EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2015

Submission of comments on Revision 1 of 'Annex 17: Real Time Release Testing' of the GMP guide'

Comments from:

Name of organisation or individual
AESGP

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	AESGP supports the proposal to revise Annex 17 to broaden its application to all product categories. The revision should achieve complete coherence of currently existing requirements for regulators and industry regarding 'parametric release' and 'real time release' and/or 'real time release testing'. In line with the principles of smart implementation, the number of regulatory documents describing the requirements should not be increased. In light of this, we object to the creation of a new document for Real Time Release Testing (RTRT). All the items listed and requested information are already covered in existing documents which describe the hierarchy of systems where risk management is the basis of control strategy. RTRT concepts are part of the control strategy and subject to validation and change control. It is not mentioned neither in the EMA guideline for Real Time Release Testing, nor in the current version of the EMA guideline on NIR.	

2. Specific comments on 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)***
Title		Comment: Real Time Release Testing (RTRT) and Parametric Release (PR) address different types of products. Although PR is seen as part of RTRT, it should be clear that requirements are different. Proposed change (if any): The title of Annex 17 should be extended and read: "Real Time Release Testing and Parametric Release".	
Lines 9-16		This section on "scope" only refers to RTRT but does not even once mention parametric release, although it is addressed later in the document. The relationship between RTRT and PR should be clearly made upfront for people less familiar with this concept.	
Lines 20-22		Comment: Clarification is needed. Proposed change (if any): "Under RTRT, a combination of in-process monitoring and controls may provide sufficient evidence to justify batch release as an alternative to release testing of a sample of the finished product."	

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)***
Lines 43-55		Comment: The requirements for the RTRT master plan, as described in draft section 3.3, are already covered by other documents – for example validation master plan and process validation (plan). To integrate the RTRT procedure in the general validation process therefore seems to be more reasonable. Proposed change (if any): The content of lines 43 to 55 should be replaced by the following: "If RTRT shall be applied, this testing procedure needs to be considered in the validation plan / process of the company."	
Line 57		Comment: We recommend not to require a separate risk assessment for RTRT. Usually a risk assessment on the RTRT method (e.g. NIR) is a standard process prior to method validation. This risk assessment identifies any potential parameters and failure mode that could potentially impact the predictive performance and reliability of the RTRT measurement system. As a consequence these parameter and failure modes constitute the robustness assessment which is part of validation and parallel testing. This document is usually provided within 3.2.P.2. Proposed change (if any): Delete 3.4	

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 76		Comment: As stated in the general comments, we recommend referring to other texts for the definition of control strategy. Proposed change (if any): Delete the whole Section 3.6	
Lines 109-112		Comment: To stay in line with "Guideline on Real Time Release Testing (MA/CHMP/QWP/811210/ 2009-Rev 1)" Point 5.3, it should be clarified that even on import from countries outside the EU no re-testing of approved RTRT besides Identity shall be deemed necessary. Proposed change (if any): "Approved RTRT should not be repeated upon importation besides Identity of the material. 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 can be acceptable if RTRT information elements are not available, for example due to analytical equipment failure (see 3.3) or in the frame of an Out of Specification Investigation."	
Line 114		Comment:	

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)*
		The title does not adequately cover the content of the paragraph. We suggest using the same title as in Section 7. of the EMA Guideline on Real Time Release Testing; i.e. "Parametric release and Sterilisation".	
Lines 130-131		Comment: To refer only to the sterilisation methods described in Ph.Eur. does not cover the complete spectrum of well-known and established sterilisation methods (e.g. compare Annex 1 of the EU-GMP Guide). The chosen method for sterilisation according to the product properties needs to be validated. If sterility is assured there is no need for the application of parametric release to demand only certain sterilisation methods. Proposed change (if any): "Parametric release can only be applied to products sterilised in their final container using thoroughly validated sterilisation processes as described in the Pharm. Eur., Annex 1 of the EU GMP Guide or other established publications, according to Pharmacopeial requirements for the SAL."	
Lines 150-153		Comment: Annexes of the EU GMP guidelines should not stipulate so specific requirements for personnel with special education. It is up to the manufacturer to fulfil the technical and operational regulatory requirements by selecting the appropriate qualified	

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)*
		and experienced employees, being checked regularly by the responsible competent authority inspections. Proposed change (if any): "Qualified personnel for parametric release processes should include persons with microbiological expertise. Personnel qualified and experienced in sterility assurance should be part of the process development of production and sterilisation. Qualification, experience, competence and training of all personnel involved in parametric release should be documented."	
Lines 162-163		Comment: In view of the provisions already stated in Annex 1, no. 88, this point is to be questioned if not omitted. Proposed change (if any): Please delete point 4.10.	
Lines 165-166		Comment: The issue of this point needs a strong reference to Annex 1. Proposed change (if any): "A pre-sterilisation product bio-burden monitoring program should be developed in accordance with Annex 1 to support parametric release."	

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 167		Comment: The word "locations" should be deleted as in this context it is misleading. Proposed change (if any): The beginning of the sentence should therefore read: "The sampling of filled units before …"	
Lines 169-170		Comment: a) Chapter 4.3 sets out the scope where parametric release can be applied. The validation process of each of the methods or agents used has to be validated with an acceptable SAL of min. 10^{-6}. Setting an identification requirement even to one organism found is not reasonable for a product sterilised in its final container. b) During validation of the sterilisation process each manufacturer has to challenge the sterilisation cycle with the most resistant organism known which is defined within the European Pharmacopeia. Presuming that a spore forming organism is more resistant to the sterilisation process than the challenge organisms prescribed in Pharmacopeias or other norms fails in the context of GMP and pharmacopoeial regulations.	

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 (if any): "Any findings exceeding the defined action limits of bioburden, approved by the competent (or regulatory) authority, should lead to a microbial identification. In case of identifying a spore forming organism this has to be evaluated by competent personnel with respect to the microbial validation of the sterilisation process and the total number of colonies found. "	
Lines 170-171		Comment: A test on endotoxins on the finished product is mandatory for parenteral preparations. Proposed change (if any): Please delete this sentence "Due to… endotoxin-producing species."	
Lines 190-191		Comment: Cf. our comment on lines 130-+131. Proposed change (if any): "Only fully validated terminal sterilisation processes can be considered for parametric release."	
Lines 199-200		Comment: With respect to the content of the new Annex 15 this should only be referred to and not set out own requirements	

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)***
		concerning requalification or revalidation. Proposed change (if any): "Periodic requalification of equipment and revalidation of processes should be planned and justified in accordance with the requirements of Annex 15 of the GMP Guide."	
Lines 244-245		Comment: To improve alignment with the definition provided in lines 116-118, we suggest the following modification: Proposed change (if any): "Parametric release for terminally sterilised products is based on the review of documentation on process monitoring…"	
Line 245		Comment: We suggest deleting the words 'moist heat'. As only examples are given, the reference to terminal sterilisation in general is seen as sufficient. Proposed change (if any): "… (e.g. temperature, pressure, time for terminal sterilisation) …"	

Please add more rows if needed.