the IPEC definition of excipient which is: *substances other than the API which are intentionally included in a drug delivery system*. The use of the term "starting material" is inappropriate if the intention of the document is to address excipient standards. Starting material is defined in ICH Q7 as *raw material, intermediate or API incorporated as a significant structural component in the API itself.* It is critical that Section 7, Repackaging And Relabeling be edited to remove all references to "combining materials of different batches". By performing this type of operation (i.e. blending) a distributor becomes a manufacturer and is subject to the respective WHO guidelines regarding Good Manufacturing Practices.	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
	0	Revise title since the proposed title may result in requirements which conflict with the GMP for APIs (= TRS 957, Annex 2, 2010, 130-189) As noted above in the general comments, the use of the term "starting material" is inappropriate if the intention of the document is to address excipient standards	Change to read: **Good Trade And Distribution Practices For Excipients** ~~**Used As Pharmaceutical Starting Materials**~~	H	
	93	Add a scope section to clarify what is included under the title. PDA suggests that the document should be limited to excipients since there are already requirements for APIs in ICH Q7 (= TRS 957, Annex 2, 2010, 130-189)	Add a section as follows: **Scope** **This guideline applies to excipients; i.e. substances other than the API which are intentionally included in a drug delivery system. Excipients can be present in large quantities and even constitute the majority of the dosage form. Guidance for Active Pharmaceutical Ingredients (API) used as starting materials is provided in the ICH Q7 document, which is included in the WHO guidance TRS 957, Annex 2, 2010, 130-189)**	H	
1.2	118	Since unacceptable suppliers should be disqualified PDA recommends adding this.	a clear documented procedure for selecting, approving**, disqualifying** and re-approving suppliers	H	
1.8	146	Compliance or adherence to internationally recognized standards is equally valid and valuable as full certification. Also HACCP is a risk assessment tool and not a quality system. PDA recommends removing this from the list of examples.	Inspection and ~~certification~~ **verification** of **appropriate** compliance with a quality system (such as applicable International Standards Organization (ISO) series, recognized national and regional standards ~~and hazard analysis and critical control point (HACCP)~~)	M	
2.3	169	Clarify that the training should apply to those persons involved in GTDP.	All personnel **involved in GTDP activities** should be aware of the principles of GTDP.	L	
4.1	220	Tampering can be indicative of counterfeit activity. PDA believes it is important to emphasize that there should be active efforts to identify this type of activity	Add text as shown: been damaged**, tampered with** or altered during transportation.	H	

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5.8	328	Requiring dedicated equipment is more stringent than what is required for API or Drug Product manufacturing. PDA recommends deleting this sentence.	~~Dedicated equipment should be used where possible when handling and/or processing pharmaceutical starting materials.~~ Where non-dedicated equipment is used cleaning validation should be performed.	H	
7.1	402	Combining material into a homogenous batch is manufacturing and covered by TRS 957 Section 8.4 page 155. A distributor should not be combining materials to form a new batch. That is a manufacturing activity requiring appropriate filing, license and inspection. Repackaging and relabeling are also manufacturing activities but can be conducted by distributors in certain situations with appropriate controls	Operations, such as combining into a homogenous batch are regarded as manufacturing and not covered by this guideline. Other than that, repackaging…….	H	
7.3	420-422	Combining material into a homogenous batch is manufacturing and covered by the respective WHO guideline. A distributor should not be combining materials to form a new batch. That is a manufacturing activity requiring appropriate filing, license and inspection. This needs to be deleted.	~~When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogenous batch the conformity of each batch with its specification should be confirmed before it is added.~~	H	
7.4	424-428	Combining material into a homogenous batch is manufacturing and covered by other WHO guidelines. A distributor should not be combining materials to form a new batch. That is a manufacturing activity requiring appropriate filing, license and inspection. This needs to be deleted.	~~Only materials from the same manufacturing site received by a distributor and conforming to the same specifications can be mixed. If different batches of the same material are mixed to form a homogenous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches.~~	H	
7.14	478	PDA recommends deleting the reference to API and adding "whichever is longer" for clarity.	Samples of ~~APIs and~~ excipients is complete**, …whichever is the longer.**	L	

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8.2	495	Not all investigations result in a requirement for the company to perform a CAPA. There may be cases, where no further action is warranted therefore we propose adding the words “where applicable.”	Corrective and preventive actions should be taken , **where applicable**,	L	
		Please add rows as necessary (with "copy and paste" empty rows)			