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Medicinal Products – Quality, Safety and Efficacy

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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

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,

- 48 iv. a personnel training program,
- 49 v. an equipment and facility design and qualification program,
- 50 vi. a deviation/CAPAs system,
- 51 vii. a process development and validation program,
- 52 viii. a contingency procedure in case of a process sensor/equipment failure,
- 53 ix. a periodic review/assessment program to measure effectiveness of the RTRT plan for
- 54 continued assurance of product quality, that includes a monitoring program over the
- 55 product's lifecycle for critical material attributes and process parameters.
- 56

57 3.4 The risk assessment should identify the critical quality attributes and critical process parameters
58 that should be part of real time release plan. If a new product or process is being considered for real
59 time release, then a risk assessment should be conducted during process development, while for an
60 existing product or process, the risk assessment should include historical data evaluation.

61
62 3.5 In accordance with the principles described in Chapter 1 and Annex 15, the change control
63 program is an important part of the real time release plan. All the changes that could potentially
64 impact product manufacturing and testing, or the validated status of facilities, systems, equipment
65 or processes, should be assessed for risk to product quality, justified by sound application of quality
66 risk management principles, and fully documented. After a change implementation, an evaluation
67 should be undertaken to demonstrate that it will not compromise the desired quality. A proactive
68 approach should be facilitated.

69
70 3.6 A control strategy should be designed not only to monitor the process, but also to maintain a
71 state of control and ensure that a product of required quality will be consistently produced. The
72 control strategy should describe and justify the selected in-process controls, material attributes and
73 process parameters to be routinely monitored and should be based on product, formulation and
74 process understanding. The control strategy is dynamic and may change throughout the lifecycle of
75 the product requiring the use of a quality risk management approach and of knowledge
76 management. The control strategy should also describe the sampling plan, acceptance/rejection
77 criteria, and include Operating Characteristic curve or the Acceptable Quality Level (AQL) and
78 Unacceptable Quality Level (UQL) associated with the plan. The sampling plan should ensure the
79 sample is representative and be designed based on the prior knowledge of the product and the risk
80 assessment for sampling locations, sampling frequency and sample size. Statistical methodologies,
81 such as established consensus standards, should be considered to carry out a risk-based sampling
82 plan that accounts for the underlying distribution of data.

83
84 3.7 Personnel should be given specific training on the RTRT technologies, principles and
85 procedures. Key personnel should demonstrate adequate experience and product and process
86 knowledge and understanding. Successful implementation of RTR testing should involve input
87 from a cross-functional/multi-disciplinary team with experience on specific topics, such as
88 statistical process control and statistical quality control.

89
90 3.8 Important parts of the RTRT plan are the facilities, systems, and equipment qualification and the
91 analytical method validation, with particular reference to advanced methods, such as rapid
92 microbiological methods, and spectroscopy techniques where the sample is evaluated by
93 chemometrics and comparison with a reference spectral library. In particular, attention should be
94 paid to the qualification, validation and management of in-line and on-line analytical methods,

95 where the sampling probe is placed within the reactor and may not be subject to traditional cleaning
96 and validation procedures.

97 These should be qualified and validated in accordance with Annex 15 of the GMP Guide.
98

99 3.9 Any deviation or process failure should be thoroughly investigated and adverse trending should
100 be followed up appropriately as indicated in Chapter 1 of the GMP Guide. A contingency procedure
101 in case of process sensor/equipment failure should be available.
102

103 3.10 Continual learning through data collection and analysis over the life cycle of a product is
104 important and should be designed as part of the quality system for implementing RTRT. With the
105 use of new measurement tools, certain data trends, intrinsic to a currently acceptable process, may
106 be observed. Manufacturers should scientifically evaluate these data to determine how or if such
107 trends could show potential quality decreases or outliers.
108

109 3.11 It is not acceptable to perform an actual test on a product (active substance or finished product)
110 motivated by an undesired or unacceptable result as determined by the approved RTRT approach.
111 End testing for release purpose can be acceptable if RTRT information elements are not available,
112 for example due to analytical equipment failure (see 3.3)
113

114 **4. Parametric Release** 115

116 4.1 This section provides guidance on parametric release which is defined as the release of a batch
117 of terminally sterilised product based on a review of critical process control data rather than
118 requiring a finished product test for sterility.
119

120 4.2 A finished product test for sterility is limited in its ability to detect contamination as: finished
121 product tests for sterility utilise only a small number of samples in relation to the overall batch size,
122 and secondly, culture media may only stimulate growth of some, but not all, microorganisms.
123 Therefore, a finished product test for sterility only provides an opportunity to detect major failures
124 of the sterility assurance system (i.e. a failure that results in contamination of a large number of
125 product units and/or that result in contamination by the specific microorganisms whose growth is
126 supported by the prescribed media). In contrast, data derived from in-process controls (e.g.
127 bioburden or environmental monitoring) and by monitoring relevant sterilisation parameters can
128 provide more accurate information regarding the sterility assurance system.
129

130 4.3 Parametric release can only be applied to products sterilised in their final container using steam,
131 dry heat and ionising radiation, according to Pharmacopoeial requirements.
132

133 4.4 To utilise this approach, the manufacturer should have a history of acceptable GMP compliance
134 and a robust sterility assurance program in place to demonstrate consistent process control and
135 process understanding. Historical test for sterility results should also be taken into consideration, if
136 available, when evaluating GMP compliance.
137

138 4.5 The sterility assurance program should include, at least, the identification and monitoring of the
139 critical process parameters, such as robust steriliser cycle development and validation, bioburden
140 control, environmental monitoring program, product segregation plan, equipment, services and

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

143

144 4.6 Risk assessment is an essential requirement for parametric release and should focus on
145 mitigating the factors which increase the risk of failure to achieve sterility in each unit of every
146 batch. If a new product or process is being considered for parametric release, then a risk assessment
147 should be conducted during process development. If an existing product or process is being
148 considered, the risk assessment should include historical data evaluation.

149

150 4.7 Personnel qualified and experienced in sterility assurance, including engineers and
151 microbiologists, should be present at the site of production and sterilisation. Qualification,
152 experience, competency and training of all personnel involved in parametric release should be
153 documented.

154

155 4.8 The product and its packaging should be designed for sterilisation and maintaining sterility over
156 the shelf life of the product.

157

158 4.9 Any proposed change which may impact on sterility assurance should be recorded in the change
159 control system and reviewed by appropriate personnel in accordance with the requirements of
160 Chapter 1 and Annex 15 of the GMP Guide.

161

162 4.10 A product segregation plan should be available to reduce the risk of mix-up between processed
163 and non- processed products, and sterilised products and products awaiting sterilisation.

164

165 4.11 A pre-sterilisation product bio-burden monitoring program should be developed to support
166 parametric release. Sampling and frequency of monitoring, depending on the sterilisation cycle
167 design approach used, must be defined and implemented. The sampling locations of filled units
168 before sterilisation should be based on a worst-case scenario and be representative of the batch.
169 Any organisms found during bioburden testing should be identified to confirm that they are not
170 spore forming which may be more resistant to the sterilising process. Due consideration should also
171 be given to significance of the presence of endotoxin-producing species.

172

173 4.12 The design of the manufacturing environment and process should ensure that product bio-
174 burden is effectively controlled by the following, as a minimum:

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

181

182 4.13 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving
183 the chemical starting materials, product fluid filtration, and sterilisation should be defined in order
184 to minimise the development of endotoxins (if applicable) and bio-burden.

185

186

187

188 **Sterilisation Process**

189

190 4.14 Only fully validated terminal sterilisation processes by moist heat, dry heat and ionising
191 radiation can be considered for parametric release.

192

193 4.15 Qualification and validation are critical activities to assure that the sterilisation system design
194 is suitable for the process and that the sterilisation equipment can consistently meet cycle
195 operational parameters and that the monitoring devices provide verification of the sterilisation
196 process. With the exception of gamma irradiation, microbiological performance qualification is
197 recommended for validation of parametric release.

198

199 4.16 Periodic requalification of equipment and revalidation of processes should be conducted in
200 accordance with the requirements of Annex 15 of the GMP Guide.

201

202 4.17 Use of an appropriate sterilisation monitoring device is a critical requirement for a parametric
203 release program and should be used for the sterilisation of every batch. The standards used to
204 calibrate process measurement instruments should be specified and the calibration should be
205 traceable to national or international standards.

206

207 4.18 Critical operational parameters should be established and defined. The operating ranges are
208 developed based on sterilisation process, process capability, calibration tolerance limits and
209 parameter criticality.

210

211 4.19 Routine monitoring of the steriliser should demonstrate that the validated conditions necessary
212 to achieve the specified process and Sterility Assurance Level are achieved in each cycle. Critical
213 parameters should routinely be monitored especially during the sterilisation phase.

214

215 4.20 The control strategy procedures should be clear that failure to meet a critical operational
216 parameter should result in rejection of the load.

217

218 4.21 The cooling phase of a steriliser cycle, where applicable should not put the products at risk of
219 microbiological contamination.

220

221 4.22 The sterilisation record should include all the critical process parameters. The sterilisation
222 records should be checked for compliance to specification by at least two independent systems.
223 These systems may consist of two people or a validated computer system plus a person.

224

225 4.23 Once parametric release has been approved by the regulatory authorities, decisions for release
226 or rejection of a batch should be based on the approved specifications and the review of critical
227 process control data. Routine checks, changes, unplanned and routine planned maintenance
228 activities should be recorded, assessed and approved before releasing the products to the market.
229 Non-compliance with the specification for parametric release cannot be overruled by a pass of a
230 finished product test for sterility.

231

232 **5. Glossary**

233

234 **Control strategy**

235

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

241

242 **Parametric release**

243

244 One form of RTRT. Parametric release is based on the review of documentation on process
245 monitoring (e.g. temperature, pressure, time for terminal moist heat sterilisation) rather than the
246 testing of a sample for a specific attribute (ICH Q8 Q&A). (Together with compliance with specific
247 GMP requirements related to parametric release this provides the desired assurance of the quality of
248 the product.) (EMA guideline on Real-Time Release Testing)

249

250 **Process analytical technology (PAT)**

251

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

255

256

257 **Real time release testing**

258

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

262

263 **State of Control**

264

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