



**EUROPEAN COMMISSION**  
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems and products  
**Medicinal products – quality, safety and efficacy**

Consultation document

**Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014**

*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 with a view to preparing the required guidelines.*

*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 TO THE PUBLIC CONSULTATION.....	3
2.	GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE .....	4
2.1.	Introduction .....	4
2.2.	Scope .....	5
2.3.	Pharmaceutical quality system .....	5
2.4.	Personnel .....	6
2.5.	Premises and equipment .....	6
2.6.	Documentation .....	7
2.6.1.	Specification and instructions.....	7
2.6.2.	Order.....	7
2.6.3.	Product specification file .....	8
2.6.4.	Manufacturing formulae and processing instructions .....	8
2.6.5.	Packaging instructions.....	9
2.6.6.	Batch records .....	9
2.7.	Production.....	9
2.7.1.	Packaging materials.....	9
2.7.2.	Manufacturing operations.....	9
2.7.3.	Blinding operations .....	10
2.7.4.	Packaging .....	10
2.7.5.	Labelling.....	11
2.8.	Quality control.....	11
2.9.	Release of batches .....	13
2.10.	Outsourcing .....	14
2.11.	Complaints.....	14
2.12.	Recalls and returns .....	15
2.12.1.	Recalls .....	15
2.12.2.	Returns .....	15
2.12.3.	Destruction .....	15
2.13.	Glossary of terms.....	16

## 1 1. INTRODUCTION TO THE PUBLIC CONSULTATION

2 Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical  
3 trials on medicinal products for human use, and repealing Directive 2001/20/EC<sup>1</sup> requires  
4 in the second subparagraph of Article 63(1) that the Commission adopts and publishes  
5 detailed guidelines of good manufacturing practice (GMP) for investigational medicinal  
6 products for human use.

7 Such detailed guidelines are necessary to complement the high-level principles and  
8 guidelines on good manufacturing practice for investigational medicinal products for  
9 human use to be set out in a Delegated Act pursuant to the first subparagraph of Article  
10 63(1) of Regulation (EU) No 536/2014.

11 Adherence to good manufacturing practice for investigational medicinal products for  
12 human use by manufacturers of such medicinal products is instrumental in ensuring the  
13 quality of the products which in turn will be an element in safeguarding the safety of the  
14 clinical trial subjects and in ensuring the reliability and robustness of the data generated  
15 in the trial.

16 As guidelines on good manufacturing practice for investigational medicinal products for  
17 human use already exists and is generally well-functioning, there is no need to reinvent  
18 the wheel and therefore, this consultation document refers, when relevant, to specific  
19 parts, chapters or annexes of EudraLex, Volume 4<sup>2</sup> or carries over relevant principles of  
20 Annex 13 to EudraLex, Volume 4. Annex 13 will be deleted from EudraLex Volume 4  
21 when the new guidelines become operational.

22 The topics of this consultation document concerning detailed guidelines on good  
23 manufacturing practice for investigational medicinal products for human use should be  
24 read in conjunction with the consultation on the Commission Delegated Act on Principles  
25 and guidelines of good manufacturing practice for investigation medicinal products for  
26 human use and inspection procedures, pursuant to the first subparagraph of Article 63(1)  
27 of Regulation (EU) No 536/2014, as the detailed Commission guideline will complement  
28 that Delegated Act.

29 Furthermore, on 23 July 2015, a targeted stakeholder consultation on the development of  
30 good manufacturing practice for advanced therapy medicinal products pursuant to Article  
31 5 of Regulation 1394/2007 was launched with a deadline for comments on 12 November  
32 2015. That consultation also addresses adaptations relevant to advanced therapy  
33 investigational medicinal products; the consultation can be found here:  
34 [http://ec.europa.eu/health/human-use/advanced-therapies/developments/index\\_en.htm](http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm).

35 With this public consultation on guidelines on good manufacturing practice for  
36 investigational medicinal products for human use, the Directorate-General for Health and  
37 Food Safety seeks the view of stakeholders regarding the content of such guideline as set  
38 out below.

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<sup>1</sup> OJ L 158, 27.5.2014, p.1.

<sup>2</sup> [http://ec.europa.eu/health/documents/eudralex/vol-4/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm)

39 **2. GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR INVESTIGATIONAL**  
40 **MEDICINAL PRODUCTS FOR HUMAN USE**

41 **2.1. Introduction**

42 These guidelines are based on the second subparagraph of Article 63(1) of  
43 Regulation (EU) No 536/2014.

44 These guidelines complement the Delegated Act on principles and guidelines on  
45 good manufacturing practice for investigational medicinal products for human use  
46 referred to in the first subparagraph of Article 63(1) of Regulation (EU) No  
47 536/2014.

48 These guidelines lay down appropriate tools to address specific issues concerning  
49 investigational medicinal products with regard to good manufacturing practice.

50 Article 63(1) of Regulation (EU) No 536/2014 provides that investigational  
51 medicinal products shall be manufactured by applying manufacturing practice which  
52 ensures the quality of such medicinal products in order to safeguard the safety of the  
53 subject and the reliability and robustness of clinical data generated in the clinical  
54 trial ("good manufacturing practice").

55 Good manufacturing practice for investigational medicinal products is set out in the  
56 Delegated Act referred to in the first subparagraph of Article 63(1) of Regulation  
57 (EU) No 536/2014 and in these guidelines. [ The Delegated Act and these guidelines  
58 are developed in parallel.]

59 Furthermore, where applicable, the manufacturers and the competent authorities  
60 should also take into account the detailed guidelines referred to in the second  
61 paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in  
62 the "Guide to good manufacturing practice for medicinal products and for  
63 investigational medicinal products" (EudraLex, Volume 4). Examples of applicable  
64 parts of EudraLex, Volume 4 to investigational medicinal products, not specifically  
65 mentioned in these guidelines, are Part I, Chapters 2, 4 and 6.

66 Procedures need to be flexible to provide for changes as knowledge of the process  
67 increases and appropriate to the stage of development of the product.

68 In clinical trials there may be added risk to the subjects compared to patients treated  
69 with authorised medicinal products. The application of GMP for the manufacture of  
70 investigational medicinal products is intended to ensure that subjects are not placed  
71 at risk, and that the results of clinical trials are unaffected by inadequate quality,  
72 safety or efficacy arising from unsatisfactory manufacture. Equally, it is intended to  
73 ensure that there is consistency between batches of the same investigational  
74 medicinal product used in the same or different clinical trials and that changes  
75 during the development of an investigational medicinal product are adequately  
76 documented and justified.

77 The production of investigational medicinal products involves added complexity in  
78 comparison with authorised medicinal products by virtue of lack of fixed routines,  
79 variety of clinical trial designs and consequent packaging designs. Randomisation  
80 and blinding add to that complexity an increased risk of product cross-  
81 contamination and mix-up. Furthermore, there may be incomplete knowledge of the  
82 potency and toxicity of the product and a lack of full process validation. Moreover,

83 authorised products may be used which have been re-packaged or modified in some  
84 way. These challenges require personnel with a thorough understanding of and  
85 training in the application of GMP to investigational medicinal products. The  
86 increased complexity in manufacturing operations requires a highly effective quality  
87 system.

88 For manufacturers to be able to apply and comply with GMP for investigational  
89 medicinal products, co-operation between manufacturers and sponsors of clinical  
90 trials is required. This co-operation may be described in a technical agreement.

## 91 **2.2. Scope**

92 These guidelines apply to manufacture of investigational medicinal products for  
93 human use. An investigational medicinal product is defined in Article 2(5) of  
94 Regulation (EU) No 536/2014 as a medicinal product which is being tested or used  
95 as a reference, including as a placebo, in a clinical trial, and manufacturing is  
96 defined as total and partial manufacture, as well as the various processes of dividing  
97 up, packaging and labelling (including blinding) in Article 2(24) of said Regulation.

98 Reconstitution is not considered manufacturing when understood as the simple  
99 process of

- 100 • dissolving or dispersing the investigational medicinal product for  
101 administration of the product to a trial subject, or
- 102 • diluting or mixing the investigation medicinal product with some other  
103 substance(s) used as a vehicle for the purpose of administering it to a trial  
104 subject.

105 Reconstitution is not mixing several ingredients, including the active substance,  
106 together to produce the investigational medicinal product.

107 An investigational medicinal product must exist before a process can be defined as  
108 reconstitution.

109 The process of reconstitution has to be undertaken as close as possible to  
110 administration and has to be defined in the clinical trial application/dossier and in  
111 the protocol, or related document, available at the clinical trial site.

112 These guidelines do not apply to the processes referred to in Article 61(5) of  
113 Regulation (EU) No 536/2014. Member States shall make those processes subject to  
114 appropriate and proportionate requirements to ensure subject safety and reliability  
115 and robustness of the data generated in the clinical trial.

116 Though not strictly in the scope of these guidelines, the guidelines do nevertheless  
117 address a few issues concerning auxiliary medicinal products, as defined in Article  
118 2(8) of Regulation (EU) No 536/2014, as manufacturing – fully or partially – of  
119 those products has to take place according to good manufacturing practice or to at  
120 least an equivalent standard according to Article 65 of said Regulation.

## 121 **2.3. Pharmaceutical quality system**

122 The pharmaceutical quality system required of the manufacturer according to the  
123 Delegated Act on GMP for investigational medicinal products pursuant to Article

124 63(1) of Regulation (EU) No 536/2014 and designed, set-up and verified by the  
125 manufacturer should also be described in written procedures taking into account  
126 EudraLex, Volume 4, Part I, Chapter 1 as applicable to investigational medicinal  
127 products.

128 The product specifications and manufacturing instructions may be changed during  
129 development but full control and traceability of the changes should be maintained.  
130 Deviations from any predefined specifications and instructions shall be investigated  
131 and corrective and preventive action (CAPA) measures initiated.

132 The selection, qualification, approval and maintenance of suppliers of starting  
133 materials, together with their purchase and acceptance, should be documented as  
134 part of the pharmaceutical quality system to ensure the integrity of the supply chain  
135 and protect against counterfeit products. The level of supervision should be  
136 proportionate to the risks posed by the individual materials, taking into account their  
137 source, manufacturing process, supply chain complexity and the final use to which  
138 the material is put in the investigational medicinal product. The supporting evidence  
139 for each supplier approval and material approval should be maintained.

#### 140 **2.4. Personnel**

141 All personnel involved with the manufacture, storage or handling of investigational  
142 medicinal products should be appropriately trained in the requirements specific to  
143 these types of product.

144 Even where the number of staff involved in the manufacturing of investigational  
145 medicinal products is small, there should be, for each batch, separate people  
146 responsible for production and quality control.

147 The qualified person has to fulfil the conditions of qualification set out in Article  
148 49(2) and (3) of Directive 2001/83/EC, cf. Article 61(2)(b) of Regulation (EU) No  
149 536/2014.

150 The responsibilities of the qualified person are set out in Article 62 of Regulation  
151 (EU) No 536/2015 and (anticipated) further elaborated in the Delegated Act on  
152 GMP for investigational medicinal products pursuant to Article 63(1) of said  
153 Regulation.

154 The final certifying qualified person should ensure that there are systems in place  
155 that meet the requirements of GMP and should have a broad knowledge of  
156 pharmaceutical development and clinical trial processes.

#### 157 **2.5. Premises and equipment**

158 The toxicity, potency or sensitising potential may not be fully understood for  
159 investigational medicinal products and this reinforces the need to minimise all risks  
160 of cross-contamination. The design of equipment and premises, inspection/test  
161 methods and acceptance limits to be used after cleaning should reflect the nature of  
162 these risks and take account of the quality risk management principles detailed in  
163 EudraLex, Volume 4, Part I, Chapters 3 and 5.

164 Consideration should be given to campaign working, where appropriate. Account  
165 should be taken of the solubility of the product in decisions about the choice of  
166 cleaning solvent.

167 A quality risk management process, which includes a potency and toxicological  
168 evaluation, should be used to assess and control the cross-contamination risks  
169 presented by the investigational medicinal products manufactured. Factors that  
170 should be taken into account include:

- 171 i. facility/equipment design and use;
- 172 ii. personnel and material flow;
- 173 iii. microbiological controls;
- 174 iv. physic-chemical characteristics of the active substance;
- 175 v. process characteristics;
- 176 vi. cleaning processes;
- 177 vii. analytical capabilities relative to the relevant limits established from the  
178 evaluation of the investigational medicinal products.

179 Premises and equipment are expected to be validated in accordance with EudraLex,  
180 Volume 4, Annex 15.

## 181 **2.6. Documentation**

### 182 *2.6.1. Specification and instructions*

183 Specifications for starting materials, immediate packaging materials,  
184 intermediate products, bulk products and finished products, manufacturing  
185 formulae and processing and packing instructions should be as comprehensive  
186 as possible given the current state of knowledge. They should be periodically  
187 re-assessed during development and updated as necessary. Each new version  
188 should take into account the latest data, current technology used, regulatory  
189 and pharmacopoeial developments and should allow traceability to the  
190 previous document. Any changes should be carried out according to a written  
191 procedure which should address any implications for product quality such as  
192 stability and bioequivalence. The approval process for instructions and  
193 changes thereof shall include management personnel at the manufacturing  
194 site.

195 Rationales for changes should be recorded and the consequences of a change  
196 on product quality and on any on-going clinical trials should be investigated  
197 and fully documented.

### 198 *2.6.2. Order*

199 The manufacturer should retain the order for investigational medicinal  
200 products. The order should request the processing and/or packaging of a  
201 certain number of units and/or their distribution and be given by or on behalf  
202 of the sponsor to the manufacturer. It should be in writing, though it may be  
203 transmitted by electronic means, and be precise enough to avoid any  
204 ambiguity. It should be formally authorised by the sponsor or his  
205 representative and refer to the product specification file and the relevant  
206 clinical trial protocol as appropriate.

207                    2.6.3. *Product specification file*

208                    Applicable sections of the product specification file shall be available at the  
209                    start of manufacturing of the first batch of investigational medicinal product  
210                    for a clinical trial.

211                    The product specification file should be continually updated as development  
212                    of the product proceeds, ensuring appropriate traceability to the previous  
213                    versions. It should include or refer to at least the following documents:

- 214                    i.    Specifications and analytical methods for starting materials, packaging  
215                    materials, intermediate product, bulk product and finished product;
- 216                    ii.   Manufacturing methods;
- 217                    iii.  In-process testing and methods;
- 218                    iv.   Approved label copy;
- 219                    v.    Relevant clinical trial authorisations and amendments thereof, clinical  
220                    trial protocol and randomisation codes, as appropriate;
- 221                    vi.   Relevant technical agreements with contract givers and acceptors, as  
222                    appropriate;
- 223                    vii.  Stability data;
- 224                    viii. Reference and retention sample plans;
- 225                    ix.   Storage and transport conditions.

226                    The list of document is neither exhaustive, nor exclusive.

227                    The contents of the product specification file will vary depending on the  
228                    product and the stage of development. The information should form the basis  
229                    for assessment of the suitability of certification and release of a particular  
230                    batch by the qualified person and should therefore be accessible to him or her.

231                    Where different manufacturing steps are carried out at different locations  
232                    under the responsibility of different qualified persons, it is acceptable to  
233                    maintain separate files limited to information of relevance to the activities at  
234                    the respective locations. The documentation of the product specification file,  
235                    including changes, shall be accessible at the manufacturing site.

236                    2.6.4. *Manufacturing formulae and processing instructions*

237                    For every manufacturing operation or supply there should be clear and  
238                    adequate written instructions and written records which are prepared using the  
239                    specific clinical study information detailed in the product specification file.  
240                    Records are particularly important for the preparation of the final version of  
241                    the documents to be used in routine manufacture once the marketing  
242                    authorisation is granted.



243 The information in the product specification file should be used to produce  
244 the detailed written instructions on processing, packaging, quality control  
245 testing, storage, distribution conditions and storage conditions.

#### 246 2.6.5. *Packaging instructions*

247 Investigational medicinal products are normally packed in an individual way  
248 for each subject included in the clinical trial. The number of units to be  
249 packaged should be specified prior to the start of the packaging operations,  
250 including units necessary for carrying out quality control and for any retention  
251 samples to be kept. Sufficient reconciliations should take place to ensure the  
252 correct quantity of each product required has been accounted for at each stage  
253 of processing.

254 Procedures should describe the specification, generation, testing, security,  
255 distribution, handling and retention of any randomisation code used for  
256 packaging investigational medicinal products as well as code-break  
257 mechanism. Appropriated records should be maintained.

#### 258 2.6.6. *Batch records*

259 Batch records should be kept in sufficient detail for the sequence of  
260 operations to be accurately determined. These records should contain any  
261 relevant remarks which justify procedures used and any changes made,  
262 enhance knowledge of the product, develop the manufacturing operations and  
263 document deviations from predefined requirements.

264 Batch manufacturing records should be retained by the manufacturer for the  
265 periods specified in the Delegated Act on GMP for investigational medicinal  
266 products pursuant to the first subparagraph of Article 63(1) of Regulation  
267 (EU) No 536/2014.

268 The sponsor has specific responsibilities for document retention of the clinical  
269 trial master file according to Article 58 of Regulation (EU) No 536/2014 and  
270 is required to retain such documentation for 25 years after the end of the trial.  
271 If the sponsor and the manufacturer are not the same entity, the sponsor has  
272 therefore to make appropriate arrangements with the manufacturer to fulfil his  
273 requirement to retain the clinical trial master file.

## 274 **2.7. Production**

### 275 2.7.1. *Packaging materials*

276 Specifications and quality control checks should include measures to guard  
277 against unintentional unblinding due to changes in appearance between  
278 different batches of packaging materials.

### 279 2.7.2. *Manufacturing operations*

280 During development critical parameters should be identified and in-process  
281 controls primarily used to control the process. Provisional production  
282 parameters and in-process controls may be deduced from prior experience,  
283 including that gained from earlier development work. Careful consideration  
284 by key personnel is called for in order to formulate the necessary instructions

285 and to adapt them continually to the experience gained in production.  
286 Parameters identified and controlled should be justifiable based on knowledge  
287 available at the time.

288 The manufacturing process is not expected to be validated to the extent  
289 necessary for routine production but shall be validated in its entirety in so far  
290 as appropriate, taking into account the stage of product development.

291 To avoid cross-contamination, written cleaning procedures and analytical  
292 methods to verify the cleaning process shall be available.

293 For sterile products, the validation of sterilising processes should be of the  
294 same standards as for authorised medicinal products and take account of the  
295 principles for the manufacture of sterile medicinal products detailed  
296 EudraLex, Volume 4, Annex 1. Likewise, when required, virus  
297 inactivation/removal and removal of other impurities of biological origin  
298 should be demonstrated, to assure the safety of biotechnologically derived  
299 products by following the scientific principles and techniques defined in the  
300 available guidance in this area.

301 Validation of aseptic processes presents special problems where the batch size  
302 is small; in these cases, the number of units filled may be the maximum  
303 number filled in production. If practicable, and otherwise consistent with  
304 simulating the process, a larger number of units should be filled with media to  
305 provide greater confidence in the results obtained. Filling and sealing is often  
306 a manual or semi-automated operation presenting great challenges to sterility  
307 so enhanced attention should be given to operator training and validating the  
308 aseptic technique of individual operators.

309 If a product is modified, data should be available, e.g. stability, comparative  
310 dissolution or bioavailability, to demonstrate that these changes do not  
311 significantly alter the original quality characteristics of the product.

### 312 *2.7.3. Blinding operations*

313 Where products are blinded, systems should be in place to ensure that the  
314 blind is achieved and maintained while allowing for identification of  
315 "blinded" products, when necessary, including batch numbers of the products  
316 before the blinding operation. Rapid identification of product should also be  
317 possible in an emergency.

318 Where products are blinded, the expiry date assigned should be stated at the  
319 expiry of the shortest dated product so that the blinding is maintained.

### 320 *2.7.4. Packaging*

321 During packaging of investigational medicinal products, it may be necessary  
322 to handle different products on the same packaging line at the same time. The  
323 risk of product mix-up must be minimised by using appropriate procedures  
324 and/or specialised equipment as appropriate and relevant staff training.  
325 Documentation must be sufficient to demonstrate that appropriate segregation  
326 has been maintained during any packaging operations.

327 Packaging and labelling of investigational medicinal products are likely to be  
328 more complex and more liable to errors which are also harder to detect than  
329 for authorised medicinal products, particularly when "blinded" products with  
330 similar appearance are used. Precautions against mislabelling such as  
331 reconciliation, line clearance, in-process control checks by appropriately  
332 trained staff should accordingly be intensified.

333 The expiry date stated for the comparator product in its original packaging  
334 might not be applicable to the product where it has been repackaged in a  
335 different container that may not offer equivalent protection. A suitable expiry  
336 date, taking into account the nature of the product, the characteristics of the  
337 container and the storage conditions to which the article may be subjected,  
338 should be determined by or on behalf of the sponsor. Such date should be  
339 justified and must not be later than the expiry date of the original package.  
340 There should be comparability of expiry dating and clinical trial duration.

341 The packaging must ensure that the investigational medicinal product remains  
342 in good condition during transport and storage at intermediate destinations.  
343 Any opening or tampering of the outer packaging during transport should be  
344 readily discernible.

#### 345 2.7.5. *Labelling*

346 Labelling of investigation medicinal products and auxiliary medicinal  
347 products should comply with the requirements of Article 66 and 67 of  
348 Regulation (EU) No 536/2014. A list of information which is to appear on the  
349 labelling is set out in Annex IV to said Regulation.

350 If it becomes necessary to change the expiry date, an additional label should  
351 be affixed to the investigational medicinal product. This additional label  
352 should state the new expiry date and repeat the batch number and/or clinical  
353 trial reference number. It may be superimposed on the old expiry date, but for  
354 quality control reasons, not on the original batch number.

355 The re-labelling operation should be performed by appropriately trained staff  
356 in accordance with GMP principles and specific and standard operating  
357 procedures and should be checked by a second person. This additional  
358 labelling should be properly documented in the batch records. To avoid mix-  
359 up, the additional labelling activity should be carried out in an area which is  
360 partitioned or separated from other activities. A line clearance at the start and  
361 end of activity should be carried out and label reconciliation performed with  
362 100 %.

363 The re-labelling operation can be outsourced only if it is subject to a written  
364 contract.

## 365 **2.8. Quality control**

366 According to the Delegated Act on GMP for investigational medicinal products  
367 pursuant to Article 63(1) of Regulation (EU) No 536/2014 the manufacturer is  
368 required to establish and maintain a quality control system place under the authority  
369 of a person who has the requisite qualifications and is independent of production.

370 As processes may not be standardised or fully validated, testing takes on more  
371 importance in ensuring that each batch meets the approved specification at the time  
372 of testing.

373 Quality control of the investigational medicinal product, including comparator  
374 product, should be performed in accordance with the information submitted  
375 according to Article 25 of Regulation (EU) No 536/2014 as authorised by the  
376 Member State.

377 Verification of the effectiveness of blinding should be performed and recorded.

378 Samples are retained to fulfil two purposes: firstly, to provide a sample for future  
379 analytical testing, and secondly, to provide a specimen of the finished product and  
380 may be used in the investigation of a product quality defect. Samples may therefore  
381 fall into two categories:

- 382 • Reference sample: a sample of a batch of starting material, packaging  
383 material or finished product which is stored for the purpose of being  
384 analysed should the need arise. Where stability permits, reference samples  
385 from critical intermediate stages, e.g. those requiring analytical testing and  
386 release, or intermediates which are transported outside of the manufacturer's  
387 control, should be kept.
- 388 • Retention sample: a sample of a packaged unit from a batch of finished  
389 product for each packaging run or trial period. It is stored for identification  
390 purposes. For example presentation, packaging, labelling, package leaflet,  
391 batch number, expiry date should the need arise.

392 For retention samples it is acceptable to store information related to the final  
393 packaging as written, photographic or electronic records, if such records provide  
394 sufficient information, e.g. examples of packaging, labelling and any accompanying  
395 documentation to permit investigations associated with the use of the product. In  
396 case of electronic records, the system should comply with the requirements of  
397 EudraLex, Volume 4, Annex 11. [Please note, that the public consultation on  
398 principles and guidelines on GMP for investigational medicinal products, pursuant  
399 to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 poses  
400 questions about requirements for retention samples.]

401 Where reference samples and retention samples are presented identically, i.e. as  
402 fully packaged units, the samples may be regarded as interchangeable.

403 Samples are not expected of an investigational medicinal product which is an  
404 unblinded comparator in its original packaging and sourced from the authorised  
405 supply chain in the EU or of a product which holds a marketing authorisation  
406 granted by a national competent authority in the EU or by the European  
407 Commission.

408 The storage location of samples should be defined in a technical agreement between  
409 the sponsor and the manufacturer(s) and should allow timely access by the  
410 competent authorities.

411 Reference samples of finished product should be stored in the EU or in a third  
412 country where appropriate arrangements have been made by the Union with the  
413 exporting country to ensure that the manufacturer of the investigational medicinal

414 product applies standards of good manufacturing practice at least equivalent to those  
415 laid down by the Union. In exceptional circumstances, the reference samples of the  
416 finished product may be stored by the manufacturer in another third country, in  
417 which case this should be justified and documented in a technical agreement  
418 between the sponsor, the importer in the EU and that manufacturer in the third  
419 country.

420 The reference sample should be of sufficient size to perform, on at least two  
421 occasions, all critical quality attribute tests as defined in the investigational  
422 medicinal product dossier accepted by the Member State. Any exception to this  
423 should be justified to, and agreed with, the national competent authority.

## 424 **2.9. Release of batches**

425 Release of investigational medicinal products should not occur until after the  
426 qualified person has certified that the requirements of Article 63 of Regulation (EU)  
427 No 536/2014 and those set out in the Delegated Act on GMP for investigational  
428 medicinal products pursuant to Article 63(1) of said Regulation are met.

429 The duties of the qualified person in relation to investigational medicinal products  
430 are affected by the different circumstances that can arise and are referred to below:

431 i. Product manufactured within EU but not subject to an EU marketing  
432 authorisation: the duties are laid down in Article 62 of Regulation (EU) No  
433 536/2014;

434 ii. Product sourced from the open market within EU in accordance with Article  
435 80(b) of Directive 2001/83/EC and subject to a marketing authorisation  
436 granted by a competent authority in the EU, regardless of manufacturing  
437 origin: the duties are as described above. However, the scope of the  
438 certification can be limited to assuring that the products are in accordance  
439 with the authorisation of the clinical trial and any subsequent processing for  
440 the purpose of blinding, trial-specific packaging and labelling.

441 iii. Product imported directly from a third country: the duties are laid down in  
442 Article 62 of Regulation (EU) No 536/2014. Where investigational  
443 medicinal products are imported from a third country and they are subject to  
444 agreements concluded between the Union and that country, such as a Mutual  
445 Recognition Agreement (MRA), equivalent standards of good manufacturing  
446 practice apply provided any such agreement is relevant to the product in  
447 question. In the absence of a MRA, the qualified person should determine  
448 that equivalent standards of good manufacturing practice apply through  
449 knowledge of the quality system employed at the manufacturer. This  
450 knowledge is normally acquired through audit of the manufacturer's quality  
451 systems. In either case, the qualified person may then certify on the basis of  
452 documentation supplied by the manufacturer in the third country and  
453 document the rationale for certification.

454 Assessment by the qualified person of each batch for certification prior to release  
455 may include as appropriate:

456 i. Batch records, including control reports, in-process test reports and release  
457 reports demonstrating compliance with the product specification file, the

458 order, protocol and randomisation code. These records should include all  
459 deviations or planned changes, and any consequent additional checks and  
460 tests, and should be completed and endorsed by the staff authorised to do so  
461 according to the quality system;

462 ii. Production conditions;

463 iii. Cleaning records;

464 iv. The validation status of facilities, processes and methods;

465 v. Examination of finished packs;

466 vi. The results of any analyses or tests performed after importation, where  
467 relevant;

468 vii. Stability reports;

469 viii. The source and verification of conditions of storage and shipment;

470 ix. Audit reports concerning the quality system of the manufacturer;

471 x. Documents certifying that the manufacturer is authorised to manufacture  
472 investigational medicinal product for export by the appropriate authorities in  
473 the country of export;

474 xi. Regulatory requirements for marketing authorisation, GMP standards  
475 applicable and any official verification of GMP compliance, where relevant;

476 xii. All factors of which the qualified person is aware that are relevant to the  
477 quality of the batch;

478 The relevance of the above elements is affected by the country of origin of the  
479 product, the manufacturer, the status of the product, i.e. with or without a marketing  
480 authorisation granted by competent authorities in the EU or in a third country, and  
481 the phase of development of the product.

482 Where investigational medicinal products are produced and packaged at different  
483 sites under the supervision of different qualified persons, EudraLex, Volume 4,  
484 Annex 16 is applicable.

485 The qualified person is not required to certify re-packaging or re-labelling carried  
486 out pursuant to Article 61(5)(a) of Regulation (EU) No 536/2014.

## 487 **2.10. Outsourcing**

488 Activities which are outsourced by the manufacturer should be defined, agreed and  
489 controlled by written contracts in accordance with the principles detailed in  
490 EudraLex Volume 4, Part I, Chapter 7.

## 491 **2.11. Complaints**

492 There should be written procedures describing the actions to be taken upon receipt  
493 of a complaint at the manufacturing, storage or importation site. All complaints  
494 should be documented and assessed to establish if they represent a potential quality

495 defect or other issue. The procedures should ensure that the sponsor could assess the  
496 complaints to determine if they meet the requirements for serious breach reporting  
497 according to Article 52 of Regulation (EU) No 536/2014.

498 The quality defect investigation should be in accordance with the principles detailed  
499 in EudraLex, Volume 4, Part I, Chapter 8.

500 The conclusions of the investigation should be discussed between the manufacturer  
501 and the sponsor, if different, in a timely manner. This should involve the qualified  
502 person and those responsible for the relevant clinical trial in order to assess any  
503 potential impact on the trial, product development and on subjects.

## 504 **2.12. Recalls and returns**

### 505 *2.12.1. Recalls*

506 Procedures for retrieving investigational medicinal products and documenting  
507 this retrieval should be agreed by the sponsor in collaboration with the  
508 manufacturer, where different. The investigator and the sponsor's  
509 representative need to understand their obligations under the retrieval  
510 procedure. The procedures for retrieval of investigational medicinal products  
511 should be in accordance with the principles detailed in EudraLex, Volume 4,  
512 Part I, Chapter 8.

### 513 *2.12.2. Returns*

514 Returned investigational medicinal products should be clearly identified and  
515 stored in an appropriately controlled, dedicated area. Inventory records of  
516 returned products should be kept.

### 517 *2.12.3. Destruction*

518 The manufacturer should destroy investigational medicinal products only with  
519 prior written authorisation by the sponsor.

520 Destruction of unused investigational medicinal products should be carried  
521 out only after reconciliation of delivered, used and recovered products and  
522 after investigation and satisfactory explanation of any discrepancies upon  
523 which the reconciliation has been accepted.

524 Recording of destruction operations should be carried out in such a manner  
525 that all operations may be accounted for.

526 When destruction of investigational medicinal products takes place the  
527 manufacturer provides a dated certificate of destruction or a receipt for  
528 destruction to the sponsor. These documents should clearly identify or allow  
529 traceability to the batches and/or patient numbers involved and the actual  
530 quantities destroyed.

531

**2.13. Glossary of terms**

Terms	Definition
Comparator product	A medicinal product used as a reference, including as a placebo, in a clinical trial.
Preparation	Enclosing the product in a container which is labelled before the product is used in a clinical trial, or where the product is already in the container, in which it is to be supplied, labelling the container before the product is used in a clinical trial.
Manufacturer	Any person engaged in activities for which the authorisation referred to in Article 61 of Regulation (EU) No 536/2014 is required.
Order	Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).
Product specification file	A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.
Randomisation	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Shipping/distribution	The operation of packaging for transportation and sending of ordered medicinal products for clinical trials.
Transportation	Moving medicinal products between two locations without storing them for unjustified periods of time.