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Guidelines

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

1 INTRODUCTION

2 These guidelines are based on the second subparagraph of Article 63(1) of Regulation
3 (EU) No 536/2014¹.

4 These guidelines complement Commission Delegated Regulation (EU) 2017/1569 of 23
5 May 2017 supplementing Regulation (EU) No 536/2014 on the good manufacturing
6 practice for investigational medicinal products for human use and arrangements for
7 inspections² that has as its legal basis the first subparagraph of Article 63(1) of
8 Regulation (EU) No 536/2014.

9 These guidelines lay down appropriate tools to address specific issues concerning
10 investigational medicinal products with regard to good manufacturing practice. The tools
11 are flexible to provide for changes as knowledge of the process increases and appropriate
12 to the stage of development of the product.

13 An investigational medicinal product is defined in Article 2(5) of Regulation (EU) No
14 536/2014 as a medicinal product which is being tested or used as a reference, including
15 as a placebo, in a clinical trial and manufacturing is defined as total and partial
16 manufacture, as well as the various processes of dividing up, packaging and labelling
17 (including blinding) in Article 2(24) of that Regulation.

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

23 Good manufacturing practice for investigational medicinal products is set out in
24 Commission Delegated Regulation (EU) No 2017/1569 and in these guidelines.

25 Furthermore, where applicable, the manufacturers and the competent authorities should
26 also take into account the detailed guidelines referred to in the second paragraph of
27 Article 47 of Directive 2001/83/EC³, published by the Commission in the "Guide to good
28 manufacturing practice for medicinal products and for investigational medicinal
29 products" (EudraLex, Volume 4). Examples of applicable parts of EudraLex, Volume 4
30 to investigational medicinal products, not specifically mentioned in these guidelines, are
31 Part I, Chapters 2, and 6, and Part III.

¹ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

² Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections (OJ L 238/12, 16.09.2017).

³ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.201, p. 67).

32 With regard to EudraLex, Volume 4, Part II, it should be noted that Regulation (EU) No
33 536/2014 does not lay down requirements for good manufacturing practice for active
34 substances of investigational medicinal products. However, if a clinical trial is to be used
35 to support the application for a marketing authorisation, Part II of EudraLex, Volume 4
36 would need to be considered.

37 Procedures need to be flexible to provide for changes as knowledge of the process
38 increases and appropriate to the stage of development of the products.

39 In clinical trials there may be added risk to the subjects compared to patients treated with
40 authorised medicinal products. The application of good manufacturing practice for the
41 manufacture and import of investigational medicinal products is intended to ensure that
42 subjects are not placed at undue risk, and that the results of clinical trials are unaffected
43 by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or
44 import. Equally, it is intended to ensure that there is consistency between batches of the
45 same investigational medicinal product used in the same or different clinical trials and
46 that changes during the development of an investigational medicinal product are
47 adequately documented and justified.

48 The production of investigational medicinal products involves added complexity in
49 comparison with authorised medicinal products by virtue of lack of fixed routines,
50 variety of clinical trial designs and consequent packaging designs. Randomisation and
51 blinding add to that complexity an increased risk of product cross-contamination and
52 mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of
53 the product and a lack of full process validation. Moreover, authorised products may be
54 used which have been re-packaged or modified in some way. These challenges require
55 personnel with a thorough understanding of and training in the application of good
56 manufacturing practice to investigational medicinal products. The increased complexity
57 in manufacturing operations requires a highly effective quality system.

58 For manufacturers to be able to apply and comply with good manufacturing practice for
59 investigational medicinal products, co-operation between manufacturers and sponsors of
60 clinical trials is required. This co-operation should be described in a technical agreement
61 between the sponsor and manufacturer, as referred to in recital 4 of Delegated Regulation
62 (EU) No 2017/1569.

63 **1. SCOPE**

64 These guidelines apply to manufacture or import of investigational medicinal products
65 for human use.

66 For advanced therapy investigational medicinal products, Article 16 of Commission
67 Delegated Regulation (EU) No 2017/1569 states that the requirements of good
68 manufacturing practice shall be adapted to the specific characteristic of such products in
69 accordance with a risk-based approach and consistent with good manufacturing
70 requirements applicable to authorised advanced therapy medicinal products. Those
71 adaptations are addressed in the Guidelines on good manufacturing practice for advanced
72 therapy medicinal products⁴. Therefore, these detailed guidelines on good manufacturing

⁴ Commission guideline on good manufacturing practice for advanced therapy medicinal products, Eudralex Volume 4, Part IV

73 practice for investigational medicinal products for human use do not apply to
74 manufacture or import of advanced therapy investigational medicinal products.

75 Reconstitution of investigational medicinal products is not considered manufacturing,
76 and therefore is not covered by this guideline.

77 The reconstitution is understood as the simple process of dissolving or dispersing the
78 investigational medicinal product for administration of the product to a trial subject, or
79 diluting or mixing the investigation medicinal product with some other substance(s) used
80 as a vehicle for the purpose of administering it to a trial subject.

81 Reconstitution is not mixing several ingredients, including the active substance, together
82 to produce the investigational medicinal product. An investigational medicinal product
83 must exist before a process can be defined as reconstitution.

84 The process of reconstitution has to be undertaken as close in time as possible to
85 administration and has to be defined in the clinical trial application dossier and document
86 available at the clinical trial site.

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

91 **2. PHARMACEUTICAL QUALITY SYSTEM**

92 The pharmaceutical quality system required of the manufacturer according to Article 5 of
93 Commission Delegated Regulation (EU) No 2017/1569 and designed, set-up and verified
94 by the manufacturer should be described in written procedures taking into account
95 EudraLex, Volume 4, Part I, Chapter 1, as applicable, to investigational medicinal
96 products.

97 The product specifications and manufacturing instructions may be changed during
98 development but full control and traceability of the changes should be documented and
99 maintained. Deviations from any predefined specifications and instructions should be
100 registered, investigated and corrective and preventive action measures initiated as
101 appropriate.

102 The selection, qualification, approval and maintenance of suppliers of starting materials,
103 together with their purchase and acceptance, should be documented as part of the
104 pharmaceutical quality system to ensure the integrity of the supply chain and protect
105 against falsified products. The level of supervision should be proportionate to the risks
106 posed by the individual materials, taking into account their source, manufacturing
107 process, supply chain complexity and the final use to which the material is put in the
108 investigational medicinal product. The supporting evidence for each supplier approval
109 and material approval should be documented and maintained.

110 **2.1. Product specification file**

111 Products specification file, in light of Article 2(3) of Commission Delegated
112 Regulation (EU) No 2017/1569, brings together and contains all of the essential

113 reference documents to ensure that investigational medicinal products are
114 manufactured according to good manufacturing practice for investigational
115 medicinal products and the clinical trial authorisation. The products specification
116 files is one of the essential elements of pharmaceutical quality system.

117 Applicable sections of the product specification file should be available at the start
118 of manufacturing of the first batch of investigational medicinal product for a clinical
119 trial.

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

- 123 i. Specifications and analytical methods for starting materials, packaging
124 materials, intermediate product, bulk product and finished product;
- 125 ii. Manufacturing methods;
- 126 iii. In-process testing and methods;
- 127 iv. Approved label copy;
- 128 v. Relevant clinical trial authorisations and amendments thereof, clinical trial
129 protocol and randomisation codes, as appropriate;
- 130 vi. Relevant technical agreements with contract givers and acceptors, as
131 appropriate;
- 132 vii. Stability plan and reports;
- 133 viii. Details of plans and arrangements for reference and retention samples;
- 134 ix. Storage and transport conditions;
- 135 x. Details of the supply chain including manufacturing, packaging, labelling
136 and testing sites for the investigational medicinal products, preferably in the
137 format of a comprehensive diagram.

138 This list of documents is neither exhaustive nor exclusive.

139 The contents of the product specification file will vary depending on the product and
140 the stage of development.

141 Where different manufacturing steps are carried out at different locations under the
142 responsibility of different qualified persons, it is acceptable to maintain separate
143 files limited to information of relevance to the activities at the respective locations.
144 The manufacturing site should have access to the necessary documentation of the
145 product specification file, including changes, to enable the relevant activities to be
146 performed.

147 **3. PERSONNEL**

148 The requirements as regards the personnel are defined in Article 6 of Commission
149 Delegated Regulation (EU) No 2017/1569. The EudraLex, Volume 4, Part I, Chapter 2
150 should also be taken into account as appropriate.

151 All personnel involved with the manufacture, import, storage or handling of
152 investigational medicinal products should be appropriately trained in the requirements
153 specific to these types of product.

154 Even where the number of staff involved in the manufacturing or import of
155 investigational medicinal products is small, there should be, for each batch, separate
156 people responsible for production and quality control.

157 The qualified person has to fulfil the conditions of qualification set out in Article 49(2)
158 and (3) of Directive 2001/83/EC, as per Article 61(2)(b) of Regulation (EU) No
159 536/2014.

160 The responsibilities of the qualified person are set out in Article 62 of Regulation (EU)
161 No 536/2015 and further elaborated in Article 12 of Commission Delegated Regulation
162 (EU) No 2017/1569.

163 The qualified person that certifies the finished batch of investigational medicinal
164 products for use in the clinical trial should ensure that there are systems in place that
165 meet the requirements of good manufacturing practice and should have a broad
166 knowledge of pharmaceutical development, clinical trial processes and supply chain of
167 the batch concerned.

168 **4. PREMISES AND EQUIPMENT**

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

175 Consideration should be given to campaign manufacturing, where appropriate. Account
176 should be taken of the solubility of the product in decisions about the choice of cleaning
177 solvent.

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

- 182 i. facility/equipment design and use;
- 183 ii. personnel and material flow;
- 184 iii. microbiological controls;

- 185 iv. physio-chemical characteristics of the active substance;
186 v. process characteristics;
187 vi. cleaning processes;
188 vii. analytical capabilities relative to the relevant limits established from the
189 evaluation of the investigational medicinal products.
- 190 Premises and equipment are expected to be qualified in accordance with EudraLex,
191 Volume 4, Annex 15.

192 **5. DOCUMENTATION**

193 Documentation should be generated and controlled in line with the principles detailed in
194 EudraLex, Volume 4, Part I, Chapter 4. The retention period for instructions and records
195 required to demonstrate compliance with good manufacturing practice should be defined
196 according to the type of document while complying with the requirement of Article 8 of
197 Commission Delegated Regulation (EU) No 2017/1569, where relevant. In line with
198 Article 8(1) of the above mentioned Delegated Regulation the documentation shall be
199 consisted with the Product Specification File. Documents which are part of the Products
200 Specification File shall be retained for the period of at least 5 years as required by Article
201 8(3) of the Delegated Regulation.

202 The sponsor has specific responsibilities for document retention of the clinical trial
203 master file according to Article 58 of Regulation (EU) No 536/2014 and is required to
204 retain such documentation for at least 25 years after the end of the trial. If the sponsor
205 and the manufacturer are not the same entity, the sponsor has to make appropriate
206 arrangements with the manufacturer to fulfil the sponsor's requirement to retain the
207 clinical trial master file. Arrangement for retention of such documents and the type of
208 documents to be retained should be defined in an agreement between the sponsor and
209 manufacturer.

210 **5.1. Specification and instructions**

211 Specifications for starting materials, immediate packaging materials, intermediate
212 products, bulk products and finished products, manufacturing formulae and
213 processing and packing instructions should be as comprehensive as possible given
214 the current state of knowledge. They should be re-assessed during development and
215 updated as necessary. Each new version should take into account the latest data,
216 current technology used, regulatory and pharmacopoeial developments and should
217 allow traceability to the previous document. Any changes should be carried out
218 according to a written procedure which should address any implications for product
219 quality such as stability and bioequivalence. The approval process for instructions
220 and changes thereof shall include responsible personnel at the manufacturing site.

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

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5.2. Order

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

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5.3. Manufacturing formulae and processing instructions

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

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The relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing, and storage, including storage conditions.

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5.4. Packaging instructions

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

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

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5.5. Batch records

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

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Batch manufacturing records should be retained by the manufacturer for at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used as set out in Article 8(3) of Commission Delegated Regulation (EU) No 2017/1569.

263 **6. PRODUCTION**

264 **6.1. Packaging materials**

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

268 **6.2. Manufacturing operations**

269 During development critical parameters should be identified and in-process controls
270 primarily used to control the process. Provisional production parameters and in-
271 process controls may be deduced from prior experience, including that gained from
272 earlier development work. Careful consideration by key personnel is called for in
273 order to formulate the necessary instructions and to adapt them continually to the
274 experience gained in production. Parameters identified and controlled should be
275 justifiable based on knowledge available at the time.

276 In line with Article 9(3) of Delegated Regulation, the manufacturing process is not
277 to be validated to the extent necessary for routine production but shall be validated
278 in its entirety, as far as is appropriate taking into account the stage of product
279 development. It should be documented in accordance with the requirements
280 detailed in EudraLex, Volume 4, Annex 15. Article 9(3) of Commission Delegated
281 Regulation (EU) No 2017/1569 states also that the manufacturer shall identify the
282 process steps that safeguard the safety of the subject and the reliability and
283 robustness of the clinical trial data generated in the clinical study.

284 To avoid cross-contamination, written cleaning procedures and analytical methods
285 to verify the cleaning process should be available.

286 For sterile products, the validation of sterilising processes should be of the same
287 standards as for authorised medicinal products and take account of the principles for
288 the manufacture of sterile medicinal products detailed EudraLex, Volume 4, Annex
289 1. Likewise, when required, virus inactivation/removal and removal of other
290 impurities of biological origin should be demonstrated, to assure the safety of
291 biotechnologically derived and biological products by following the scientific
292 principles and techniques defined in the available guidance in this area.

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

301 **6.3. Modification of comparator products**

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

305 The expiry date stated for the comparator product in its original packaging might
306 not be applicable to the product where it has been repackaged in a different
307 container that may not offer equivalent protection, or be compatible with the
308 product. A suitable retest date, taking into account the nature of the product,
309 the characteristics of the container and the storage conditions to which the
310 product may be subjected, should be determined by or on behalf of the sponsor.
311 Such a date should be justified and must not be later than the expiry date of the
312 original package. There should be compatibility of expiry dating and clinical trial
313 duration.

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315 A reference sample of comparator product, which has been repackaged or over
316 encapsulated for blinding purposes, should be taken at a point representative of the
317 additional processing and retained, as the additional processing step could have an
318 impact on stability or be needed for identification purposes in the event of a quality
319 defect investigation, which would not be covered by the commercial retained
320 sample.

321 **6.4. Blinding operations**

322 Where products are blinded, systems should be in place to ensure that the blind is
323 achieved and maintained while allowing for identification of "blinded" products,
324 when necessary, including batch numbers of the products before the blinding
325 operation. Rapid identification of product should also be possible in an emergency.
326 Where the manufacturer has been delegated the responsibility for generation of
327 randomisation codes, the manufacturer should enable that unblinding information is
328 available to the appropriate responsible investigator site personnel before
329 investigational medicinal products are supplied.

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

332 **6.5. Packaging**

333 During packaging of investigational medicinal products, it may be necessary to
334 handle different products on the same packaging line at the same time. The risk of
335 product unintentional mixing (mix-ups) must be minimised by using appropriate
336 procedures and/or specialised equipment as appropriate and relevant staff training.
337 Documentation must be sufficient to demonstrate that appropriate segregation has
338 been maintained during any packaging operations.

339 Packaging and labelling of investigational medicinal products are likely to be more
340 complex and more liable to errors which are also harder to detect than for authorised
341 medicinal products, particularly when blinded products with similar appearance are
342 used. Precautions against mislabelling such as reconciliation, line clearance, in-
343 process control checks by appropriately trained staff should accordingly be
344 intensified.

345 The packaging must ensure that the investigational medicinal product remains in
346 good condition during transport and storage at intermediate destinations. Any
347 opening or tampering of the outer packaging during transport should be readily
348 discernible.

349 Re-packaging operations may be performed by authorised personnel at a hospital,
350 health centre or clinic that meet the requirements of Article 61(5)(a) of Regulation
351 (EU) No 536/2014.

352 **6.6. Labelling**

353 Labelling of investigation medicinal products shall comply with the requirements of
354 Article 66, 67, 68 and 69 of Regulation (EU) No 536/2014. A list of information
355 which shall appear on the labelling is set out in Annex VI to the said Regulation.
356 The labelling operation should be performed at an authorised manufacturing site that
357 complies with the requirements of Article 61(1) of Regulation (EU) No 536/2014.

358 If it becomes necessary to change the expiry date, an additional label should be
359 affixed to the investigational medicinal product. This additional label should state
360 the new expiry date and repeat the batch number and clinical trial reference number.
361 It may be superimposed on the old expiry date, but for quality control reasons, not
362 on the original batch number.

363 The re-labelling operation should be performed by appropriately trained staff in
364 accordance with good manufacturing practice principles and specific standard
365 operating procedures and should be checked by a second person. This additional
366 labelling should be properly documented in the batch records. To avoid mistakes the
367 additional labelling activity should be carried out in an area which is partitioned or
368 separated from other activities. A line clearance at the start and end of activity
369 should be carried out and label reconciliation performed. Any discrepancies
370 observed during reconciliation should be investigated and accounted for before
371 release.

372 The re-labelling operation may be performed by authorised personnel at a hospital,
373 health centre or clinic that meet the requirements of Article 61(5)(a) of Regulation
374 (EU) No 536/2014.

375 **7. QUALITY CONTROL**

376 According to Article 10 of Commission Delegated Regulation (EU) No 2017/1569, the
377 manufacturer is required to establish and maintain a quality control system placed under
378 the authority of a person who has the requisite qualifications and is independent of
379 production.

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

383 Quality control of the investigational medicinal product, including comparator product,
384 should be performed in accordance with the information submitted according to Article
385 25 of Regulation (EU) No 536/2014, as authorised by the Member State.

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

387 Retention periods for samples of investigational medicinal products have to fulfil the
388 requirements of Article 10(4) of Commission Delegated Regulation (EU) No 2017/1569.

389 Samples are retained to fulfil two purposes: firstly, to provide a sample for future
390 analytical testing, and secondly, to provide a specimen of the finished investigational
391 medicinal product which may be used in the investigation of a product quality defect.
392 Samples may therefore fall into two categories:

- 393 • Reference sample: a sample of a batch of starting material, packaging material or
394 finished product which is stored for the purpose of being analysed should the
395 need arise. Where stability permits, reference samples from critical intermediate
396 stages, e.g. those requiring analytical testing and release, or intermediates which
397 are transported outside of the manufacturer's control, should be kept.
- 398 • Retention sample: a sample of a fully packaged unit from a batch of finished
399 product. It is stored for identification purposes. For example, presentation,
400 packaging, labelling, package leaflet, batch number, expiry date should the need
401 arise during the shelf life of the batch concerned.

402 There may be exceptional circumstances where this requirement can be met without
403 retention of duplicate samples, e.g. where small amounts of a batch are packaged for
404 different markets or in the production of very expensive medicinal products.

405 For retention samples it is acceptable to store information related to the final packaging
406 as written, photographic or electronic records, if such records provide sufficient
407 information, e.g. examples of packaging, labelling and any accompanying documentation
408 to permit investigations associated with the use of the product. In case of electronic
409 records, the system should comply with the requirements of EudraLex, Volume 4, Annex
410 11.

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

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

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

420 Reference samples of finished product should be stored under defined storage conditions
421 in the EU or in a third country where appropriate arrangements have been made by the
422 Union with the exporting country to ensure that the manufacturer of the investigational
423 medicinal product applies standards of good manufacturing practice at least equivalent to
424 those laid down by the Union. In exceptional circumstances, the reference samples of the
425 finished product may be stored by the manufacturer in another third country, in which
426 case this should be justified and documented in a technical agreement between the
427 sponsor, the importer in the EU and that manufacturer in the third country.

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

432 **8. RELEASE OF BATCHES**

433 Release of investigational medicinal products should not occur until after the qualified
434 person has certified in line with Article 62(1) of Regulation (EU) No 536/2014 that the
435 requirements of Article 63(1) and (3) of Regulation (EU) No 536/2014 and those set out
436 in Article 12 of the Commission Delegated Regulation (EU) No 2017/1569 are met.

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

439 i. Product manufactured within the EU but not subject to an EU marketing
440 authorisation: the duties are laid down in Article 62 of Regulation (EU) No
441 536/2014 and Article 12(1)(a) of the Delegated Regulation;

442 ii. Product sourced from the open market within the EU in accordance with Article
443 80(b) of Directive 2001/83/EC and subject to a marketing authorisation granted
444 by a competent authority in the EU, regardless of manufacturing origin: the duties
445 are as described above. However, the scope of the certification can be limited to
446 assuring that the products are in accordance with the authorisation of the clinical
447 trial and any subsequent processing carried out by the manufacturer for the
448 purpose of blinding, trial-specific packaging and labelling.

449 iii. Product imported directly from a third country: the duties are laid down in Article
450 62 of Regulation (EU) No 536/2014 and Article 12(1)(b) of Delegated
451 Regulation. Where investigational medicinal products are imported from a third
452 country and they are subject to agreements concluded between the Union and that
453 country, such as a Mutual Recognition Agreement (MRA), equivalent standards
454 of good manufacturing practice apply provided any such agreement is operational
455 for investigational medicinal products. In the absence of a MRA, the qualified
456 person should determine that equivalent standards of good manufacturing practice
457 apply through knowledge of the quality system employed at the manufacturer.
458 This knowledge is normally acquired through audit of the manufacturer's quality
459 systems. In either case, the qualified person may then certify on the basis of
460 documentation supplied by the manufacturer in the third country and document
461 the rationale for certification.

462 The information in the product specification file should form the basis for assessment of
463 the suitability for certification and release of a particular batch by the qualified person
464 and should therefore be accessible to him or her.

465 Assessment by the qualified person of each batch for certification prior to release should
466 take account of the principles detailed in EudraLex, Volume 4, Annex 16 and may
467 include as appropriate:

468 i. Batch records, including control reports, in-process test reports and release
469 reports demonstrating compliance with the product specification file, the order,
470 protocol and randomisation code. These records should include all deviations or
471 planned changes, and any consequent additional checks and tests, and should be
472 completed and endorsed by the staff authorised to do so according to the quality
473 system;

474 ii. Production conditions;

- 475 iii. Cleaning records;
- 476 iv. The qualification status of facilities, validation status of processes and methods;
- 477 v. Examination of finished packs;
- 478 vi. The results of any analyses or tests performed after importation, where relevant;
- 479 vii. Stability plan and reports;
- 480 viii. The source and verification of conditions of storage and shipment;
- 481 ix. Audit reports concerning the quality system of the manufacturer;
- 482 x. Documents certifying that the manufacturer is authorised to manufacture
483 investigational medicinal product for export by the appropriate authorities in the
484 third country;
- 485 xi. Where relevant, regulatory requirements for marketing authorisation, good
486 manufacturing practice standards applicable and any official verification of
487 compliance with good manufacturing practice;
- 488 xii. Verification of the supply chain including manufacturing, packaging, labelling
489 and testing sites for the investigational medicinal products;
- 490 xiii. All factors of which the qualified person is aware that are relevant to the quality
491 of the batch.

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

496 Where investigational medicinal products are produced and packaged at different sites
497 under the supervision of different qualified persons, sharing of responsibilities amongst
498 qualified persons in relation to compliance of a batch must be defined in a document
499 formally agreed by all parties.

500 Where required to support certification, the qualified person has to ensure that
501 investigational medicinal products have been stored and transported under conditions to
502 maintain product quality and supply chain security. Relevant situations may include short
503 expiry date products released prior to final qualified person certification, or where return
504 of investigational medicinal products to an authorised manufacturer for re-labelling and
505 re-packaging remains a possibility.

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

508 Where the manufacturer is delegated by the sponsor to perform the regulatory release in
509 addition to certification by the qualified person, the arrangements should be defined in an
510 agreement between the sponsor and the manufacturer. Relevant clinical trial
511 authorisation and amendment information should be available for reference in the

512 product specification file and the manufacturer should ensure the necessary clinical trial
513 authorisations are in place and prior to shipping product for use in the trial.

514 After certification by the qualified person, investigational medicinal products should be
515 stored and transported under conditions to maintain product quality and supply chain
516 security.

517 **9. OUTSOURCED OPERATIONS**

518 Activities which are outsourced should be defined, agreed and controlled by written
519 contracts between the contract giver and the party to whom the operations are outsourced
520 in accordance with Article 13 of Delegated Regulation and the principles detailed in
521 EudraLex Volume 4, Part I, Chapter 7.

522 **10. COMPLAINTS**

523 There should be written procedures describing the actions to be taken upon receipt of a
524 complaint at the manufacturing, storage or importation site. All complaints should be
525 documented and assessed to establish if they represent a potential quality defect or other
526 issue. The procedures should ensure that the sponsor is able to assess the complaints to
527 determine if they justify the reporting of a serious breach, as required by Article 52 of
528 Regulation (EU) No 536/2014.

529 The investigation of quality defect should be performed in accordance with the principles
530 detailed in EudraLex, Volume 4, Part I, Chapter 8.

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

535 **11. RECALLS AND RETURNS**

536 **11.1. Recalls**

537 Procedures for retrieving investigational medicinal products and documenting this
538 retrieval should in line with Article 14 of the Delegated Regulation be agreed by the
539 sponsor in cooperation with the manufacturer, where different. The manufacturer,
540 investigator and the sponsor's representative need to understand their obligations
541 under the retrieval procedure. The procedures for retrieval of investigational
542 medicinal products should be in accordance with the principles detailed in
543 EudraLex, Volume 4, Part I, Chapter 8.

544 To facilitate recall, a detailed inventory of the shipments made by the manufacturer
545 should be maintained.

546 **11.2. Returns**

547 Returned investigational medicinal products should be clearly identified and stored
548 in an appropriately controlled, dedicated area. Inventory records of returned
549 products should be kept.

550 **11.3. Destruction**

551 The manufacturer or sponsor's representative should destroy investigational
552 medicinal products only with prior written authorisation by the sponsor. The
553 arrangements for destruction of investigational medicinal products have to be
554 described in the protocol. Any arrangement between sponsor and manufacturer in
555 this regard should be defined in their technical agreement.

556 Destruction of unused investigational medicinal products should be carried out only
557 after reconciliation of delivered, used and recovered products and after investigation
558 and satisfactory explanation of any discrepancies upon which the reconciliation has
559 been accepted.

560 Records of destruction operations should be retained, including a dated certificate of
561 destruction or a receipt for destruction to the sponsor. These documents should
562 clearly identify or allow traceability to the batches and/or patient numbers involved
563 and the actual quantities destroyed.

GLOSSARY OF TERMS APPLICABLE TO THESE GUIDELINES

Terms	Definition
Campaign manufacturing	Manufacturing a series of batches of the same product in sequence in a given period of time followed by an appropriate (validated) cleaning procedure.
Comparator product	An investigational medicinal product used as a reference, including as a placebo, in a clinical trial.
Expiry date	The date placed on the container/labels of an investigational medicinal products designating the time during which the investigational medicinal products is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
Order	The order should request the processing and/or packaging of a certain number of units and/or their shipment and be given by or on behalf of the sponsor to the manufacturer.
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.
Retest date	The date when a material should be re-examined to ensure that it is still suitable for use.
Shipping	The operation of packaging for and sending of ordered medicinal products for clinical trials.