European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON THE GUIDELINE ON THE REPLACEMENT OF RABBIT PYROGEN TESTING BY AN ALTERNATIVE TEST FOR PLASMA DERIVED MEDICINAL PRODUCTS (EMEA/CHMP/BWP/452081/2007)

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

Name of Organisation or individual	Country
IPFA (International Plasma Fractionation Association)	The Netherlands
PPTA Europe	Belgium
BAXTER AG	Austria

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE			
Line no[1]. + paragraph no.	**Comment and Rationale**		**Outcome**
		Proposed change (if applicable)	
Lines 54 (BAXTER) (PPTA)	Replace “text” by “test”	“It complies with the ~~text~~ test for pyrogens or, preferably and where justified and authorised, a validated *in vitro* test, such as the bacterial endotoxins test.”	The spelling mistake has been corrected
Lines 71 and 177 (IPFA)	in vivo and in vitro must be written in italic because it is Latin words	*in vivo* and *in vitro*	The format of the words has been changed as proposed
Lines 60, 72, 133, 134, 138 and 143 (IPFA)	Ph. Eur. abbreviation doesn't correspond to *European Pharmacopeia*	*Eur. Ph.*	The official abbreviation for European Pharmacopeia is Ph. Eur. Please refer Ph. Eur. *General Notices* (01/2008:10000). No change necessary.

[1] Where available

Line 81 paragraph about "Fever induced cytokines in plasma derivatives" (IPFA)	About the sentence "It should be validated that the finished products consistently contain non-physiopathologically relevant concentrations of fever inducing cytokines." It is unfortunate that any specification is indicated for pro-inflammatory cytokines concentrations. Without reference values, it is impossible to appreciate and compare concentration levels of this molecules.	Please insert specifications for fever inducing cytokines (ng/ml or IU/ml or IU/g of immunoglobulin) and explicit the list of the pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, INF-γ, ...) that should be titrated.	Spelling of TNF-α is corrected. Interferon-gamma (INF-γ) was not added to the list of cytokines that should be titrated because we focused on pyrogenic cytokines. It is not intended to provide limits for cytokines in finished products: The paragraph deals with the possibility that the fractionation/purification process of a plasma-derived medicinal product could enrich pro-inflammatory cytokines. To show this, limits are not necessary.
Line 95 (PPTA)	It should be left to the manufacturers of new products to use the RPT for a defined period of time / number of batches marketed and collect the clinical experience and then change to an alternative test as an alternative to validate that the finished products consistently contain non-pathophysiogically relevant concentrations of cytokines. During submission and approval by the competent authorities the time period and/or number of batches using the RPT prior to changing to an alternative test has to be defined.	Add: “For new products when there is sufficient clinical experience an alternative test would also be acceptable”.	The sentence “For marketed products, where there is extensive clinical experience with no indications of pyrogenic adverse events, an investigation for pro-inflammatory cytokines would not be required as part of the justification to move to LAL testing” has been moved from this paragraph to line 154 and the words “For marketed products” have been deleted. This was done because this is a regulatory issue and this paragraph has been moved now to the right place which is dealing with regulatory issues for already licensed products. It reads: “Where there is extensive clinical experience with no indications of pyrogenic adverse events, an investigation for pro-inflammatory cytokines in plasma fractions and finished product would not be required as part of the justification to move to LAL testing.“ In line 148 the sentence “The number of batches of a given product to be tested in parallel …” has been amended to include a clarification when further parallel testing is required after the approval of a variation. It reads now: “During such intermediate periods, further experience is needed and the RPT and the endotoxin test are applied in parallel and batches cannot be released when the results of the two tests are discrepant. The proposed wording “For new products when there is sufficient clinical experience an alternative test would also

			be acceptable" was not included. For new products validations as outlined in paragraph "Fever inducing cytokines in plasma derivatives" (lines 83-91) should be provided.
Line 95 (BAXTER)	It should be left to the manufacturers of new products to use the RPT for a defined period of time / number of batches marketed and collect the clinical experience and then change to an alternative test. Using RPT and collecting clinical experience should be an acceptable alternative to validation that the finished product consistently contains non-pathophysiologically relevant concentrations of fever inducing cytokines.	Add the following text in line 95: For new products extensive clinical experience with no indications of pyrogenic adverse events might also be considered acceptable. During submission and approval by the competent authorities the time period and/or number of batches using the RPT prior to changing to an alternative test has to be defined.	See comment above.
Lines 116 to 119 (BAXTER + PPTA)	As already stated in lines 110 to 114, any excursion of bioburden action limits requires thorough root cause analysis and identification of the microorganism. In case of a gram-positive bacterial contamination, and after careful risk assessment, release of the batch should be possible based on the RPT. As requested by GMP and implemented through the Quality Systems at the manufacturers, thorough root cause analysis and appropriate corrective / preventive actions have to be implemented following any such deviation. If at any time later another gram-positive contamination would be identified, again a thorough root cause analysis and appropriate corrective / preventive actions are performed and implemented. If such batch is undoubtedly pyrogen-free, releasing this batch should be acceptable also based on the RPT. Informing the Competent Authority (as required in	Delete text in lines 116 to 119	It is acknowledged that following the wording of lines 110-114 a thorough root cause analysis is performed. Identification and correction of deficiencies are the important factors. Exceeding bioburden limits does not question the validation of the LAL versus the RPT and unnecessary additional validation would be requested. Therefore, the wording of lines 116 to 119 have been rephrased to restrict competent authorities informing to situations where the manufacture appears not to be under control. In addition the sentence in lines 112-114 has been slightly modified to make clear that a negative alternative test is the basis for all further considerations with respect to batch release. It reads now: "If bioburden action limits are exceeded and gram-positive contaminations are identified on consecutive occasions although a root cause analysis and corrective

	line 119) will not add any value in this situation. All such decisions made at the manufacturer (number of deviations resulting in release based on the RPT, appropriateness of corrective / preventive actions, etc.) will be discussed during the GMP-inspections carried out by the authorities. By keeping this requirement in line 116 to 119 the whole alternative test approach might only be able to cover a transition period back to routine use of the RPT.		actions have been performed, the Competent Authority should be informed"
Lines 168 to 169 (BAXTER)	If a batch of product is undoubtedly pyrogen-free using the RPT, release of such batch should not be precluded by this document. In any case of a failing endotoxin testing thorough root cause analysis and appropriate corrective / preventive actions have to be implemented following any such deviations. All such decisions will be discussed during the GMP-inspections carried out by the authorities.	Delete last sentence of this section	The change in the monographs allows a manufacturer to replace the RPT by an endotoxin test and to license e.g. the LAL as the release test for a given product. If the LAL test is the licensed release test for finished products, release of batch that fails this test is not possible. However, to provide clear guidance, procedures to be followed are outlined for the case that within a variation for a licensed product more data are needed: "During such intermediate periods, further experience is needed and the RPT and the endotoxin test are applied in parallel and batches cannot be released when the results of the two tests are discrepant." For new products the situation could be different. This is taken into account with the following wording: "A risk assessment for the respective plasma derived medicinal product considering the potential of a non-endotoxin pyrogen burden of the final product should be provided. Data on release testing of the finished product with the RPT and LAL tests on as many batches as possible should be provided with the application. If there are not enough data to license the new product with the alternative test for batch release without further parallel testing, then the time period and/or number of batches using the RPT and LAL test in parallel should be defined

			during the licensing procedure. At this time batch release should be based on the licensed test, the RPT. After the agreed time of parallel testing a variation for the change to an alternative test should be submitted.”
Lines 174 to 193 (BAXTER +PPTA)	Lines 174 to 181 contain some suppositions: "potentially able", "does not specifically address justification needed"or "In some cases" and are thus not giving the guidance expected from such document. Lines 174 to 193 should be replaced by a statement confirming that EMEA encourages every effort to further develop and establish this type of alternative test. It would be advisable to refer to a harmonized protocol for use in detecting both endotoxins and a wide range of non-endotoxin pyrogens developed under the auspices of the Ph. Eur. Expert Group 6B.	Lines 174 to 193 should be replaced with: “In the past ten years, a new principle in pyrogen testing has been developed, the so called Monocyte Activation Tests (MAT). The EMEA encourages every effort to further develop and establish this type of alternative tests.”	The proposal was accepted.