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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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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,

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

52

53 3.4 In accordance with the principles described in EudraLex, Volume 4, Part I Chapter 1, Part II
54 Chapter 13 and Annex 15, the change control program is an important part of the real time release
55 testing approach. Any change that could potentially impact product manufacturing and testing, or
56 the validated status of facilities, systems, equipment, analytical methods or processes, should be
57 assessed for risk to product quality and impact on reproducibility of the manufacturing process. Any
58 change should be justified by the sound application of quality risk management principles, and fully
59 documented. After change implementation, an evaluation should be undertaken to demonstrate that
60 there are no unintended or deleterious impact on product quality.

61

62 3.5 A control strategy should be designed not only to monitor the process, but also to maintain a
63 state of control and ensure that a product of the required quality will be consistently produced. The
64 control strategy should describe and justify the selected in-process controls, material attributes and
65 process parameters which require to be routinely monitored and should be based on product,
66 formulation and process understanding. The control strategy is dynamic and may change throughout
67 the lifecycle of the product requiring the use of a quality risk management approach and of
68 knowledge management. The control strategy should also describe the sampling plan and
69 acceptance/rejection criteria.

70

71 3.6 Personnel should be given specific training on RTRT technologies, principles and procedures.
72 Key personnel should demonstrate adequate experience, product and process knowledge and
73 understanding. Successful implementation of RTRT requires input from a cross-functional/multi-
74 disciplinary team with relevant experience on specific topics, such as engineering, analytics,
75 chemometric modeling or statistics.

76

77 3.7 Important parts of the RTRT strategy are validation and qualification policy, with particular
78 reference to advanced analytical methods. Particular attention should be focused on the
79 qualification, validation and management of in-line and on-line analytical methods, where the
80 sampling probe is placed within the manufacturing equipment.

81

82 3.8 Any deviation or process failure should be thoroughly investigated and any adverse trending
83 indicating a change in the state of control should be followed up appropriately.

84

85 3.9 Continuous learning through data collection and analysis over the life cycle of a product is
86 important and should be part of the PQS. With advances in technology, certain data trends, intrinsic
87 to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate the
88 data, in consultation if appropriate, with the regulatory authorities, to determine how or if such
89 trends indicate opportunities to improve quality and/or consistency.

90

91 3.10 When RTRT has been approved, this approach should be routinely used for batch release. In
92 the event that the results from RTRT fail or are trending toward failure, a RTRT approach may not
93 be substituted by end-product testing. Any failure should be thoroughly investigated and considered
94 in the batch release decision depending on the results of these investigations, and must comply with

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

97
98 3.11 Attributes (e.g. uniformity of content) that are indirectly controlled by approved RTRT should
99 still appear in the Certificate of Analysis for batches. The approved method for end-product testing
100 should be mentioned and the results given as “Complies if tested” with a footnote: “Controlled by
101 approved Real Time Release Testing”.

102 **4. Parametric release and sterilization**

103
104
105 4.1 This section provides guidance on parametric release which is defined as the release of a batch
106 of terminally sterilised product based on a review of critical process control parameters rather than
107 requiring an end-product testing for sterility.

108
109 4.2 An end-product test for sterility is limited in its ability to detect contamination as it utilises only
110 a small number of samples in relation to the overall batch size, and secondly, culture media may
111 only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for
112 sterility only provides an opportunity to detect major failures in the sterility assurance system (i.e. a
113 failure that results in contamination of a large number of product units and/or that result in
114 contamination by the specific microorganisms whose growth is supported by the prescribed media).
115 In contrast, data derived from in-process controls (e.g. pre-sterilization product bioburden or
116 environmental monitoring) and by monitoring relevant sterilization parameters can provide more
117 accurate and relevant information to support sterility assurance of the product.

118
119 4.3 Parametric release can only be applied to products sterilised in their final container using either
120 moist heat, dry heat or ionising radiation (dosimetric release), according to European
121 Pharmacopoeial requirements.

122
123 4.4 To utilise this approach, the manufacturer should have a history of acceptable GMP compliance
124 and a robust sterility assurance program in place to demonstrate consistent process control and
125 process understanding.

126
127 4.5 The sterility assurance program should be documented and include, at least, the identification
128 and monitoring of the critical process parameters, sterilizer cycle development and validation,
129 container/packaging integrity validation, bioburden control, environmental monitoring program,
130 product segregation plan, equipment, services and facility design and qualification program,
131 maintenance and calibration program, change control program, personnel training, and incorporate
132 a quality risk management approach.

133
134 4.6 Risk management is an essential requirement for parametric release and should focus on
135 mitigating the factors which increase the risk of failure to achieve and maintain sterility in each unit
136 of every batch. If a new product or process is being considered for parametric release, then a risk
137 assessment should be conducted during process development including an evaluation of production
138 data from existing products if applicable. If an existing product or process is being considered, the
139 risk assessment should include an evaluation of any historical data generated.

141 4.7 Personnel involved in the parametric release process should have experience in the following
142 areas: microbiology, sterility assurance, engineering, production and sterilization. The
143 qualifications, experience, competency and training of all personnel involved in parametric release
144 should be documented.

145
146 4.8 Any proposed change which may impact on sterility assurance should be recorded in the change
147 control system and reviewed by appropriate personnel who are qualified and experienced in sterility
148 assurance.

149
150 4.9 A pre-sterilization bio-burden monitoring program for the product and components should be
151 developed to support parametric release. The bioburden should be performed for each batch. The
152 sampling locations of filled units before sterilization should be based on a worst-case scenario and
153 be representative of the batch. Any organisms found during bioburden testing should be identified
154 to confirm that they are not spore forming which may be more resistant to the sterilizing process.

155
156 4.10 Product bio-burden should be minimized by appropriate design of the manufacturing
157 environment and the process by:

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

165
166 4.11 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving
167 the starting materials, product fluid filtration, and sterilization should be defined in order to
168 minimise the development of bioburden and an increase in endotoxins (if applicable).

169 **Sterilization Process**

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171
172 4.12 Qualification and validation are critical activities to assure that sterilization equipment can
173 consistently meet cycle operational parameters and that the monitoring devices provide verification
174 of the sterilization process.

175
176 4.13 Periodic requalification of equipment and revalidation of processes should be planned and
177 justified in accordance with the requirements of Annexes 1 and 15.

178
179 4.14 Appropriate measurement of critical process parameters during sterilization is a critical
180 requirement in a parametric release program. The standards used for process measuring devices
181 should be specified and the calibration should be traceable to national or international standards.

182
183 4.15 Critical process parameters should be established, defined and undergo periodic re-evaluation.
184 The operating ranges should be developed based on sterilization process, process capability,
185 calibration tolerance limits and parameter criticality.

186

187 4.16 Routine monitoring of the sterilizer should demonstrate that the validated conditions necessary
188 to achieve the specified process is achieved in each cycle. Critical processes should be specifically
189 monitored during the sterilization phase.

190
191 4.17 The sterilization record should include all the critical process parameters. The sterilization
192 records should be checked for compliance to specification by at least two independent systems.
193 These systems may consist of two people or a validated computer system plus a person.

194
195 4.18 Once parametric release has been approved by the regulatory authorities, decisions for release
196 or rejection of a batch should be based on the approved specifications and the review of critical
197 process control data. Routine checks of the sterilizer, changes, deviations, unplanned and routine
198 planned maintenance activities should be recorded, assessed and approved before releasing the
199 products to the market. Non-compliance with the specification for parametric release cannot be
200 overruled by a finished product passing the test for sterility.
201

202 **5. Glossary**

203

204 **Control strategy**

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

210

211 **Critical Process Parameters:**

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

215

216 **Critical Quality Attributes**

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

219

220 **Parametric release**

221 One form of RTRT. Parametric release for terminally sterilised product is based on the review of
222 documentation on process monitoring (e.g. temperature, pressure, time for terminal sterilization)
223 rather than the testing of a sample for a specific attribute (ICH Q8 Q&A). (Together with
224 compliance with specific GMP requirements related to parametric release this provides the desired
225 assurance of the quality of the product.) (EMA guideline on Real-Time Release Testing)

226

227 **Real time release testing**

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

231

232 **State of Control**

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