



Consultation document

Commission Implementing Act on Principles and guidelines on good manufacturing practices for medicinal products for human use, pursuant to the first paragraph of Article 47 of Directive 2001/83/EC

The sole purpose of this consultation is to collect views, relevant evidence and information from stakeholders to help the European Commission develop its thinking in this area.

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

Table of Contents

1. INTRODUCTION	2
2. PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS FOR HUMAN USE	2
2.1. Inspections	3
2.2. Conformity with good manufacturing practice	3
2.3. Compliance with marketing authorisation.....	3
2.4. Pharmaceutical quality system	3
2.5. Personnel	4
2.6. Premises and equipment	4
2.7. Documentation	4
2.8. Production.....	5
2.9. Quality control.....	5
2.10. Work contracted out	6
2.11. Complaints and product recall.....	6
2.12. Self-inspection.....	6
2.13. Advanced therapy medicinal products	6

1 **1. INTRODUCTION**

2 Directive 2001/83/EC of the European Parliament and of the Council of 6 November
3 2001 on the Community code relating to medicinal products for human use¹ provides in
4 1st paragraph of Article 47 an obligation for the Commission to adopt principles and
5 guidelines of good manufacturing practice for medicinal products for human use in the
6 form of a Directive.

7 This delegation is the legal basis for Commission Directive 2003/94/EC of 8 October
8 2003 laying down the principles and guidelines of good manufacturing practice in respect
9 of medicinal products for human use and investigational medicinal products for human
10 use².

11 However, Regulation (EU) No 536/2014 of the European Parliament and of the Council
12 on clinical trials on medicinal products for human use, and repealing Directive
13 2001/20/EC³ requires that the Commission adopt delegated acts to specify the principles
14 and guidelines of good manufacturing practice and the detailed arrangements for
15 inspection for ensuring the quality of investigational medicinal products.

16 It is therefore necessary that Directive 2003/94/EC is repealed and replaced by a
17 Delegated Act on principles and guidelines of good manufacturing practice for
18 investigational medicinal products with its legal basis as Article 63(1) of Regulation
19 (EU) No 536/2014 and a new Implementing Directive on principles and guidelines of
20 good manufacturing practice for medicinal products for human use with 1st paragraph of
21 Article 47 of Directive 2001/83/EC as its legal basis.

22 With this public consultation, the Directorate-General for Health and Food Safety seeks
23 the view of stakeholders regarding the content of a new Implementing Directive on
24 principles and guidelines of good manufacturing practice for medicinal products for
25 human use.

26 **2. PRINCIPLES AND GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR**
27 **MEDICINAL PRODUCTS FOR HUMAN USE**

28 Manufacturers have to comply with the principles and guidelines of good manufacturing
29 practice for medicinal products for human use. Compliance with good manufacturing
30 practice for medicinal products for human use is instrumental in ensuring the quality of
31 the products.

32 Currently, Directive 2003/94/EC provides the principles and guidelines for
33 manufacturing practice for medicinal products for human use.

34 As good manufacturing practice for medicinal products for human use already exists and
35 is generally well-functioning, there is no need to reinvent the wheel and therefore, this
36 consultation document carries over the majority of the principles and guidance set out in
37 Directive 2003/94/EC relating to medicinal products for human use.

¹ OJ L 311, 28.11.2001, p. 67.

² OJ L 262, 14.10.2003, p. 22.

³ OJ L 158, 27.5.2014, p. 1.

38 However, a new provision is introduced with regard to adaptation of good manufacturing
39 practice for advanced therapy medicinal products.

40 **2.1. Inspections**

41 By means of the repeated inspections referred to in Article 111(1a), the Member
42 States shall ensure that manufacturers respect the principles and guidelines of good
43 manufacturing practice laid down by the new Implementing Directive concerned by
44 this consultation.

45 Member States shall also take into account the compilation, published by the
46 Commission, of Union procedures in inspections and exchange of information.

47 For the interpretation of the principles and guidelines of good manufacturing
48 practice, manufacturers and the competent authorities shall take into account the
49 detailed guidelines referred to in the second paragraph of Article 47 of Directive
50 2001/83/EC, published by the Commission in the EudraLex, Volume 4.

51 **2.2. Conformity with good manufacturing practice**

52 The manufacturer shall ensure that the manufacturing operations are carried out in
53 accordance with good manufacturing practice and with the manufacturing
54 authorisation. This provision shall also apply to medicinal products intended only
55 for export.

56 For medicinal products imported from third countries, the importer shall ensure that
57 the products have been manufactured in accordance with standards which are at
58 least equivalent to the good manufacturing practice standards laid down by the
59 Union.

60 In addition, an importer of medicinal products shall ensure that such products have
61 been manufactured by manufacturers duly authorised to do so.

62 **2.3. Compliance with marketing authorisation**

63 The manufacturer shall ensure that all manufacturing operations for medicinal
64 products subject to a marketing authorisation are carried out in accordance with the
65 information provided in the application for marketing authorisation as granted by
66 the competent authorities.

67 The manufacturer shall regularly review his manufacturing methods in light of
68 scientific and technical progress.

69 If a variation to the marketing authorisation dossier is necessary, the application for
70 modification shall be submitted to the competent authorities.

71 **2.4. Pharmaceutical quality system**

72 The manufacturer shall establish, implement and maintain an effective
73 pharmaceutical quality system, involving the active participation of the management
74 and personnel of the different departments.

75 **2.5. Personnel**

76 At each manufacturing site, the manufacturer shall have a sufficient number of
77 competent and appropriately qualified personnel at his disposal to achieve the
78 objective of the pharmaceutical quality system.

79 The duties of the managerial and supervisory staff, including the qualified persons,
80 responsible for implementing and operating good manufacturing practice, shall be
81 defined in job descriptions. Their hierarchical relationships shall be defined in an
82 organisation chart. Organisation charts and job descriptions shall be approved in
83 accordance with the manufacturer's internal procedures.

84 The managerial and supervisory staff shall be given sufficient authority to discharge
85 their responsibility correctly.

86 The personnel shall receive initial and on-going training, the effectiveness of which
87 shall be verified, covering in particular the theory and application of the concept of
88 quality assurance and good manufacturing practice.

89 Hygiene programmes adapted to the activities to be carried out shall be established
90 and observed. These programmes shall, in particular, include procedures relating to
91 health, hygiene practice and clothing of personnel.

92 **2.6. Premises and equipment**

93 Premises and manufacturing equipment shall be located, designed, constructed,
94 adapted and maintained to suit the intended operations.

95 Premises and manufacturing equipment shall be laid out, designed and operated in
96 such a way as to minimise the risk of error and to permit effective cleaning and
97 maintenance in order to avoid contamination, cross contamination and, in general,
98 any adverse effect on the quality of the product.

99 Premises and equipment to be used for manufacturing operations, which are critical
100 to the quality of the products, shall be subjected to appropriate qualification and
101 validation.

102 **2.7. Documentation**

103 The manufacturer shall establish and maintain a documentation system based upon
104 specifications, manufacturing formulae and processing and packaging instructions,
105 procedures and records covering the various manufacturing operations performed.
106 Documents shall be clear, free from error and kept up to date. Pre-established
107 procedures for general manufacturing operations and conditions shall be kept
108 available, together with specific documents for the manufacture of each batch. That
109 set of documents shall enable the history of the manufacture of each batch.

110 For a medicinal product, the batch documentation shall be retained for at least one
111 year after the expiry date of the batches to which it relates or at least five years after
112 the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is
113 the longer period.

114 When electronic, photographic or other data processing systems are used instead of
115 written documents, the manufacturer shall first validate the systems by showing that

116 the data will be appropriately stored during the anticipated period of storage. Data
117 stored by those systems shall be made readily available in legible form and shall be
118 provided to the competent authorities at their request. The electronically stored data
119 shall be protected, by methods such as duplication or back-up and transfer to
120 another storage system, against loss or damage or data, and audit trails shall be
121 maintained.

122 **2.8. Production**

123 The different production operations shall be carried out in accordance with pre-
124 established instructions and procedures and in accordance with good manufacturing
125 practice. Adequate and sufficient resources shall be made available for the in-
126 process controls. All process deviations and product defects shall be documented
127 and thoroughly investigated.

128 Appropriate technical and organisational measures shall be taken to avoid cross
129 contamination and mix-ups.

130 Any new manufacturing or important modification of a manufacturing process of a
131 medicinal product shall be validated. Critical phases of manufacturing processes
132 shall be regularly re-validated.

133 **2.9. Quality control**

134 The manufacturer shall establish and maintain a quality control system placed under
135 the authority of a person who has the requisite qualifications and is independent of
136 production.

137 That person shall have at his disposal, or shall have access to, one or more quality
138 control laboratories appropriately staffed and equipped to carry out the necessary
139 examination and testing of starting materials and packaging materials and the testing
140 of intermediate and finished products.

141 For medicinal products, including those imported from third countries, contract
142 laboratories may be used if authorised by written contract, see below in section 2.10,
143 and point (b) of Article 20 of Directive 2001/83/EC.

144 During the final control of the finished product before its release for sale or
145 distribution, the quality control system shall take into account, in addition to
146 analytical results, essential information such as the production conditions, the results
147 of in-process controls, the examination of the manufacturing documents and the
148 conformity of the product to its specifications, including the final finished pack.

149 Samples of each batch of finished medicinal product shall be retained for at least
150 one year after the expiry date.

151 Unless a longer period is required under the law of the Member State of
152 manufacture, samples of starting materials, other than solvents, gases or water, used
153 in the manufacturing process shall be retained for at least two years after the release
154 of the product. That period may be shortened if the period of stability of the
155 material, as indicated in the relevant specification, is shorter. All those samples shall
156 be maintained at the disposal of the competent authorities.

157 Other conditions may be defined, by agreement with the competent authority, for
158 the sampling and retaining of starting materials and certain products manufactured
159 individually or in small quantities, or when their storage could raise special
160 problems.

161 **2.10. Work contracted out**

162 Any manufacturing operation or operation linked thereto which is carried out under
163 contract shall be the subject of a written contract.

164 The contract shall clearly define the responsibilities of each party and shall define,
165 in particular, the observance of good manufacturing practice to be followed by the
166 contract acceptor and the manner in which the qualified person responsible for
167 certifying each batch is to discharge his responsibilities.

168 The contract acceptor shall not subcontract any of the work entrusted to him under
169 the contract without written authorisation from the contract-giver.

170 The contract acceptor shall comply with the principles and guidelines of good
171 manufacturing practice and shall submit to inspections carried out by competent
172 authorities pursuant to Article 111 of Directive 2001/83/EC.

173 **2.11. Complaints and product recall**

174 The manufacturer shall implement a system for recording and reviewing complaints
175 together with an effective system for recalling, promptly and at any time, medicinal
176 products in the distribution network. Any complaint concerning a defect shall be
177 recorded and investigated by the manufacturer. The manufacturer shall inform the
178 competent authority of any defect that could result in a recall or an abnormal
179 restriction on supply and, in so far as possible, indicate the countries of destination.

180 Any recall shall be made in accordance with the requirements referred to in Article
181 123 of Directive 2001/83/EC.

182 **2.12. Self-inspection**

183 The manufacturer shall conduct repeated self-inspections as part of the quality
184 assurance system in order to monitor the implementation and respect of good
185 manufacturing practice and to propose any necessary corrective measures. Records
186 shall be maintained of such self-inspections and any corrective actions subsequently
187 taken.

188 **2.13. Advanced therapy medicinal products**

189 The requirements provided for in the Directive shall be adapted to the specific
190 characteristics of advanced therapy medicinal products in accordance with a risk-
191 based approach.

192 The adaptation to the specific characteristics of those products will be elaborated in
193 a Commission guideline. On 23 July 2015, a targeted stakeholder consultation on
194 the development of good manufacturing practice for advanced therapy medicinal
195 products pursuant to Article 5 of Regulation 1394/2007 was launched with a
196 deadline for comments on 12 November 2015; the consultation can be found here:

197 [http://ec.europa.eu/health/human-use/advanced-](http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm)
198 [therapies/developments/index_en.htm](http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm).