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Medicinal Products – Quality, Safety and Efficacy

EudraLex
The Rules Governing Medicinal Products in the European Union

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EU Guidelines for Good Manufacturing Practice
for Medicinal Products for Human and Veterinary Use

Annex 17: Real Time Release Testing and Parametric Release

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision 1

Reasons for changes: The previous guideline only focused on the application of Parametric Release for the routine release of terminally sterilised products waiving the performance of a test for sterility on the basis of successful demonstration that predetermined and validated sterilising conditions have been achieved. Moreover, advances in the application of process analytical technology (PAT), quality by design (QbD) and quality risk management (QRM) principles to pharmaceutical development and manufacturing have shown that an appropriate combination of process controls together with timely monitoring and verification of pre-established material attributes provides greater assurance of product quality than finished product testing (conventionally regarded as the end-product testing) alone.

This revision to Annex 17 takes into account changes to other sections of the EudraLex, Volume 4, Part I, Chapter 1, Annex 1 and 15, ICH Q8, Q9, Q10 and Q11, QWP Guideline on Real Time Release Testing, and changes in manufacturing and analytical technology.

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Table of Contents

1. Principle

1.1 Medicinal products must comply with their approved specifications and subject to compliance with GMP, can normally be released to market by performing a complete set of tests on active substances and/or finished products as defined in the relevant marketing authorization or clinical trial authorization. In specific circumstances, where authorised, based on product knowledge and process understanding, information collected during the manufacturing process can be used instead of end-product testing for batch release. Any separate activities required for this form of batch release should be integrated into the Pharmaceutical Quality System (PQS).

2. Scope

2.1 This document is intended to outline the requirements for application of Real Time Release Testing (RTRT) and parametric release, where the control of critical parameters and relevant material attributes are authorized as an alternative to routine end-product testing of active substances and/or finished products. A specific aim of this guideline is to incorporate the application of RTRT to any stage in the manufacturing process and to any type of finished products or active substances, including their intermediates.

3. Real time release testing (RTRT)

3.1 Under RTRT, a combination of in-process monitoring and controls may provide, when authorized, substitute for end-product testing as part of the batch release decision.
Interaction with all relevant regulatory authorities prior and during the assessment process preceding regulatory approval is required. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.

3.2 When designing the RTRT strategy, the following minimum criteria are expected to be established and met:

(i) Real time measurement and control of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.
(ii) The valid combination of relevant assessed material attributes and process controls to replace finished product attributes should be established with scientific evidence based on material, product and process knowledge.
(iii) The combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process should provide a robust foundation for RTRT and the batch release decision.

3.3 A RTRT strategy should be integrated and controlled through the PQS. This should include or reference information at least of the following:

- quality risk management, including a full process related risk assessment, in accordance with the principles described in EudraLex, Volume 4, Part I Chapter 1 and Part II Chapter 2,
- change control program,
- control strategy,
- specific personnel training program,
- qualification and validation policy,

- deviation/CAPA system,
- contingency procedure in case of a process sensor/equipment failure,
- periodic review/assessment program to measure the effectiveness of the RTRT plan for continued assurance of product quality.

3.4 In accordance with the principles described in EudraLex, Volume 4, Part I Chapter 1, Part II Chapter 13 and Annex 15, the change control program is an important part of the real time release testing approach. Any change that could potentially impact product manufacturing and testing, or the validated status of facilities, systems, equipment, analytical methods or processes, should be assessed for risk to product quality and impact on reproducibility of the manufacturing process. Any change should be justified by the sound application of quality risk management principles, and fully documented. After change implementation, an evaluation should be undertaken to demonstrate that there are no unintended or deleterious impact on product quality.

3.5 A control strategy should be designed not only to monitor the process, but also to maintain a state of control and ensure that a product of the required quality will be consistently produced. The control strategy should describe and justify the selected in-process controls, material attributes and process parameters which require to be routinely monitored and should be based on product, formulation and process understanding. The control strategy is dynamic and may change throughout the lifecycle of the product requiring the use of a quality risk management approach and of knowledge management. The control strategy should also describe the sampling plan and acceptance/rejection criteria.

3.6 Personnel should be given specific training on RTRT technologies, principles and procedures. Key personnel should demonstrate adequate experience, product and process knowledge and understanding. Successful implementation of RTRT requires input from a cross-functional/multi-disciplinary team with relevant experience on specific topics, such as engineering, analytics, chemometric modeling or statistics.

3.7 Important parts of the RTRT strategy are validation and qualification policy, with particular reference to advanced analytical methods. Particular attention should be focused on the qualification, validation and management of in-line and on-line analytical methods, where the sampling probe is placed within the manufacturing equipment.

3.8 Any deviation or process failure should be thoroughly investigated and any adverse trending indicating a change in the state of control should be followed up appropriately.

3.9 Continuous learning through data collection and analysis over the life cycle of a product is important and should be part of the PQS. With advances in technology, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate the data, in consultation if appropriate, with the regulatory authorities, to determine how or if such trends indicate opportunities to improve quality and/or consistency.

3.10 When RTRT has been approved, this approach should be routinely used for batch release. In the event that the results from RTRT fail or are trending toward failure, a RTRT approach may not be substituted by end-product testing. Any failure should be thoroughly investigated and considered in the batch release decision depending on the results of these investigations, and must comply with

the content of the marketing authorisation and GMP requirements. Trends should be followed up appropriately.

3.11 Attributes (e.g. uniformity of content) that are indirectly controlled by approved RTRT 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".

4. Parametric release and sterilization

4.1 This section provides guidance on parametric release which is defined as the release of a batch of terminally sterilised product based on a review of critical process control parameters rather than requiring an end-product testing for sterility.

4.2 An end-product test for sterility is limited in its ability to detect contamination as it utilises only a small number of samples in relation to the overall batch size, and secondly, culture media may only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for sterility only provides an opportunity to detect major failures in the sterility assurance system (i.e. a failure that results in contamination of a large number of product units and/or that result in contamination by the specific microorganisms whose growth is supported by the prescribed media). In contrast, data derived from in-process controls (e.g. pre-sterilization product bioburden or environmental monitoring) and by monitoring relevant sterilization parameters can provide more accurate and relevant information to support sterility assurance of the product.

4.3 Parametric release can only be applied to products sterilised in their final container using either moist heat, dry heat or ionising radiation (dosimetric release), according to European Pharmacopoeial requirements.

4.4 To utilise this approach, the manufacturer should have a history of acceptable GMP compliance and a robust sterility assurance program in place to demonstrate consistent process control and process understanding.

4.5 The sterility assurance program should be documented and include, at least, the identification and monitoring of the critical process parameters, sterilizer cycle development and validation, container/packaging integrity validation, bioburden control, environmental monitoring program, product segregation plan, equipment, services and facility design and qualification program, maintenance and calibration program, change control program, personnel training, and incorporate a quality risk management approach.

4.6 Risk management is an essential requirement for parametric release and should focus on mitigating the factors which increase the risk of failure to achieve and maintain sterility in each unit of every batch. If a new product or process is being considered for parametric release, then a risk assessment should be conducted during process development including an evaluation of production data from existing products if applicable. If an existing product or process is being considered, the risk assessment should include an evaluation of any historical data generated.

4.7 Personnel involved in the parametric release process should have experience in the following areas: microbiology, sterility assurance, engineering, production and sterilization. The qualifications, experience, competency and training of all personnel involved in parametric release should be documented.

4.8 Any proposed change which may impact on sterility assurance should be recorded in the change control system and reviewed by appropriate personnel who are qualified and experienced in sterility assurance.

4.9 A pre-sterilization bio-burden monitoring program for the product and components should be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified to confirm that they are not spore forming which may be more resistant to the sterilizing process.

4.10 Product bio-burden should be minimized by appropriate design of the manufacturing environment and the process by:

- good equipment and facility design to allow effective cleaning, disinfection and sanitisation;
- availability of detailed and effective procedures for cleaning, disinfection and sanitisation;
- use of microbial retentive filters where possible;
- availability of operating practices and procedures which promote personnel hygiene and enforce appropriate garment control;
- -appropriate microbiological specifications for raw materials, intermediates and process aids (e.g. gases)

4.11 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving the starting materials, product fluid filtration, and sterilization should be defined in order to minimise the development of bioburden and an increase in endotoxins (if applicable).

Sterilization Process

4.12 Qualification and validation are critical activities to assure that sterilization equipment can consistently meet cycle operational parameters and that the monitoring devices provide verification of the sterilization process.

4.13 Periodic requalification of equipment and revalidation of processes should be planned and justified in accordance with the requirements of Annexes 1 and 15.

4.14 Appropriate measurement of critical process parameters during sterilization is a critical requirement in a parametric release program. The standards used for process measuring devices should be specified and the calibration should be traceable to national or international standards.

4.15 Critical process parameters should be established, defined and undergo periodic re-evaluation. The operating ranges should be developed based on sterilization process, process capability, calibration tolerance limits and parameter criticality.

4.16 Routine monitoring of the sterilizer should demonstrate that the validated conditions necessary to achieve the specified process is achieved in each cycle. Critical processes should be specifically monitored during the sterilization phase.

4.17 The sterilization record should include all the critical process parameters. The sterilization records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

4.18 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 of the sterilizer, changes, deviations, 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 finished product passing the test for sterility.

5. Glossary

Control strategy
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Critical Process Parameters:
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8 (R2)].

Critical Quality Attributes
A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. [ICH Q8 (R2)]

Parametric release
One form of RTRT. Parametric release for terminally sterilised product is based on the review of documentation on process monitoring (e.g. temperature, pressure, time for terminal sterilization) 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.) (EMA guideline on Real-Time Release Testing)

Real time release testing
The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. (ICH Q8)

State of Control
A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)