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December 17, 2015

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: EudraLex Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
Annex 17: Real Time Release Testing

PDA welcomes this revision that will allow full realization of real time release testing and harmonization throughout Europe. The expansion of the concepts beyond just parametric release provides opportunities for the use of new and future technology to improve ongoing process control, overall product quality and patient safety.

PDA requests this document be more specific on when end product testing for release is appropriate in a process designated for RTRT and proposes the specific language in our comments. PDA also recommends this document include a definition of Critical Process Parameter in the glossary as it is a key fundamental, non-negotiable part of parametric release.

PDA notes that Ethylene Oxide sterilisation follows the same rationale and process as the other sterilisation methods. Because parametric release is referenced in the ISO 11135 standard for EO and is used frequently in the device industry, PDA recommends EO be added throughout the document as a method covered by this Annex. Additional specific and detailed comments are noted in the attachment to this letter.

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 microbiology and sterilisation experts representing our Science Advisory Board and Board of Directors.

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

With very best regards,

Georg Roessling, Ph.D., Senior VP, PDA Europe

Cc: Richard Johnson, President PDA
Rich Levy, Senior VP PDA Science and Regulatory Affairs.

<11 December 2015>

European Commission EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
Annex 17: Real Time Release Testing

Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
	PDA welcomes this revision that will allow full realization of real time release testing and harmonization throughout Europe. The expansion of the concepts beyond just parametric release provides opportunities for the use of new and future technology to improve ongoing process control, overall product quality and patient safety.	
	PDA requests this document be more specific on when end product testing for release is appropriate in a process designated for RTRT and proposes the	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	following language: "It is not acceptable to perform an actual test on a product (active substance or finished product) motivated by an undesired or unacceptable result as determined by the approved RTRT approach. End testing for release purpose including confirmation that all CQAs have been met can be acceptable if RTRT information elements are not available, for example due to analytical equipment failure (see 3.3). This approach is not applicable for sterility testing in association with a parametric release program. "	
	PDA recommends this document include a definition of Critical Process Parameter in the glossary as it is a key fundamental, non-negotiable part of parametric release. ICH Q8 (R2) defines CPP as "A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality."	
	PDA notes that Ethylene Oxide sterilisation follows the same rationale and process as the other sterilisation methods. Also parametric release is referenced in the ISO 11135 standard for EO and is used frequently in the device industry. Therefore PDA recommends EO be added throughout the document as a method covered by this Annex. Specific sections are noted below in the detailed comments.	

2. Specific comments to the text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Section 2.0 Scope, Line 16		PDA recognizes that the RTRT and risk assessment principles are not appropriate in all settings particularly those of highest risk to patients and recommends a statement added to the scope section stating sterile products (APIs and finished Dosage forms) that are produced in open systems and/or conventional cleanroom are outside the scope of this annex.	
60		Comment: To provide additional detail, PDA recommends the following which is consistent with global requirements. Proposed Change:-The risk assessment should include experience with the proposed or similar product (and container closure system) and proposed or similar sterilization process, the overall risks to sterility, and the steps you have taken to assess and control these risks. For new	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		products, prior knowledge from developmental and registration/exhibit batches may suffice.	
127		Comment: EM data is not as relevant for terminally sterilised product as pre sterilisation bioburden. Proposed Change: …(e.g. **pre-sterilisation product** bioburden or ~~environmental monitoring~~)	
128		Comment: For clarification Proposed Change: …accurate **and relevant** information	
130		Comment: The term moist heat is a more accurate and commonly used term. Also parametric release is referenced in the ISO 11135 standard for EO and has been common practice in the device industry. PDA recommends EO be added to this document. Proposed Change: …final container using ~~steam~~ **moist heat**, dry heat, **EO** and ionising	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		radiation…	
131		Comment: Sterilisation by radiation is based on dosimetric release not true PR. PDA acknowledges that this is a technicality, but recommends being technically precise and consistent in the use of terms. Proposed Change: … and ionizing radiation**(dosimetric release)** , according to…	
135-136.		Comment: One should not use the ability to perform a successful sterility test as an exclusive indicator of process control. Other process data including bioburden testing results, success rate of sterilization process delivery and process requalification history are more valuable indictors of process control. In PDA's opinion, the science and technology of sterility testing is less reliable than newer parametric release. Older technology should not preclude moving to an improved test. Proposed Change (if any): Delete this sentence:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~Historical test for sterility results should also be taken into consideration, if available, when evaluating GMP compliance.~~	
Line 139		Comment: The sterility assurance program should include the evaluation of adverse effects on packaging. Proposed Change: …sterilser cycle development and validation, **container/packaging integrity validation**, bioburden…	
Line 145		Comment: For clarification Proposed Change: …failure to achieve **and maintain** sterility…	
Line 147		Comment: Data from similar marketed products should be included if applicable. Proposed Change: then a risk assessment should be conducted during process development **including data from similar products if applicable.**	
Line 155		Comment: For consistency	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed Change: …designed **and validated** for sterilisation…	
Line 170		Comment: PDA recommends spore heat resistance characterization is not needed for overkill sterilization processes. Agree this is needed for product-specific approach. This aligns with other guidance on bioburden based sterilisation. Proposed Change: **For biological indicator / bioburden-based sterilizing processes, the resistance of any spores detected in the product bioburden should be characterized to ensure that it does not exceed the resistance level of the biological indicator used to qualify the sterilisation process.** ~~Any organisms found during bioburden testing should be identified to confirm that they are not spore forming which may be more resistant to sterilising process.~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 190		Comment: EO follows the same rationale and process as the other sterilisation methods. Also parametric release is referenced in the ISO 11135 standard for EO. Proposed Change: …by moist heat, dry heat, **EO** and ionising radiation	
197		Comment: ISO 11137 calls for ongoing monitoring through a dose audit program based on product bioburden and its associated resistance. Dose audit is a form of microbiological performance qualification. Please clarify that use of biological indicators is not appropriate for the microbiological qualification of radiation sterilisation processes. Proposed Change: . ~~With the exception of gamma irradiation, m~~**M**icrobiological performance qualification is recommended for validation of parametric release. **However, the use of biological indicators is not appropriate for the qualification of radiation**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		sterilisation processes.	
202-204		Comment: PDA is concerned that "sterilization monitoring device" and "instruments" may be interpreted to refer only to a load probe in which case only load probe processes would be eligible for parametric release. Proposed Change: Use of ~~an~~ appropriate sterilisation monitoring ~~device~~ is a critical requirement…. The standards used **for process measurement calibration**…	
195, 207- 216		Comment: The terms "critical operational parameter" and "cycle operational parameters" are not clear. Proposed Change: PDA recommends using the more common term critical process parameter.	
Line 215-216 4.20		Comment: PDA recommends using the language from step 3.17 in current Annex 17, to explain what should occur in the case of a failure. Proposed Change: 4.20 **Once parametric**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		release has been granted, decision for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be over ruled by a pass of sterility testing.	
Glossary		PDA Recommends the following other terms that should be added to this glossary because they are discussed in the text. **Critical Process Parameters A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8 (R2)].** **Critical Quality Attributes A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. [ICH Q8 (R2)]**	

Please add more rows if needed.