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Medicinal Products – Quality, Safety and Efficacy

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

Annex 17: Real Time Release Testing

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 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 guideline is brought into line with ICH, Q8, Q9, Q10 and Q11 documents and will detail regulatory expectations for a batch release system based on the information collected during the manufacturing process, through product knowledge and process understanding and control.

Deadline for coming into operation: [6 months after publication]

1. Principle

Medicinal products must comply with their approved specifications and can normally be released to market by performing a complete set of tests on active substances and/or finished products. In specific circumstances, where authorised, batch release can be based on information collected during the manufacturing process, product knowledge, process understanding and control. The process for this form of batch release should be integrated into the pharmaceutical quality system.

2. Scope

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.

3. Real time release testing (RTRT)

3.1 Under RTRT, a combination of in-process monitoring and controls may provide sufficient evidence to justify batch release without the tests being repeated on a sample of the finished product.

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. 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.

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 as the surrogates of finished product attributes should be established with scientific evidence founded on material, product and process knowledge.
iii. The combined process measurements (process parameters and material attributes) and any other test data generated/gathered during the manufacturing process should provide a robust foundation for RTRT and batch disposition decision.

3.3 A RTRT master plan should be prepared which is appropriately integrated and controlled through the pharmaceutical quality system. This should include, as a minimum, but not limited to:

i. a quality risk assessment, including a full process related risk assessment,
ii. a change control program,
iii. a control strategy,

iv. a personnel training program,
v. an equipment and facility design and qualification program,
vi. a deviation/CAPAs system,
vii. a process development and validation program,
viii. a contingency procedure in case of a process sensor/equipment failure,
ix. a periodic review/assessment program to measure effectiveness of the RTRT plan for continued assurance of product quality, that includes a monitoring program over the product's lifecycle for critical material attributes and process parameters.

3.4 The risk assessment should identify the critical quality attributes and critical process parameters that should be part of real time release plan. If a new product or process is being considered for real time release, then a risk assessment should be conducted during process development, while for an existing product or process, the risk assessment should include historical data evaluation.

3.5 In accordance with the principles described in Chapter 1 and Annex 15, the change control program is an important part of the real time release plan. All the changes that could potentially impact product manufacturing and testing, or the validated status of facilities, systems, equipment or processes, should be assessed for risk to product quality, justified by sound application of quality risk management principles, and fully documented. After a change implementation, an evaluation should be undertaken to demonstrate that it will not compromise the desired quality. A proactive approach should be facilitated.

3.6 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 required quality will be consistently produced. The control strategy should describe and justify the selected in-process controls, material attributes and process parameters 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, acceptance/rejection criteria, and include Operating Characteristic curve or the Acceptable Quality Level (AQL) and Unacceptable Quality Level (UQL) associated with the plan. The sampling plan should ensure the sample is representative and be designed based on the prior knowledge of the product and the risk assessment for sampling locations, sampling frequency and sample size. Statistical methodologies, such as established consensus standards, should be considered to carry out a risk-based sampling plan that accounts for the underlying distribution of data.

3.7 Personnel should be given specific training on the RTRT technologies, principles and procedures. Key personnel should demonstrate adequate experience and product and process knowledge and understanding. Successful implementation of RTR testing should involve input from a cross-functional/multi-disciplinary team with experience on specific topics, such as statistical process control and statistical quality control.

3.8 Important parts of the RTRT plan are the facilities, systems, and equipment qualification and the analytical method validation, with particular reference to advanced methods, such as rapid microbiological methods, and spectroscopy techniques where the sample is evaluated by chemometrics and comparison with a reference spectral library. 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.
These should be qualified and validated in accordance with Annex 15 of the GMP Guide.

3.9 Any deviation or process failure should be thoroughly investigated and adverse trending should be followed up appropriately as indicated in Chapter 1 of the GMP Guide. A contingency procedure in case of process sensor/equipment failure should be available.

3.10 Continual learning through data collection and analysis over the life cycle of a product is important and should be designed as part of the quality system for implementing RTRT. With the use of new measurement tools, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate these data to determine how or if such trends could show potential quality decreases or outliers.

3.11 It is not acceptable to perform an actual test on a product (active substance or finished product) motivated by an undesired or unacceptable result as determined by the approved RTRT approach. End testing for release purpose can be acceptable if RTRT information elements are not available, for example due to analytical equipment failure (see 3.3)

4. Parametric Release

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 data rather than requiring a finished product test for sterility.

4.2 A finished product test for sterility is limited in its ability to detect contamination as: finished product tests for sterility utilise 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, a finished product test for sterility only provides an opportunity to detect major failures of 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. bioburden or environmental monitoring) and by monitoring relevant sterilisation parameters can provide more accurate information regarding the sterility assurance system.

4.3 Parametric release can only be applied to products sterilised in their final container using steam, dry heat and ionising radiation, according to 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. Historical test for sterility results should also be taken into consideration, if available, when evaluating GMP compliance.

4.5 The sterility assurance program should include, at least, the identification and monitoring of the critical process parameters, such as robust steriliser cycle development and validation, bioburden control, environmental monitoring program, product segregation plan, equipment, services and

facility design and qualification program, change control program, personnel training, and incorporate a quality risk management approach.

4.6 Risk assessment is an essential requirement for parametric release and should focus on mitigating the factors which increase the risk of failure to achieve 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. If an existing product or process is being considered, the risk assessment should include historical data evaluation.

4.7 Personnel qualified and experienced in sterility assurance, including engineers and microbiologists, should be present at the site of production and sterilisation. Qualification, experience, competency and training of all personnel involved in parametric release should be documented.

4.8 The product and its packaging should be designed for sterilisation and maintaining sterility over the shelf life of the product.

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.

4.10 A product segregation plan should be available to reduce the risk of mix-up between processed and non- processed products, and sterilised products and products awaiting sterilisation.

4.11 A pre-sterilisation product bio-burden monitoring program should be developed to support parametric release. Sampling and frequency of monitoring, depending on the sterilisation cycle design approach used, must be defined and implemented. The sampling locations of filled units before sterilisation 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 sterilising process. Due consideration should also be given to significance of the presence of endotoxin-producing species.

4.12 The design of the manufacturing environment and process should ensure that product bio-burden is effectively controlled by the following, as a minimum:

- Equipment and facility design to allow effective cleaning, disinfection and sanitisation;
- Availability of detailed and effective procedures for cleaning, disinfection and sanitisation;
- Definition of process and holding time limits for bulk fluid and filled containers;
- Use of microbial retentive filters where possible;
- Availability of personnel hygiene, garments and operating practices and procedures;
- Definition of microbiological specifications for raw materials and intermediates.

4.13 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving the chemical starting materials, product fluid filtration, and sterilisation should be defined in order to minimise the development of endotoxins (if applicable) and bio-burden.

Sterilisation Process

4.14 Only fully validated terminal sterilisation processes by moist heat, dry heat and ionising radiation can be considered for parametric release.

4.15 Qualification and validation are critical activities to assure that the sterilisation system design is suitable for the process and that the sterilisation equipment can consistently meet cycle operational parameters and that the monitoring devices provide verification of the sterilisation process. With the exception of gamma irradiation, microbiological performance qualification is recommended for validation of parametric release.

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.

4.17 Use of an appropriate sterilisation monitoring device is a critical requirement for a parametric release program and should be used for the sterilisation of every batch. The standards used to calibrate process measurement instruments should be specified and the calibration should be traceable to national or international standards.

4.18 Critical operational parameters should be established and defined. The operating ranges are developed based on sterilisation process, process capability, calibration tolerance limits and parameter criticality.

4.19 Routine monitoring of the steriliser should demonstrate that the validated conditions necessary to achieve the specified process and Sterility Assurance Level are achieved in each cycle. Critical parameters should routinely be monitored especially during the sterilisation phase.

4.20 The control strategy procedures should be clear that failure to meet a critical operational parameter should result in rejection of the load.

4.21 The cooling phase of a steriliser cycle, where applicable should not put the products at risk of microbiological contamination.

4.22 The sterilisation record should include all the critical process parameters. The sterilisation 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.

4.23 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.

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.

Parametric release

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

Process analytical technology (PAT)

A system for designing, analysing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

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)