26 August 2010

European Medicines Agency
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdon

Attn: Quality Working Party

SUBMISSION OF COMMENTS ON Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) Draft

ISPE is pleased to provide comments using the EMA supplied template on the above document, as requested.The Guideline is welcomed and will facilitate the use of Real Time Release testing, however, we would like to highlight the following points:

The guideline implies that RTR testing is an extension of the concepts of parametric release to tests other than sterility tests; however, this is not how the concept was developed under ICH. Parametric release combines process data with GMP compliance to give an assurance of product quality. RTR testing requires a valid combination of measured material attributes and process controls and this is a rather different concept.

We recommend that the guideline repeat the definition of the two concepts at its outset and contrasts the two approaches.

The Guideline could also give more assistance to applicants and reviewers regarding application of quality risk management to assess the proposed RTR testing control strategy

Please let me know if you have any questions.

Yours sincerely,

Robert P. Best
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 August 2010

Submission of comments on 'Guideline on Real Time Release Testing (Formerly Guideline on Parametric Release Testing ' (EMA/CHMP/QWP/811210/2009 Rev.1)

Comments from:

ISPE (International Society for Pharmaceutical Engineering)

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Guideline is welcomed and will facilitate use of Real Time Release testing.	
	The guideline implies that RTR testing is an extension of the concepts of parametric release to tests other than sterility tests. This is not how the concept was developed under ICH. Parametric release combines process data with GMP compliance to give an assurance of product quality. RTR testing requires a valid combination of measured material attributes and process controls and this is a rather different concept. We recommend that the guideline repeats the definition of the two concepts at its outset and contrasts the two approaches.	
	The Guideline could give more assistance to applicants and reviewers regarding application of quality risk management to assess the proposed RTR testing control strategy	

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)*
52		Comment: RTR testing is not simply an accumulation of in-process controls. Moreover, the concept of 'comprehensive' is unhelpful. Proposed change (if any): …..an appropriate combination of process controls (critical process parameters) together with pre-defined material attributes may provide….	
57		Comment: Proposed change (if any): change 'adequate' to 'effective'	
73-82		Comment: At time of release, there is a single specification. There may be an additional, shelf-life specification. However, the text implies there may be several (different) specifications applying at release and for stability. Same comment applies in several other places (Lines 94, 95). Proposed change (if any): Where it should be used in the singular, change "specifications" to "specification".	
78-89		Comment: This section is both over-prescriptive and insufficiently defined at the same time. What is 'adequate'? What is the proposed mechanism in Europe for communicating and agreeing that this 'adequate' period has been completed	

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		successfully? Many agree that RTR testing provides superior assurance of quality so why a running-in period? IF a second site wants to use an old-fashioned control strategy, does it need a running in period? Companies need to be able to avoid doing parallel testing, especially if there is a simple transfer of RTR testing from one site to another. Proposed change (if any): Revise sentence to remove need for running-in period. If this cannot be agreed, be more specific around expectations, acceptance criteria and communications mechanism and describe what should be done where a site (primary or secondary) wishes to change from RTR testing to off-line/remote sample and test processes.	
81		Comment: This sentence suggests that there will be something that reflects approval of a RTR testing proposal; ..”an approved RTR testing”. This is ambiguous. It is surely the application that is approved? Additionally, the implication is that where results do not trend towards failure, then end-product testing may be substituted: is it the intention to imply that the two are interchangeable in these circumstances? Proposed change (if any): In the situation where the results of RTR testing fail or are trending towards failure, RTR testing may not be substituted by end-product testing.	
85		Comment: Strongly support 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)*
95		Comment: We welcome this proposal. It is quite possible to envisage a situation where all specification tests are covered by RTR testing, even including product identification. Does this then mean that no tests would be required for such a product entering from a 3rd country? Proposed change (if any):	
108		Comment: We strongly support the guideline's discussion of attribute based control for RTR testing, but it needs to be much clearer about the acceptability of process control. "RTR testing will in general comprise other technologies" is a clause that both confuses and may not be correct. What are "other" technologies? RTR testing should comprise a combination of process controls (which may employ PAT tools) plus the control of material attributes. Proposed change (if any): RTR testing will, in general, comprise a combination of process controls which may utilise PAT tools, plus the control of relevant material attributes.	
151 et seq		Comment: This section is essentially identical to the equivalent section of the NfG on parametric release. As such it contains errors of syntax and it does not take into account the new thinking and terminology developed in the referenced ICH guidelines. For example, there can be no bioavailability of the packaging, nor is stability of packaging generally assessed. Furthermore the paragraph completely fails to support the concept of establishing and then controlling the identified CPPs which may not the attributes of the output of a particular process step.	

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		Proposed change (if any): Rewrite paragraph using ICH terminology such as CQAs and CPPs instead of technical characteristics and critical parameters. Ensure the rewrite clarifies the acceptability of true process control rather than implying the need for upstream in-process testing. Surely there should be a reference to the overall control strategy rather than 'methods of controlling critical parameters'?	
157		Comment: What is the meaning of 'founded'. Surely RTR testing should be based on product and process understanding as defined in the MA? Proposed change (if any): …programme will be granted on the basis of an assessment of the product and process understanding together with the proposed control strategy as described in the submission.	
163		Comment: Any assessment of RTR testing should be based on a demonstration of product and process understanding, and not on a period of 'running in' (an undefined term on line 79), or 'sufficient experience' since experience without understanding has limited value. Proposed change (if any):	
141		Comment: The example cites a 'high dose tablet'. The dose is immaterial if the relationships between the material attributes	

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		and CPPs to the relevant CQA(s) has been demonstrated. Proposed change (if any): A combination of tablet weight, blend content uniformity measurement e.g. by NIR, drug substance purity and particle size could serve as a control strategy for drug content of a tablet if the relationships have been demonstrated.	
165		Comment: To be consistent with Q8, both CPPs and CQAs should be identified and there may be more than one risk assessment. Then the relationship between the CPPs (and material attributes) and the CQAs should be demonstrated. Proposed change (if any): This section should be rewritten in line with the thinking behind the RTR testing concept from Q8.	

Please add more rows if needed.