29 March 2012
EMA/CHMP/QWP/142288/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft Guideline on Real Time Release Testing (formerly Guideline on Parametric Release)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Federation of Pharmaceutical Industries and Associations (EFPIA)
2	Active Pharmaceutical Ingredients Committee (APIC)
3	Bristol-Myers Squibb (BMS)
4	GE Healthcare Ltd. (GEH)
5	International Plasma Fractionation Association (IPFA)
6	International Society for Pharmaceutical Engineering (ISPE)
7	Therapeutic Goods Administration (TGA)

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
An agency of the European Union

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	EFPIA very much welcomes the development of this guideline on Real Time Release Testing and fully support the guiding principles it is promoting. Whilst we do not have major concerns with the draft guideline, we believe that sections could be expanded or reworded to improve applicability and clarity.	Noted.
1	We believe that there are opportunities to further clarify the scope and the context of the guideline. We recommend that a statement is included in the Executive Summary that the context for RTR testing is an integral part of the Control Strategy as defined in ICH Q10.	Accepted. “and the context as such be an integral part of the control strategy” added to the Introduction in line 53 (*57*).
1	There would be value in further elaborating on the key principles for RTR testing in the guideline. This could be achieved by incorporating the relevant statements from Section 2.2 Real Time Release Testing of the ICH Quality IWG on Q8, Q9 and Q10 Q&As document, as a new paragraph under proposed Section 4.	Most of the topics are covered in the GL. It is not considered appropriate to put them together in separate section. “RTR testing” is changed throughout the document to “RTRT”.
1	Whilst the scope of the guideline is intended to outline requirements for applications that propose RTR testing for active substances, intermediates and finished products, the guideline focuses on application of RTR testing for finished product. We believe that there would be more value in including examples of RTR testing for active substances. Also the level of the guidance on Parametric Release and Sterilisation seems disproportionate to the level of guidance on RTR testing applications for finished product.	It is acknowledged that there is an imbalance. More examples from industry have been asked for. Some improvement has been made to the chapter on examples. Active substance is introduced in the “Executive summary”.
1	We very much welcome the clarifying statement that acknowledges relief from “testing on importation” (per Directive 2001/83/EC) will be accepted where approval has been given for a medicinal product for which the control strategy is based on RTR testing (lines 90-98(*238-247*)). We believe that it is essential to carry this statement through into the	Noted.

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	final guideline.	
2	APIC welcome this guideline. We consider it as a good document, very useful for the industry.	Noted.
2	Important information is scattered over the whole document and sometimes difficult to find.	Noted. Hopefully improved in the new version.
2	The documentation requirements list in section 5.2 seems to be a combination of GMP documents part of the quality systems and regulatory information, typically part of an MAA or variation. Will the RTR concept require a regulatory submission and an inspection of the API manufacturer prior to approval for implementation? Or could a regulatory submission be sufficient?	This may be understood from 5.1, but is more clearly stated in the new section “General Considerations”
2	Can the RTR concept also apply to processes used to produce clinical materials? How should the requirement for process validation be interpreted for these cases?	Clinical material is outside the scope of this GL and it is proposed to be clarified in the section “Scope”. “This guideline is not applicable to investigational medicinal products although a company may be at various stages of development aiming at RTR testing of the final product.
2	Throughout the document should be clear how it can be applicable to the APIs. E.g.: RTR should be allowed for continuous API processes, but also for distillations, hydrogenations, crystallisations and all sorts of other chemical reactions or separations (e.g. diastereoisomers). Especially when PAT can be used.	Accepted. A clarification is introduced in 4.2: “In active substance manufacturing, RTR testing can apply to continuous manufacturing processes, but also to discrete unit operations such as distillations, hydrogenations, crystallisations and all sorts of other chemical reactions or separations (e.g. diastereoisomers).”

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2	For some unit operations in API processes, a generic approach instead of a product specific approach may be applied. A drying process for example may require certain process parameters related to the type of drying equipment used to control the loss on drying, but when those parameters are set, they may apply to all products using this unit operation in the same equipment type without requiring much product specific process experience.	Not accepted. However, this may possibly be referred to as prior knowledge when applying for RTRT for a specific product.
2	What is the health authorities expectation for content of the Certificates of analysis if RTR is applied? E.g.: (using the example of the guideline): If polymorphism, particle size, water content are accepted as relevant criteria for dissolution, there will not be dissolution data to include on the CoA. Will then the material attributes with their criteria and batch specific results have to be included on the CoA? How does that impact process confidentiality for API's?	A clarification in section 4.1 has been added: "Attributes (e.g. uniformity of content) that is indirectly controlled by approved RTR testing should still appear in the Certificate of Analysis for batches. The approved method for end-product testing should be mentioned and the results given as "Complies if tested" with a footnote "Controlled by approved Real Time Release testing".
2	It is difficult to find out the requirements for RTR. A list of requirements which should be fulfilled before starting with RTR would be helpful, e.g. → validated analytical test methods for final product, which should be also stability indicating. → validated online test methods for RTR → documented evidence of the measuring uncertainty of RTR methods on the analytical results of the final product, *resp*. API.	It is difficult to get such list complete and the needs may vary case by case.

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	→ Backup strategy for RTR equipment failure	
2	Which analytical methods or experimental set ups are recommended to be used for RTR: e.g. → at line measurements including limit tests → on line measurements including limit tests	It is not the purpose of this guideline to recommend analytical methods or experimental set ups. It is for the applicant to propose and justify case by case.
2	Recommendation, how to verify the RTR methods and how long are the periods between full analysis of the final product with reference analysis.	How to verify the RTR methods are for the applicant to propose. Periodic full analysis of the final product is not a regulatory expectation in case of an approved RTR testing (contrary to approved skip testing).
2	A decision tree could help to decide if a process is fit for RTR	The enhanced knowledge expected for RTR testing is not easily converted to a decision tree.
2	A flow chart how to implement RTR in a process would be helpful in this guideline	It is probably not possible to construct a flow chart for the implementation of RTR testing.
2	There should be a separate chapter dealing with OOS investigations because this topic is critical and difficult and could be the killing argument not to change to RTR if no practical solution will be found: → OOS procedure of RTR results → OOS procedure of analytical results of the final product when an OOS result was found, e.g. during full analysis of the final product	This is discussed at line 80-82. See also General Considerations. It is also explained in Question 7 of the ICH Q&A.
3	Overall the guidance is well written. Additional clarifications are	The FDA guidance has already been taken into consideration

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	needed as proposed below. In regards to Section 6.1 on Sterilisation by heat, BMS recommends harmonizing this section with the FDA guidance on the same topic.	and where relevant the RTRT- guideline has been harmonised with the FDA document, although the FDA document is more detailed with respect to documentation requirements.
5	LFB Biomédicaments and IPFA welcome the revision of the guideline aiming to widening the parametric release strategy to other critical quality attributes than sterility. The scope of the document is well defined regarding the substances on which the RTR testing is applicable (active substances, intermediates and finished products). Nevertheless, as first comment to the scope, we would appreciate a clarification regarding the scope of the applicability of the RTR Testing on the aseptic manufacture of sterile products: - Part 6. "Parametric Release and Sterilisation" remains unchanged to the previous version and applies to a "… fully validated terminal sterilisation method by steam, dry heat or ionising radiation…" (lines 179-180). Hence, this part clearly does not apply to aseptic manufacture of sterile products. - Part 4.2. "Application of RTR testing" gives examples of parameters that should be part of the scope of the RTR Testing. Line 114 gives "sterility" as example for attribute that is indirectly controlled. We understand it is rather sterilization which is indirectly controlled, as there is not, up to now, methods allowing sterility in-	It is clearly stated (line 195-196) that the quality attribute sterility of aseptically manufactured medicinal products cannot be release by the concept presented in this guideline. The reason for that is that it is not possible to monitor the process to ensure sterility as it is with the methods mentioned. It is not deemed necessary to include that information in the Scope. The discussion regarding whether "sterility" or "sterilisation" is the attribute is not endorsed. The critical quality attribute is certainly "sterility" even if there exist no in-process control methods.

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	process control. Thus this part does not clearly identify the aseptic manufacture of sterile product as being part of the guideline. In conclusion to this point, this is for us unclear wither the aseptic manufacturing is under the scope of the guideline or not and we would appreciate a clarification on this point.	
5	As second comment to the scope of the document, we would like to emphasise that despite "the guideline highlights the different requirements that have to be fulfilled in the application and the role of related inspections (pre authorization and routine GMP inspections)" (lines 65 to 67), we do not found clear position on authorities expected requirements regarding the obtention of the authorisation to apply the RTR testing. Hence, the way authorities will privilege to authorise the use of RTR testing during manufacture, either by inspection, submission of a variation to the marketing authorisation dossier or both, is still to be clarified.	This topic is to some extent covered in the new section "General considerations".
6	The Guideline is welcomed and will facilitate use of Real Time Release testing.	Noted.
6	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	The current definition of Parametric release is taken from Question 11 in the ICH Q&A. It has been amended for further clarity (see comments 31, 131): **Parametric Release:** One form~~type~~ of RTR testing. Parametric release is based on the review of documentation on process monitoring~~data~~ (e.g. temperature, pressure,

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	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.	time for terminal moist heat sterilisation) rather than the testing of a sample for a specific attribute (ICH Q8 Q&A). (Together with compliance with specific GMP requirements related to parametric release this provides the desired assurance of the quality of the product.) The Executive summary is clarified.
6	The Guideline could give more assistance to applicants and reviewers regarding application of quality risk management to assess the proposed RTR testing control strategy	It is not obvious how to do this as no proposal is given.
7	The requirement to submit run-in data (4.1) should be repeated under Documentation (5.2).	A bullet point has been added in 5.2: "comparative test results (parallel testing) supporting the relationship between the end-product specification and the RTR testing where applicable
7	Given that so many variables can affect the dissolution rate, perhaps RTR of dissolution rate might only be envisaged for highly soluble drugs in immediate release dosage forms.	It may be true, but it is for the applicant to demonstrate that any proposed RTR testing is valid. The complexity of the variables affecting a CQA is not in it self a reason for introducing limitations.
7	Regarding Section 4.2.1), This guideline is likely to have limited impact on biotech products. However, as stated in the guideline, the levels of host cell DNA and protein are amenable to this approach. The current de facto approach has been to show significant clearance levels and then, after sufficient numbers of batches have been released, to show the levels never approached the agreed specification, then to simply drop any monitoring of the parameters. This RTR would actually improve the control of this type of	Comment noted.

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	parameter, in that some testing would be done early on and if over certain levels or showing sufficiently high trends would pick aberrant batches that would (now) be approved by default.	
7	No separate paragraph on process of application and approval to apply RTR, including acceptance criteria are used. Acceptance criteria can indirectly be drawn from Ch. 5.2, but are not directly given.	Some information is given in the new section “General Considerations”, but it is difficult to elaborate in the light of the broad scope of this guideline.
7	Lines 91-98 contain a decision for third country manufacturers applying RTR to waive the requirement for re-testing upon importation into EU. The justification for this decision is unclear, as no evidence exists that application of RTR results in a significantly higher level of QC assurance than traditional testing.	Approval of RTR testing involves a more thorough assessment of the applicants control strategy and capability to produce the target product quality. It is therefore considered possible to waive the requirement for re-testing upon importation into EU.
7	Reference 2, the GMP Guidelines Annex 17, do not clarify whether under the current system, parametric release of non-sterile products is allowed. Only by default (no clauses on this option) one can conclude it isn't. For that reason, adoption of this document could lead to potential revision of GMP Annex 17.	It is noted that GMP annex 17 may need to be revised.
7	The current guideline Note for Guidance on Parametric Release (that this document replaces) does not restrict the definition of 'parametric release' to the replacement of the sterility test for sterile products. The use of the term 'parametric release' in this draft RTR testing guideline implies that it differs from RTR in that it applies only to replacement of the sterility test for sterile products, however the definitions of RTR testing and parametric release (255 and 259) are essentially the same as each other. If the definitions of RTR testing	The difference between Parametric Release and Real Time Release is explained in the Definitions. Further clarification is given.

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	and parametric release are the same, it is not clear why the term parametric release is used in place of RTR testing.	
7	The scope (65-67) states that the guideline highlights the different requirements that have to be fulfilled in the application and the role of related inspections (pre-authorization and routine GMP inspections). However, little guidance is given on the role of the pre-authorization and routine GMP inspections in applications for RTR testing. A paragraph describing the authorization process and assessment of applications for RTR testing, including the role of GMP inspectors would be useful.	This topic is to some extent covered in the new section "General considerations". It is also proposed to reformulate the sentence on the scope: "~~The guideline highlights~~ It also outlines the different requirements that have to be fulfilled in the application and the need for interaction between quality assessors and GMP inspectors in the approval process.~~role of related inspections (pre-authorization and routine GMP inspections)~~"

2. Specific comments on text

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
39	1	**Comment:** The statement "alternative strategy to routine testing is possible" would benefit from rewording. **Proposed change:** "alternative strategy to systematic end product testing"	Accepted.
39 – 40	1	**Comment:** The guideline doesn't take into account that RTR applications have already been approved and the current wording will quickly date. **Proposed change**: "So far this concept has been mainly applied to sterility testing of terminally sterilised products and has become associated with parametric release applications. Recent guidelines adopted in the ICH context (ICH Q8, Q9 and Q10)…."	Accepted.
45- 46	1	**Comment:** We are not sure of the value of including the sentence beginning "The guideline replaces the previous guideline on parametric release…." We assume that the previous parametric release guideline will be withdrawn once the Real Time Release testing is finalised and implemented. The latter should stand alone. **Proposed change**: Delete the sentence.	Partially accepted. Paragraph reformulated: The guideline ~~replaces~~is a revision of the ~~previous~~ guideline on parametric release and does not introduce new requirements~~, so the parametric release part on the previous guideline is retained unchanged~~.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
51	1	**Comment:** "..and on enhanced process understanding", the word "enhanced" appears to be not appropriate as it is setting a clear expectation. **Proposed change**: Delete the word "enhanced".	Accepted. "Enhanced" is part of the ICH Q8 vocabulary but is superfluous in this location.
52	2	**Comment:** a comprehensive set of in-process controls **Proposed change**: a set of in-process controls for critical process parameters (critical means: change of the parameters have influence on the API, respectively, drug product, quality)	Accepted.
52	6	**Comment:** RTR testing is not simply an accumulation of in-process controls. Moreover, the concept of 'comprehensive' is unhelpful. **Proposed change:** an appropriate combination of process controls (critical process parameters) together with pre-defined material attributes may provide….	Accepted.
57	1	**Proposed change**: Change the word "adequate" to "appropriate".	Accepted.
57	6	**Proposed change:**	Partially accepted.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		change 'adequate' to 'effective'	'adequate changed to 'appropriate'.
57-59	1	**Comment:** As the scope includes active substances and intermediates it might be worth making a reference to ICH Q11, if this reaches step 4 before the RTR testing guideline is finalised.	If Q11 is ready before this GL is finalised a reference will be added.
59	1	**Comment:** There is a need of a clarifying statement here. It should be possible to test some quality attributes with the real-time release approach and others with the conventional approach **Proposed change**: Insert the following sentence at the end of the paragraph: "Release of a product can be a combination of a RTR approach for certain critical quality attributes (CQAs) and a more conventional evaluation for other CQAs (partial RTR)."	Accepted.
60-61	1	**Comment:** This sentence would benefit from some rewording to improve clarity. **Proposed change**: "This guideline elaborates on the application of RTR testing to drug substances, intermediates and to sterile and non-sterile finished products."	Partially accepted. "This guideline elaborates on the application of RTR testing to drug substances, intermediates and ~~to sterile and non-sterile~~ finished products."
61-62	1	**Comment:** We believe that once the RTR Testing guideline is finalised, it should stand alone and not make a	Accepted.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		reference to the guidance on Parametric Release, which we assume will be withdrawn. **Proposed change**: Delete "It will thereby replace the Note for Guidance on Parametric Release."	
65	3	**Comment:** Please add biological/biotechnological products. **Proposed change:** "....active substances, intermediates and finished products including biological/biotechnological products"	Not accepted. "Finished products" include biologics and it is evident elsewhere in the guideline that they are included.
69 – 70	2	**Comment:** Not only the directive 2001/83 and its Annex I should be read in conjunction with this guideline. Behind it should also be the Directive 2003/94 related with GMPs. **Proposed change:** consider to add the GMP directive	Accepted.
71-148	1	**Comment**: We recommend some amendments and reformatting of Section 4 (*5*) to improve overall flow and applicability. **Proposed change:** 4. Real Time Release Testing	Partially accepted. Most aspects from the Q&A is already incorporated in the guideline and it is therefore not considered necessary to introduce a chapter on Key Principles. It is however acknowledged that overall flow may benefit from a slight restructuring. Due to the introduction of a section "General considerations" it will be chapter 5:

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		4.1. Key Principles (new sub-section, incorporating relevant statements from Section 2.2 Real Time Release Testing section of the ICH Quality IWG on Q8, Q9 and Q10 Q&As document) 4.2. Application of RTR testing 4.3. Application of RTR testing to biological/biotechnological products 4.4 RTR testing examples (expanded to include drug substance and intermediate examples) 4.5. RTR testing and specifications. Refer to more detailed comments in later sections.	5 Real Time Release Testing 5.1 RTR testing as part of a Control Strategy 5.2 Application of RTR testing 5.2.1 Application of RTR testing to biological/biotechnological products 5.2.2 RTR testing examples 5.3 Retest upon importation from 3rd country
72-98	1	**Comment:** Section 4.1 Real Time Release Testing and Specifications focuses almost entirely on finished product specifications. **Proposed change**: Requirements for drug substances should also be clarified.	Partially accepted. Text has been made more general by removal of references to "product" that could be interpreted as "finished product".
73 to 98	2	**Comment:** No reference to API is noticed in this item, which is not in line with the Scope	Partially accepted. Text has been made more general by removal of references to "product" that could be interpreted as "finished product".

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		Proposed change: please consider to rewording the item to include APIs.	
73-82	6	**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 (*148, 149*)). **Proposed change:** Where it should be used in the singular, change "specifications" to "specification".	Proposal accepted. Specification is sometimes used in the meaning "a test, a method and acceptance criteria" and sometimes in the meaning "a set of tests with a corresponding method and acceptance criteria".
74-76	1	**Comment:** The possibility of partial RTRT (only for some of the specifications, while for others a traditional approach would be followed) is not explicitly mentioned. **Proposed change**: Mention this possibility.	Accepted.
76	1	**Comment:** We believe that "product specifications" here refers to "finished product release specifications". **Proposed change**: Please clarify and adapt sentence	Partially accepted. We propose to delete "product", to include also API specification.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		to make it clear what is meant.	
76-77	1	**Comment:** It is not stated that Certificates of Analysis do not need to have the full range of traditional specifications. **Proposed change**: Clarify that a statement of compliance would be acceptable.	Accepted.
77	1	**Comment:** We believe that “product specifications” here refers to “finished product shelf-life specifications”. **Proposed change**: Please clarify and adapt sentence to make it clear what is meant.	Partially accepted. We propose to delete “product”, to include also API specification.
77	3	**Comment:** Provide clarity on the RTRT versus stability testing since the latter will not use the methodology used in the RTRT. **Proposed change:** None	Stability studies are one of the reasons why a (shelf-life) specification with tests, methods and acceptance criteria, is needed.
77-78	4	**Comment:** Please provide an explanation of the abbreviation OMCL	Accepted.
78	2	**Comment:** meaning of OMCL	Not accepted.

Line no.	Stakeholder no. (See cover page)	Comment and rationale; proposed changes	Outcome
		Proposed change: please add the definition of OMCL under line 254	
78- 79 and 163-164	1	**Comment:** The statement "running in" period is ambiguous and implies that there must always be a "running in period" post approval, with parallel end-product testing to RTR testing to demonstrate equivalency. This is very restrictive if the applicant has sufficient experience and data with the RTR testing control strategy at the time of the initial filing or via a variation, to justify that a "running in period" is not necessary. **Proposed change**: "The application of RTR testing should be supported by adequate validation of the RTR test method. The relationship between the RTR test, including acceptance criteria, and the end product test and associated specification should be well understood and, where applicable, supported by comparative data. This approach can be used to support a new application or a variation to a marketed product."	Partially accepted with some adjustments. "The application of RTR testing should be supported by adequate validation of the RTR test method. The relationship between the RTR test, including acceptance criteria, and the end product test and associated specification should be well understood and, where applicable, supported by comparative data *(parallel testing)*. The following sentence in the proposal from EFPIA is considered covered in the new "General considerations": "*This approach can be used to support a new application or a variation to a marketed product*." The following change is made to 4.3: "Therefore a relief from this testing will be accepted, although the competent authority may request a period of parallel testing"
78, 79	3	**Comment:** The phrase "running in period" is not a commonly understood term. In addition, clarify that the end-product testing is to be used for releasing the batches during the period of parallel testing. **Proposed change:** The application for RTR testing should contain adequate data ~~of a running in period~~ by parallel testing of batches with both end product testing ~~data and~~ RTR	Partially accepted.

Line no.	Stakeholder no. (See cover page)	Comment and rationale; proposed changes	Outcome
		testing ~~data~~.	
78-79	4	**Comment:** The application for RTR testing should contain adequate data of a running in period with both end product testing data and RTR testing data' If the intent is that once it has been satisfactorily demonstrated, the end product testing can be dropped routinely, and products can be released based on RTR testing data only. If this assumption is correct, can this be clarified more in the text.	Partially accepted with some adjustment (see comments above).
78-89	6	**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 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:** Revise sentence to remove need for running-in period. If this cannot be agreed, be more specific around	Partially accepted. Clarification hopefully provided by new formulation.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		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.	
80-82 and 85-87	1	**Comment:** The two paragraphs are not consistent. It must be possible to change to end product testing in case of a system failure or failure investigation. **Proposed change**: Rephrase Line 80 -89 as follows: "When RTR testing has been approved this should be routinely used for batch release. It is not acceptable to switch from Real Time Release testing to the corresponding end-product testing for non-compliance reasons. If the Real Time Release testing data does not meet the Real Time Release testing control specification, then a full investigation must be carried out. If a problem occurs with the Real Time Release technology preventing the use of the methodology and/or data collection then a switch to end-product testing can be considered on a temporary basis, provided that the alternate control strategy has been registered. This temporary change and the justification should be fully documented in the change control system."	Partially accepted. Current wording considered consistent, but the following change of Line 85-87 is proposed for enhanced clarity: "In the case of equipment failure t~~T~~he control strategy provided in the application should include a ~~proposal for~~ contingency plan specifying the use of alternative testing or monitoring approaches on a temporary basis ~~in the case of equipment failure~~.
80-84 and 243-246	2	**Comment:** Not for all processes the current design criteria will have been used. However, process knowledge that is gained during the product life cycle may require change.	Not accepted. The current wording is considered to be valid. In particular with regard to sterility (Line 243-246) returning to end-product testing is not applicable under any circumstances.

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		Therefore end-product testing should be allowed as part of the investigation. As a result it may be concluded that there is no impact on batch and batch complies with all specification, hence batch release by investigational decision. All to be documented in investigation mgmt. (cfr lines 88-89)	
81	6	**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:** 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.	Partially accepted. In the ~~situation where~~ event that the results of RTR testing fail or are trending towards failure, RTR testing may not be substituted by end-product testing.
85	6	**Comment:** Strongly support this sentence.	Noted.
87	3	**Comment:** Clarify what is meant by “other options.”	The possible alternative approach in a situation of equipment failure is not limited to end-product testing. However, it is not considered appropriate to elaborate in this guideline on what that could be. It should be noted that the wording “other options”

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		Proposed change: None	is taken from ICH Q&A on Control strategy, Question 4.
88, 89	3	**Comment:** Why should monitoring equipment breakdown be managed as part of the deviation process? **Proposed change:** ~~Testing~~ Breakdown of PAT equipment used for control ~~or monitoring equipment breakdown~~ needs to be managed in the context of a deviation under the Quality Management System and can be covered by GMP. If the monitoring equipment is for knowledge gathering (for example, for information only), then breakdown of such PAT equipment should be managed through the local change control process.	Not accepted. It is considered self-evident that the monitoring equipment mentioned in the guideline refers to such equipment that is part of the RTR testing and not only intended for information.
90 – 98	1	**Comment:** We very much welcome the clarifying statement that acknowledges relief from "testing on importation".	Noted.
94	4	**Comment:** It is our understanding that "complete reanalysis" of a product from third countries into the EU is not always the "normal way". The manufacturer in the third country should perform those tests which are defined and agreed upon in a Quality Assurance Agreement. This needs not to be all the tests in the product specification. Member states interpret the "reanalysis issue" differently and we believe that the issue could be handled by the Quality Assurance Agreement principle.	Not accepted. It is acknowledged that the reanalysis may not include a complete testing. There may be differences in how the requirements in the Directive are fulfilled and what can be considered as the "normal", but it is not the purpose of this guideline to elaborate on that. The message here is what relief can be expected when applying RTR testing.

Line no.	Stakeholder no. (See cover page)	Comment and rationale; proposed changes	Outcome
		Directive 2001/83/EC defines what must be done at the importing site in EEA and not what must be done at the manufacturer in the third country. **Proposed change:** Remove the sentence on line 94. Alternatively, include a sentence about the possibility to reduce the testing regime at the manufacturing site in the third country by the Quality Assurance Agreement system.	
95	6	**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?	Accepted. Sentence added to 5.3 to clarify: Identification testing upon receipt of material as part of GMP will apply even if subject to RTRT.
100-118	1	**Comment:** Rather than moving immediately into a tabletting example, there would be benefit in outlining that RTR can be supported by a number of different elements (e.g. in line process monitoring, process parameter control or combinations of these). **Proposed change**: Suggest insert before line 100*:* "The exact approach to RTR testing will vary depending on the process requirements. The RTR testing strategy may be based on control of process parameters, monitoring of product attributes or on a combination of both	Accepted.

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		at appropriate steps throughout the process. Critically, the RTR testing strategy should be based on a firm understanding of the process and of the relationship between process parameters and product attributes." In line 100 we would suggest changing "manufacturing processes" to "manufacturing steps" or "unit operations".	
100 to 118	2	**Comment:** consider to rewording the item to be applicable to APIs including additional examples.	Accepted. A clarification is introduced in 4.4: "In active substance manufacturing, RTR testing can apply to continuous manufacturing processes, but also to discrete unit operations such as distillations, hydrogenations, crystallisations and all sorts of other chemical reactions or separations (e.g. diastereoisomers)."
107	3	**Comment:** Add a paragraph on sampling **Proposed change:** Proposal to add the following paragraph: A sampling strategy should be defined that provides the number of locations sampled throughout the batch as well as the number of dosage units tested at each location. A statistically valid acceptance criterion should be used to evaluate the results.	Accepted with amendment. In the sentence just before, replace "number of tested units" with "amount of data". Change the proposed addition: "If testing of units is part of the RTR testing a~~A~~ sampling strategy should be defined that provides the number of locations sampled throughout the batch as well as the number of dosage units tested at each location. ~~A statistically valid acceptance criterion should be used to evaluate the results.~~"
108	6	**Comment:**	Accepted with amendments.

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		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:** RTR testing will, in general, comprise a combination of process controls which may utilise PAT tools, plus the control of relevant material attributes.	"RTR testing will, in general, comprise a combination of process controls which may utilise process analytical technology (PAT) tools, e.g. near infrared spectroscopy (NIR) and Raman spectroscopy (usually in combination with multivariate analysis), together with ~~plus~~ the control of relevant material attributes."
108-109	1	**Comment:** Should "process analytical chemistry test methods" be "process analytical technologies (PAT)"? **Proposed change**: Amend as appropriate.	Accepted.
114	3	**Comment:** Two sets of specifications (one by RTRT and the other by reference method) for the same parameter can lead to ambiguity of quality. This needs to be clarified in line 114(*183*). **Proposed change:** When RTR testing is applied, the attribute that is indirectly controlled (e.g., sterility, uniformity of content) together with a reference to the associated test procedure, should still be included in the	Accepted with amendments. "When RTR testing is applied, the attribute that is indirectly controlled (e.g., sterility, uniformity of content) together with a reference to the associated test procedure, should still be included in the specifications as "Complies if tested" (see 5.1). The relationship between ~~among~~ end-product testing, material attributes ~~and~~, process monitoring and acceptance criteria, should be fully explained and justified. In addition, the use of any prediction models should be fully explained and

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		specifications as "if tested". The relation among end-product testing, ~~and,~~ material attributes ~~and~~, process monitoring, ~~including~~ and acceptance criteria, should be fully explained and justified, ~~including the~~. In addition, the use of any prediction models should be fully explained and justified.	justified."
114-116	7	**Comment:** This sentence is unclear. We question how a reference to the associated test procedure is relevant to parametric release of sterile product. Do you mean reference to the procedure that lists the batch release criteria, details of parameters identified as critical and where failure leads to batch rejection? Clarify meaning.	The associated test procedure is that of the specification with which it should comply if tested.
116-117	1	**Comment:** We believe that the relationship is between drug product CQAs and material attributes/process parameters rather than between end-product testing and process monitoring. **Proposed change:** "The relation between the drug product critical quality attributes and material attributes and process parameters, including acceptance criteria, …"	Not accepted. The comment is not agreed and the text in the draft guideline is considered correct.
119-137	1	**Comment:** We believe that focus of this section is too narrow, for the following reasons: (1) focuses only on impurity removal and does not state that RTR testing could also be applicable to other quality attributes; (2) overly emphasizes a "validation approach", again primarily in the context of impurity removal, which is not a novel approach.	Accepted.

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		The approach of DNA (and to a lesser degree HCP) clearance validation and removal of end product testing for this attribute is already quite widely used and accepted. Similarly to virus clearance validation, once clearance is validated the quality attribute does not get tested again and it does not lead to a "complies if tested" entry on the final specification. **Proposed change**: Consider expanding the scope to cover more than impurity removal. Add after line 137: "With appropriate justification and process understanding, approaches to replace end product testing with either in-process parametric control or attribute testing at an earlier step in the process may be applicable to other quality attributes as well."	
122, 124 and 133	1	**Comment:** The use of "routine" testing to describe conventional and RTR testing approach is confusing i.e. it is unclear if the use of the word "routine" refers to current or future RTR testing approach. Should the second "routine" in line 122(*199*) be "RTR testing "? **Proposed change**: Wording should be modified to clarify the intent.	Accepted. Section 4.2.1 is modified.
130-132	1	**Comment:** The sentence "In such situations, the review of the documentation on process monitoring may be carried out during manufacturing without direct measurements of the quality attributes." is difficult to understand. **Proposed change**: We would propose the following alternative text: " In such situations, review of the	Accepted.

Line no.	Stakeholder no. (See cover page)	Comment and rationale; proposed changes	Outcome
		manufacturing process monitoring documentation may be carried out without direct measurements of the quality attributes"	
135-137	1	**Comment**: The sentence structure is confusing and the intent unclear. **Proposed change**: Clarify intent and improve wording.	Accepted. Changed to: "In this situation, routine testing at an earlier step, before a purification step which has been demonstrated to appropriate clearance capability with regards to the given impurities, can be allowed ~~in order to ensure acceptable levels in the final product level, if tested~~.**"**
135-137	4	**Comment:** The following sentence is unclear "In this situation, routine testing at an earlier step, before a purification step which has been demonstrated to appropriate clearance capability with regards to the given impurities, in order to ensure acceptable levels in the final product level, if tested."	Accepted. Changed to: "In this situation, routine testing at an earlier step, before a purification step which has been demonstrated to appropriate clearance capability with regards to the given impurities, can be allowed ~~in order to ensure acceptable levels in the final product level, if tested~~.**"**
138	3	**Comment:** In this section, is it possible to add additional RTRT examples on drug substance and biologics? For example, in-process drying of drug substance to eliminate release testing of drug substance batches for moisture content or residual solvent.	Accepted. Amendment about drug substance is added.
138 – 148	1	**Comment:** States that "some examples are given" ' but only one tablet example is presented. **Proposed change**: Suggest add more examples e.g. those described in the EFPIA proposals on RTR testing	The benefit of more examples is fully endorsed. However, the remaining examples in the EFPIA proposal where considered less suitable and has therefore not been included. Nevertheless, some improvement has been made to the chapter.

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		(sections 6.1 and 6.2), including application to Marketed Products.	
138-148	1	**Comment:** Recommend that some examples of applications of RTR testing to active substances and/or intermediates are included in this section. **Proposed change:** For example, insert following text: "RTR testing for impurities for an active substance may be achieved through control of starting materials and process parameters which directly impact impurity levels, supported by empirical and mechanistic knowledge of impurity formation and purging during processing."	Accepted.
141	6	**Comment:** The example cites a 'high dose tablet'. The dose is immaterial if the relationships between the material attributes and CPPs to the relevant CQA(s) have been demonstrated. **Proposed change:** 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.	Partially accepted. "high dose" deleted.
142	3	**Comment:** Add a comment on sampling plan.	Not accepted. It is explicitly mentioned that the examples are not intended in

Line no.	Stakeholder no. *(See cover page)*	Comment and rationale; proposed changes	Outcome
		Proposed change: A combination of in-process tablet weight (sampled at equally spaced locations throughout the entire batch), blend content uniformity measurement (e.g. by NIR), drug substance purity and particle size or other surrogate could serve as a control strategy for drug content of a high dose tablet.	any way to limit the scope of the application of RTR testing.
146	1	**Proposed change**: Replace "properties" with "attributes".	Accepted.
146	3	**Comment:** This sentence is unclear. **Proposed change:** ~~Properties~~ Control of quality attributes ~~relating to the properties~~ of a tablet granule such as porosity, particle size, and surface area could be shown to have a relationship with tablet dissolution behaviour and serve as RTR testing surrogates for dissolution testing.	Partially accepted. Sentence to read: Attributes relating to the properties of a tablet granule such as porosity, particle size, and surface area could be shown to have a relationship with tablet dissolution.
149 – 176	1	**Comment:** We believe there would be value in changing the title of Chapter 5. **Proposed change**: change "Documentation for RTR testing" to "Submission requirements".	Accepted. Chapter describes what should be submitted but more documentation will be available at the company.
151 et seq	6	**Comment:** This section is essentially identical to the equivalent	Accepted

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		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. **Proposed change:** 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'?	
153	1	**Comment:** The text "… the manufacturing process may be more or less continuous," is somewhat ambiguous and would benefit from rewording. **Proposed change:** ".. the manufacturing process may be partially or wholly continuous,…"	Accepted.

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156 and 267	4	**Comment:** There seems to be missing a reference [1] to Notes of Guidance (sentence # 267). **Proposed change:** Add number referring to reference	Not accepted. "Note for Guidance" does not refer to the NfG of Parametric Release in the reference list.
156	7	**Comment:** Question: Can the word "requirements" be used in conjunction with "Notes for Guidance"? Confirm that "requirements" is the appropriate term.	Confirmed.
157	6	**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:** …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.	Accepted.
157-158 and 163 – 164	1	**Comment:** The guideline indicates that RTR will be "granted for specified sites". It is not clear whether this is allowing multi-sites to be registered for RTR testing or not. Companies should be able to file RTR testing to be multi-site if more than one site supplies the product, where relevant experience and data can justify this.	Not accepted. Current text is considered to cover multi-site applications. However, every site intended to be included must be specified.

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		Proposed change: Amend text as appropriate.	
157-160	1	**Comment:** It is not clear if this relates to the process control strategy, the RTR testing strategy or both. Whatever the intent, neither is restricted to critical parameters. The guideline already includes an example where the in-process material attribute of blend homogeneity is used. **Proposed change**: Clarify intent and update scope to include critical attributes as well as critical parameters.	It is not clear what change is expected.
160 – 162	1	**Comment :** Original text states "In addition, assessors will evaluate the choice and limits of the critical parameters in relation to their effect on the technical characteristics, stability and bioavailability of the product and its packaging." This implies a direct relationship and there may be none. **Proposed change:** "In addition, assessors will evaluate the choice and limits of the critical parameters in relation to their effect on the technical characteristics, and their potential impact on stability and bioavailability of the product and its packaging."	Accepted.
163	6	**Comment:**	Accepted with some adjustment.

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		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 (*125*)), or 'sufficient experience' since experience without understanding has limited value.	
164	3	**Comment:** Please add the following sentence at the end of sentence in line 164. **Proposed change:** Once a specified site (dosage form, manufacturing line and RTR testing capability) has an authorized RTR testing programme demonstrating sufficient experience and GMP compliance, introduction of similar dosage forms into the same manufacturing line and RTR testing programme will not require reauthorization but can be implemented and reviewed during inspection.	Not accepted.
165	6	**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:** This section should be rewritten in line with the thinking behind the RTR testing concept from Q8.	Accepted. Section rewritten.

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166-176	1	**Comment:** We recommend that this section rewritten to align with ICH Q8 (R2) and to improve overall flow and readability. **Proposed change:** The application upon which an authorization may be granted should demonstrate: • that pharmaceutical development studies have identified the critical quality attributes for the finished product; • that a risk based development program has been carried out; • that a scientifically based control strategy has been developed; • that the manufacturing process is, or will be, validated adequately; • the relationship between end-product attributes and RTR testing, including justification of acceptance criteria; • that in process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the development studies; • that clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection. “	Partially accepted. The proposal to align with ICH Q ((R2) is in principle implemented but with some modifications. The additional bullet point is not accepted since it does not align with the previous bullets and is covered by section 4.1.

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		In addition add a bullet : • "Certificate of Analysis should state that the tested attributes conform to the limits in the specification without showing numerical values."	
168	2	**Comment:** under ICH Q8 validation is not a discrete task. The process developed under these guidelines will have a continuous assessment instead of validation activity **Proposed change:** consider to reword the item to be aligned with ICH Q8	Accepted.
168	3	**Comment:** Clarify what is meant by "adequately" or delete "adequately."	Accepted.
168-169 and 176	4	**Comment:** Three of the items are ambiguous and should be more specific: sentence # 168: '*that the manufacturing process is validated* adequately'; sentence # 169: '*that it is* reliably *controlled*'; sentence # 176: '*that the applied technologies gives an* adequate *quality*'	Accepted.
168-173	1	**Comment:** Often the product manufacturing process may not be formally validated at the time of the marketing application in the EU, but only at time of	Accepted.

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		commercialisation, so we wouldn't expect any difference for a finished product with RTR testing. **Proposed change:** Refer to recommended changes to Lines 166 – 176.	
176	7	**Comment:** The applied technologies need to be of the required sensitivity and specificity Change to: "that the applied technologies are of adequate sensitivity and specificity, and five s an adequate quality"	Not accepted. The statement is not specific to RTR testing.
177	1	**Comment:** In order to be aligned with ICH Q6A and ICHQ6B, parametric release shouldn't be limited to sterility attributes. **Proposed change:** Add the following sentence at the beginning of Chapter 6: "Parametric release can be used as an operational alternative to end product testing for the drug product in certain cases when approved by the competent authority. Sterility testing for terminally sterilized drug products is one example. Parametric release is referred to in the European Pharmacopoeia monograph....."	Accepted with some modification: "Parametric release is based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring during manufacturing, without direct measurement of quality attributes. It can be used as an operational alternative to end product testing for the drug product in certain cases when approved by the competent authority. Sterility testing for terminally sterilized drug products is one example. Parametric release is referred to in the European Pharmacopoeia monograph....."
178	7	**Comment:** "Methods of preparation of sterile products". This document is currently being revised by Ph. Eur.	Noted.
179-180	7	**Comment:** Ethylene oxide can be used to sterilise medicine containers prior to aseptic filling. These containers can be released parametrically. Add "ethylene oxide" as a method of sterilisation for	Not accepted. Ethylene oxide is normally used for containers and not for product sterilisation. It will therefore not be included in the guideline.

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		containers.	
187	7	**Comment:** Missing text. Add "…sterilisation parameters e.g. **for moist heat sterilisation** - temperature, pressure and time, data…."	Accepted.
193	7	**Comment:** The parametric release of product also involves demonstration of package integrity to maintain sterility and the factors listed in lines 204-206. Add to the end of sentence "…the load and other factors e.g. package integrity, etc"	Not accepted. It is true, but this should always be demonstrated, not only when parametric release is applied.
194	7	**Comment:** Use of incorrect terms "…of sterility…" Change to: "…for parametric release for sterile products must in accordance with…"	Not accepted. It is the quality attribute "Sterility" which is complied with based on monitoring of parameters.
194-196	3	**Comment:** Radiopharmaceuticals that have short shelf lives and are aseptically produced must be administered before completion of a sterility test. It is therefore inaccurate to state in this sentence that only products that have been terminally sterilised in their final container can be Real Time Release tested. It would be a useful clarification to make it clear that such products can be released under these provisions.	Not accepted. The necessity to release radiopharmaceutical products with short shelf lives before completion of a sterility test is not to be seen as RTRT.
202	7	**Comment:** Missing word Insert: "…significance for **product** sterility are in	Accepted.

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		place…"	
205	7	**Comment:** "quality of the cooling medium" is appropriate for dry heat and moist heat sterilisation methods but not for radiation. Consider rewording the final sentence.	Accepted.
207	1	**Comment:** Suggest that heading reflects both 'dry and moist' heat, since lines 179-80 refers to 3 types of sterilisation and only 2 sections (6.1 and 6.2) appear. **Proposed change**: Amend as appropriate.	Accepted.
211-212	7	**Comment:** This sentence should be a separate paragraph. "Biological validation" is referred to as "microbiological performance qualification" in European (EN) and International (ISO) sterilisation standards. New paragraph "The technical validation of a heat sterilisation method **should** be complemented by **microbiological performance qualification**."	Accepted.
212	7	**Comment:** "Consideration shall…" "shall" is inappropriate in a guideline" Change to: "Consideration should…."	Accepted.
216	7	**Comment:** Repetition: "…segregation of non-sterile products from sterilised products"	True, but this was not changed since this is an important GMP aspect.

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		This point is already mentioned in line 206.	
221	7	**Comment:** Incorrect term: "sterility" Change to: "An application for parametric release **for sterile product** should be supported by… "	Not accepted. It is the quality attribute "Sterility" which is complied with based on monitoring of parameters.
223	7	**Comment:** What about F_H value for dry heat processes? Add: "(time, temperature, pressure, F_o value, **F_H value**)"	Accepted.
228	7	**Comment:** Missing word. See also comment on lines 211-212 above. Insert "…and a microbiological **performance** qualification showing…."	Accepted.
233-235	1	**Comment:** This sentence does not really add any value. **Proposed change**: Suggest deleting sentence.	Not accepted.
235	7	**Comment:** "It is suggested that the risk assessment…." This text should start a new paragraph leading into the 4 dot points.	Accepted.
235-242	1	**Comment:** Inclusion of risk assessments for parametric release of sterility is an escalation of regulatory requirements. However, there if parametric release could be	Not accepted. The revised document is identical to the old text in this perspective.

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		approved at the time of the initial filing, then this might be justified.	
243-246	1	**Comment:** Consider moving to overview within Section 6.0, as equally applicable to both section 6.1 and 6.2 (*7.2*) However, need to clarify what "contrary to some other approaches of real time release (see section 4.2.1)" means.	Accepted. Paragraph moved. The following deleted since it has little added value: "~~contrary to some other approaches of real time release (see section 4.2.1)~~
250 (*383*)	7	**Comment:** It should be emphasised that bioburden counts without characterisation are not acceptable. With regard to radiation sterilisation both the count and the type of microorganism(s) making up the bioburden are required. (Refer to EN/ISO 11137). It is no longer appropriate to use biological indicators to validate a radiation sterilisation process. Note that the EN/ISO has revoked the standard for biological indicators used in radiation sterilisation processes. This paragraph should also direct the reader to the EN/ISO series of standards on radiation sterilisation which should be used to establish the radiation dose and the fact that even 25kGy must be validated. Add a reference in this paragraph to: "EN/ISO 11137-1 Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (2006)" and to "EN/ISO 11137-2 Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose (2006)".	Partially accepted. The text is partly revised according to the comment, i.e. "count and type of microorganisms" is emphasised. No additional comment regarding validation of a >25 kGy process, since validation is required for all sterilisation processes, including overkill processes.

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255-257	7	**Comment:** Shouldn't this definition clarify that RTR is ensuring the quality of a product based on only process data?	Not accepted. Definition taken from ICH Q8 (R) is deemed to be sufficient.
259-261	7	**Comment:** Definition does not exclude non-sterile products, whereas lines 39-40 suggest parametric release is only applicable to sterility testing or to sterile products. In fact, this definition does not distinguish parametric release from RTR at all.	Accepted.
260	7	**Comment:** Missing text and spelling of “sterilization” Proposed change: Insert: “…(e.g. temperature, pressure, time for terminal **moist heat** sterili**s**ation)	Accepted.
278	7	**Comment:** EN552:1994 has been superseded and is no longer available through the CEN website Change to EN/ISO 11137 Parts 1 and 2 (2006). Refer to comment on line 250 above.	Accepted.
278	1	**Comment:** We believe that EN 552 has been replaced by ISO 11137.	Accepted.
278	4	**Comment:** EN 552, for Irradiation Sterilization, has been withdrawn. ISO 11137." Should be quoted. **Proposed change:** ISO 11137." Should be quoted.	Accepted.