Comments and suggestions from reviewer

Title: Eudralex Volume 4, Annex 17 Real Time Release Testing

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GENERAL COMMENTS				
The title of the Annex has changed from “Parametric Release” to “Real Time Release Testing” (RTRT). However, it is suggested that the two terms are interchangeable and for clarity it may be beneficial to use the term RTRT for the whole document (e.g. RTRT of terminally sterilized products. Another option would be to retain the original title is retained as Parametric Release is a broad concept that encompasses both real time release, PAT and the release of sterile products without a final sterility test. It is of note that the existing Annex 17 referred to both parametric release of sterile products (by omitting the sterility test) as well as parametric release of products other than terminally sterilized products, refer Section 2 in the existing document. There are a number of good clauses that reside under the RTRT section (3) that would be equally relevant in section (4), and it would be useful to the end-user to clarify which clauses apply to each scenario – or both. A general reformatting of the document in this manner to avoid duplication and provide clarity is suggested.			

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It is suggested that this annex may be expanded to encompass other scenarios such as the extemporaneous compounding of sterile dosage forms for specific patients where chemical and sterility testing is not performed directly on the product (due to a batch size of usually 1) prior to release. These compounded products also include aseptically prepared parenterals, ophthalmic and parenteral nutrition products manufactured in a GMP environment.				
SCOPE				
11-16	This document is intended to outline the requirements for application of a Real Time Release Testing (RTRT) approach in manufacturing, where the control of critical parameters and relevant material attributes may be used as an alternative to routine finished product testing of medicinal products. The main aim of the changes to this guideline is to incorporate the application of RTRT to any stage in the manufacturing process and to any type of finished products, including active substances and intermediates.	As the scope applies to finished dosage forms and actives, the wording should be reflective of the scope. Suggest that the scope defines parametric release and outlines the basic approaches that are described, but does not necessarily limit the scope to these methods. Suggest previous wording regarding the authorization of parametric release be retained as it is critical that manufacturers are aware that parametric release practices are dependent on both MA approval through evaluation and GMP	This annex is intended to outline the requirements for application of a Real Time Release Testing (RTRT) approach in manufacturing, where the control of critical parameters and relevant material attributes may be used as an alternative to routine finished material/product testing of medicinal products. RTRT release may be authorized for certain specific parameters as an alternative to routine testing of finished materials/products. RTRT release methods may be applied to any stage in the manufacturing process and to any type of finished products, including active substances and intermediates. However, authorisation for RTRT should be given, refused or withdrawn jointly by those responsible for	

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			assessing products together with the GMP inspectors.	
REAL TIME RELEASE TESTING				
24-26	Interaction with the relevant regulatory authority during the assessment process should be considered. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.	RTRT release should only be implemented after authorization is given by the regulator and should be confirmed within a MA/ Suggest changing wording to re-inforce the notion that regulatory approval should be sought before implementation of RTRT.	Interaction with the relevant regulatory authority during the assessment process must be undertaken, and approval sought before implementation. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.	
26-28	Where a RTRT procedure has been established and authorised in the Marketing Authorisation, the Qualified Person can certify the batches based on the compliance of the process data to the approved release criteria together with appropriate GMP compliance.	Clarity	Where a RTRT strategy has been established and authorised in the Marketing Authorisation, the Qualified Person may certify the batches based on the compliance of the process data to the approved release criteria, together with appropriate GMP compliance.	
47	iii. a control strategy,	Clarify It is suggested that this clause is equally relevant to the control strategy for all parametrically released products (including terminally sterilized products) and therefore this clause could be placed in a general section of the document.	A documented control strategy, as per clause 3.6	
66	After a change implementation,	Clarification	After change implementation,	

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	an evaluation should be undertaken to demonstrate that it will not compromise the desired quality. A proactive approach should be facilitated.		an evaluation should be undertaken to demonstrate that the desired quality will not be compromised. Change management principles (as described in Annex 15) should be applied proactively.	
93-96	In particular, attention should be paid to the qualification, validation and management of in-line and on-line analytical methods, where the sampling probe is placed within the reactor and may not be subject to traditional cleaning and validation procedures.	Suggest clarifying statement to be broader - It is assumed that the concern relating to these sensors is fouling that may affect the results?	In particular, attention should be paid to the qualification, location, validation and management of in-line and on-line analytical methods, to ensure that sampling probes are placed in an appropriate location to provide a representative result, be easily cleaned and maintained and avoid fouling or any other deleterious treatment that may affect the operability of the probe.	
PARAMETRIC RELEASE				
Title	Parametric Release	Clarify	Parametric Release for terminally sterilized medicinal products	
138	4.5 The sterility assurance program should include, at least, the	Clarify the requirement that the sterility assurance program should be clearly documented.	4.5 The sterility assurance program should be fully documented and include, at least, the	
155	4.8 The product and its packaging should be designed for sterilisation and maintaining sterility over the shelf life of the product.	Add clarity regarding which barrier provides/maintains sterility.	4.8 The product and its packaging should be designed for sterilisation and maintaining sterility over the shelf life of the product. The critical	

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			components of the container and any protective overwrap that ensure/maintain product sterility should be defined and controlled through appropriate specifications and testing	
158-160	4.9 Any proposed change which may impact on sterility assurance should be recorded in the change control system and reviewed by appropriate personnel in accordance with the requirements of Chapter 1 and Annex 15 of the GMP Guide.	Re-instate requirement that changes should be reviewed by the sterility assurance microbiologist/engineer should review changes to the sterility assurance program.	4.9 Any proposed change which may impact on sterility assurance should be recorded in the change control system and reviewed by authorized personnel qualified and experienced in sterility assurance in accordance with the requirements of Chapter 1 and Annex 15 of the GMP Guide.	
STERILISATION PROCESS				
190-191	4.14 Only fully validated terminal sterilisation processes by moist heat, dry heat and ionising radiation can be considered for parametric release.	Clarify that this section applies to terminally sterilized medicinal products only. Suggest this is a sub-heading under Parametric release of terminally sterilized products.	4.14 Only fully validated terminal sterilisation processes by moist heat, dry heat and ionising radiation can be considered for parametric release of sterile medicinal products.	
196-197	With the exception of gamma irradiation, microbiological performance qualification is recommended for validation of parametric release.	The statement is not clear as to its intent. Does microbiological performance qualification mean the use of biological indicators in cycle development? If so then this practice should be mandated unless a regulatory authority doesn't require this practice.	The use of biological indicators during sterilisation cycle development and validation is required for the validation of parametric release cycles, unless otherwise authorized by the relevant competent authorities.	

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199	4.16 Periodic requalification of equipment and revalidation of processes should be conducted in accordance with the requirements of Annex 15 of the GMP Guide.	The re-validation of sterilization cycles should be performed annually as per Annex 1 requirements (Ax1§84)	4.16 Periodic requalification of equipment and revalidation of processes should be conducted in accordance with the requirements of Annex 15 of the GMP Guide. Sterilisation processes should be verified at scheduled intervals, at least annually.	
225-230	4.23 Once parametric release has been approved by the regulatory authorities, decisions for release or rejection of a batch should be based on the approved specifications and the review of critical process control data. Routine checks, changes, unplanned and routine planned maintenance activities should be recorded, assessed and approved before releasing the products to the market. Non-compliance with the specification for parametric release cannot be overruled by a pass of a finished product test for sterility.	Suggest amending this clause to align with the current practice outlined in clause 3.16 of the current Annex 17. The current wording of Annex 17 provides a clear overview of the critical checks that need to be performed, whereas the new wording is less specific.	4.23 Once parametric release has been approved by the regulatory authorities, decisions for release or rejection of a batch should be based on the approved specifications and the review of critical process control data. In addition, other critical elements of the sterility assurance program should be assessed and approved before releasing the products to the market including, but not limited to: - Confirmation that all planned and unplanned maintenance and routine checks have been completed for the sterilizer used. - All repairs and modifications have been approved by the sterility assurance engineer and	

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			microbiologist. - All instrumentation was within calibration. - The sterilizer had a current validation for the load processed. - Any changes associated with the sterility assurance program have been documented and approved. Non-compliance with the specification for parametric release cannot be overruled by a pass of a finished product test for sterility.	
GLOSSARY				
77	Operating Characteristic Curve	Add to glossary	-	