

Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

The sole purpose of this consultation is to collect relevant evidence and information from stakeholders to help the 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.

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101 **1. Introduction**

102 Quality plays a major role in the safety and efficacy profile of ATMPs. It is the responsibility
103 of the ATMP manufacturer to ensure that the manufacturing process is adequate and that
104 appropriate measures are put in place to safeguard the quality of the product (so-called
105 “pharmaceutical quality system”). Senior management should be actively involved to ensure
106 the effectiveness of the pharmaceutical quality system.

107 Compliance with Good Manufacturing Practice (“GMP”) is an essential part of the
108 pharmaceutical quality system. The main objectives of GMP are that:

- 109 - the personnel is adequately trained and there is clear allocation of responsibilities;
- 110 - the premises and equipment are suitable for the intended use and that there is
111 appropriate maintenance thereof;
- 112 - there is an adequate documentation system that ensures that appropriate specifications
113 are laid down for starting and raw materials, as well as intermediates and bulk
114 products, that the production process is clearly understood, and that appropriate
115 records are kept;
- 116 - the manufacturing process is adequate to ensure consistent production (appropriate to
117 the relevant stage of development), the quality of the product and the compliance
118 thereof with the relevant specifications, and the identification of any process deviation
119 as well as the implementation of appropriate corrective action(s);
- 120 - there is a quality control system which is operationally independent from production;
- 121 - quality defects are identified as soon as possible, the causes investigated, and
122 appropriate measures are taken,
- 123 - adequate systems are implemented to ensure traceability of the ATMPs and its starting
124 and raw materials.

125 Self-inspections should be conducted to monitor compliance with GMP and the specific
126 requirements provided for in the marketing authorisation or clinical trial authorisation and to
127 implement corrective measures where appropriate.

128 These Guidelines develops the GMP that should be applied in the manufacturing of advanced
129 therapy medicinal products in the EU (including advanced therapy investigational medicinal
130 products). Throughout these Guidelines, the term “ATMP” should be understood as referring
131 to both advanced therapy medicinal products that have been granted a marketing authorisation
132 and advanced therapy medicinal products that are being tested or used as reference in a
133 clinical trial. When specific provisions are only relevant for advanced therapy medicinal
134 products that have been granted a marketing authorisation, the term “authorised ATMPs” is

135 used. When specific provisions are only relevant for advanced therapy investigational
136 medicinal products, the term “investigational ATMPs” is used.

137 No provision in these Guidelines (including the risk-based approach) can be regarded as
138 derogation to the terms of the marketing authorisation or clinical trial authorisation. It is
139 recalled, however, that non-substantial amendments can be introduced in the investigational
140 medicinal product dossier without the agreement of the competent authorities.¹ Throughout
141 this document, the term “clinical trial authorisation” should be understood as including also
142 non-substantial amendments that have been made to the investigational medicinal product
143 dossier.

144 **2. Risk-based approach**

145 **2.1. Introduction**

146 ATMPs are complex products and risks may differ according to the type of product,
147 nature/characteristics of the starting materials and level of complexity of the manufacturing
148 process. It is also acknowledged that the finished product may entail some degree of
149 variability due to the use of biological materials and complex manipulation steps (*e.g.*
150 cultivation of cells, manipulations that alter the function of the cells, *etc.*). In addition, the
151 manufacture and testing of autologous ATMPs (and allogenic products in a donor-matched
152 scenario) poses specific challenges and the strategies implemented to ensure a high level of
153 quality must be tailored to the constraints of the manufacturing process, limited batch sizes
154 and the inherent variability of the starting material.

155 It follows that it is important to recognise some flexibility in the application of the GMP
156 requirements so that the ATMP manufacturer can implement the measures that are most
157 appropriate having regard to specific characteristics of the manufacturing process and of the
158 product. Any flexibility applied must, however, be compatible with the need to ensure the
159 quality, safety and efficacy of the product.

160 The possibility for the manufacturer to apply alternative, more flexible approaches is
161 particularly important in the case of investigational ATMPs, specially in early phases of
162 clinical trials (phase I and phase I/II) due to the often incomplete knowledge about the product
163 (*e.g.* potency) as well as the evolving nature of the routines (in order to adjust the
164 manufacturing process to the increased knowledge of the product). Additionally, ATMPs are
165 also often developed in an academic or hospital setting operating under quality systems
166 different to those typically required for the manufacture of conventional medicinal products.

167 The risk-based approach is applicable in an equal fashion to all type of operators. The
168 quality, safety and efficacy attributes of the ATMPs and compliance with GMP should be
169 ensured for all ATMPs (including investigational ATMPs), regardless of whether they are
170 developed in a hospital, academic or industrial setting.

¹Regulation (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 L158, 27.5.2014, p.1).

171 **2.2 Application of the risk-based approach by ATMP manufacturers**

172 Manufacturers are responsible for the quality of the ATMPs they produce. The risk-based
173 approach (“RBA”) permits the manufacturer to design the organisational, technical and
174 structural measures that are put in place to comply with GMP -and thus to ensure quality-
175 according to the specific risks of the product and the manufacturing process. While the risk-
176 based approach brings flexibility, it also implies that the manufacturer is responsible to put in
177 place additional measures, if that is necessary to address the specific risks of the product or
178 the manufacturing process.

179 The quality risks associated with an ATMP are highly dependent on the biological
180 characteristics and origin of the cells, the biological characteristics of the vectors, the level
181 and characteristics of the expressed protein (for gene therapy products), the properties of other
182 non-cellular components (raw materials, matrixes), and the manufacturing process. The
183 manufacturing process, including in-process testing and batch release testing, should be
184 adequate to address the identified risks.

185 When identifying the control measures that are most appropriate in each case, the ATMP
186 manufacturer should consider all the potential risks related to the product or the
187 manufacturing process on the basis of all information available, including an assessment of
188 the potential implications for the quality, safety and efficacy profile of the product. The level
189 of effort and documentation should be commensurate with the level of risk.

190 Investigational ATMPs

191 The safety of the product needs to be ensured from the first stages of development.
192 Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the
193 product and that the level of effort in the design and implementation of the strategy to ensure
194 quality will step up gradually. It follows that, while additional waivers/flexibilities may be
195 possible in early phases of clinical trials (phase I and I/II), manufacturing procedures and
196 control methods are expected to become more detailed and refined during the more advanced
197 phases of the clinical trial.

198 It is important to ensure that data obtained from the early phases of clinical trial can be used
199 in subsequent phases of development. A too immature quality system may compromise the
200 use of the study in the context of a marketing authorisation application (*e.g.* if the product has
201 not been adequately characterised). A weak quality system may also compromise the
202 approval of the clinical trial if the safety of trial subjects is at risk. Accordingly, it is strongly
203 encouraged that the advice of the competent authorities is sought in connection with the
204 implementation of the risk-based approach for investigational ATMPs and, in particular,
205 regarding early phases of clinical trials.

206 The description of the manufacturing process and process controls in the clinical trial
207 authorisation application should also describe, as appropriate, the quality strategy of the
208 manufacturer when the risk-based approach is applied. For aspects that are not specifically

209 covered by the clinical trial authorisation, it is incumbent upon the manufacturer to document
210 the reasons for the approach implemented and to justify that the totality of the measures
211 applied are adequate to ensure the quality of the product.

212 Authorised ATMPs

213 For authorised ATMPs, the starting point for the application of the risk-based approach is the
214 marketing authorisation. When providing the description of the manufacturing process and
215 process controls in the marketing authorisation application (or, as appropriate, in the context
216 of the submission of a variation), account can be taken of the specific characteristics of the
217 product/manufacturing process to justify flexibility/deviation from standard expectations.
218 Thus, the strategy to address specific limitations that may exist in connection with the
219 manufacturing process, including controls of raw materials and starting materials, the
220 manufacturing facilities and equipment, tests and acceptance criteria, process validation,
221 release specifications, or stability data should be agreed as part of the marketing authorisation.

222 For aspects that are not specifically covered by the marketing authorisation, it is incumbent
223 upon the manufacturer to document the reasons for the approach implemented when the risk-
224 based approach is applied, and to justify that the totality of the measures applied are adequate
225 to ensure the quality of the product.

226 **2.3 Examples of the application of the risk-based approach**

227 This section contains a non-exhaustive list of examples to illustrate some of the possibilities
228 and limitations of the risk-based approach (“RBA”).

229 *2.3.1. RBA in connection with raw materials*

230 The application of the risk-based approach when determining the strategy to ensure the
231 quality of the raw materials is explained in Section 7.2.

232 The application of the risk-based approach requires that the manufacturer has a good
233 understanding of the role of the raw material in the manufacturing process and, in particular,
234 of the properties of the raw material that are key to the manufacturing process and final
235 quality of the product.

236 Additionally, it is important to take into account the level of risk of the raw material due to
237 the intrinsic properties thereof (*e.g.* basic media vs. growth factors), or the use thereof in the
238 manufacturing process (higher risk if the raw material is in direct contact with the starting
239 materials).

240 Finally, it needs to be assessed if the control strategy (*i.e.* qualification of suppliers) is
241 sufficient to eliminate the risks or to mitigate them to an acceptable level.

242 *2.3.2. RBA in connection with the testing strategy*

243 It is acknowledged that in some cases it may not be possible to perform the release tests on
244 the active substance or the finished product, for example due to technical reasons (*e.g.* it may

245 not be possible to perform the release tests on the combined components of certain combined
246 products, time restrictions (*i.e.* the product needs to be administered immediately after
247 completion of manufacturing), or when the amount of available product is limited to the
248 clinical dose. In these cases, an adequate control strategy should be designed (and, as
249 appropriate, be explained in the marketing authorisation/clinical trials authorisation
250 application) based on the validation of the manufacturing process and the in-process controls.
251 For example, consideration can be given to the following options:

- 252 - Testing of intermediates (instead of the finished product) or in-process controls
253 (instead of batch release testing) if the relevance of the results from these tests to the
254 finished product can be demonstrated.
- 255 - Replacement of routine batch testing by process validation. While process validation is
256 usually not required for investigational medicinal products, it may be very important
257 when routine in-process or release testing is limited or not possible.

258 The following examples may also be considered:

- 259 - The application of the sterility test to the final product in accordance with the
260 European Pharmacopoeia (Chapter 2.6.27) may not always be possible due to the
261 scarcity of materials available, or it may not be possible to wait for the result of the
262 test before the product is released due to short shelf-life. In these cases, the strategy
263 regarding sterility assurance may need to be adapted (*e.g.* use of alternative methods
264 for preliminary results, combined with sterility testing of media or intermediate
265 product at subsequent (relevant) time points, *etc.*). If the results of the sterility test of
266 the product are not available at release, appropriate mitigation measures should be
267 implemented, including information of the treating physician (*see* Section 11.3.2).
- 268 - As cells in suspension are not clear solutions, it is acceptable to limit the particulate
269 matter test to foreign visible particles, provided that alternative measures are put in
270 place such as controls of input of particles from materials and equipment used during
271 manufacturing, or the verification of the ability of the manufacturing process to
272 produce low particle products with simulated samples (without cells).
- 273 - It may be justified to waive the on-going stability program for products with a very
274 short shelf-life.

275 2.3.3. *Additional considerations specifically relevant for ATMPs that are not subject to* 276 *substantial manipulation*²

277 The manufacturing process of ATMPs which does not involve substantial manipulation of the
278 cells/tissues is typically associated with lower risks than the manufacturing of ATMPs that

² Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L324, 10.12.2007, p.121).

279 require complex substantial manipulations. However, it cannot be inferred that processes that
280 are not qualified as “substantial manipulation” are risk-free, notably if the processing of the
281 cells entails long exposure of the cells/tissues to the environment. Accordingly, an analysis
282 of the risks of the specific manufacturing process should be performed in order to identify the
283 measures that are necessary to ensure the quality of the product.

284 With a view to avoid unnecessary administrative burden, in the application of the GMP
285 requirements to ATMPs the manufacturing process of which does not involve substantial
286 manipulation, account may be taken of equivalent standards that are applied by ATMP
287 manufacturers in compliance with other legislative frameworks. For instance, premises and
288 equipment that have been duly validated to process cells/tissues for transplantation purposes
289 in accordance with standards that can be deemed comparable to those laid down in these
290 Guidelines need not being validated again (for the same type of manufacturing operation).
291 However, premises/equipment used to process cells/tissues under the same surgical procedure
292 derogation³ or for research purposes should be validated in accordance with these Guidelines.

293 It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing
294 of ATMPs is done under aseptic conditions, also when the manufacturing process does not
295 involve substantial manipulation. When manufacturing operations take place in an open
296 environment in premises other than a critical room of grade A in a background clean area of
297 grade B, a risk-analysis study should be conducted (particular consideration should be paid to
298 the time that the product is exposed to the environment) and it should be demonstrated that
299 the implemented control measures are adequate to ensure aseptic manufacturing. Under no
300 circumstances it is acceptable to conduct manufacturing operations in premises with air
301 quality classification lower than a critical clean room of grade A in a background clean area
302 of grade D.

303 There are certain elements of GMP that are intended to ensure the quality, safety and efficacy
304 of the ATMPs which are not specifically addressed under other legislative frameworks and
305 which, therefore, should follow the requirements in these Guidelines, also when the
306 manufacturing process does not involve substantial manipulation. In particular, the product
307 characterisation, process validation and quality controls as required for in these Guidelines are
308 critical to ensure that the ATMP administered to the patient is the one that has been
309 authorised. Additionally, in a clinical trial setting, lack of appropriate product characterisation
310 and adequate quality controls may affect the reliability of the results of the clinical trial.
311 Moreover, QP release is an essential requirement applicable to all medicinal products,
312 including authorised and investigational ATMPs the manufacturing of which does not involve
313 substantial manipulation.

³ Article 2(2) of Directive 2004/23 of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L102, 7.04.2004,p.48).

314 2.3.4. *Additional considerations specifically relevant for investigational ATMPs*

315 The application of GMP requires certain level of flexibility in the case of investigational
316 ATMPs. However, the quality of the product should be ensured, also in an investigational
317 setting. Accordingly, particular attention should be paid to personnel training (in particular
318 on aseptic manufacturing), ensuring conditions for aseptic manufacturing, and equipment
319 calibration.

320 The following are examples of the additional flexibilities that are acceptable in the case of
321 investigational ATMPs:

- 322 - For first-in-man clinical trials, production in an open environment may be performed
323 in a critical clean area of grade A in a background clean area of grade C if appropriate
324 controls of microbiological contamination, separation of processing procedures, and
325 validated cleaning and disinfection are put in place. A risk-analysis study should be
326 conducted and it should be demonstrated that the implemented control measures are
327 adequate to ensure aseptic manufacturing.
- 328 - In early phases of clinical research (clinical trial phases I/II) when the manufacturing
329 activity is very low, annual calibration, inspection or checking can be limited to the
330 facility, cabinets, incubators, isolators, freezers, air sampler and particle counters,
331 unless a lower frequency is justified due to periodicity of use. The rest of equipment
332 could be tested less frequently based on a risk analysis and the production activity.
333 The suitability for use of all equipment should be verified before it is used.
- 334 - The level of formality and detail for the documentation should be adapted to the stage
335 of development.
- 336 - During early phases of clinical development (phase I/II clinical trials) specifications
337 can be based on wider acceptance criteria taking due account of the current knowledge
338 of the risks.
- 339 - Additional flexibilities regarding qualification of premises and equipment, process
340 validation, and validation of analytical methods are described in Section 10.

341

342 **3. Personnel**

343 **3.1. General principles**

344 The ATMP manufacturer should have an adequate number of personnel with the necessary
345 qualifications and adequate practical experience relevant to the intended operations.

346 All personnel involved in the manufacturing or testing of an ATMP should have a clear
347 understanding of their tasks and responsibilities, including knowledge of the product
348 appropriate to the assigned tasks.

349 **3.2. Training**

350 All personnel should be aware of the principles of GMP that affect them and receive initial
351 and periodic training relevant to their tasks.

352 There should be appropriate (and periodic) training in the requirements specific to the
353 manufacturing, testing, and traceability of the product. Personnel working in areas where
354 contamination is a hazard should be given specific training on aseptic manufacturing. Prior to
355 participating in routine aseptic manufacturing operations, personnel should participate in a
356 successful process simulation test (*see* Section 9.5.3). Training in gowning requirements set
357 out in section 3.3 is also required.

358 In addition, there should be appropriate training to prevent the transfer of communicable
359 diseases from biological raw and starting materials to the operators. Personnel handling
360 GMOs may require additional training to prevent cross-contamination risks and potential
361 environmental impacts.

362 Cleaning and maintenance personnel should also receive training relevant to the tasks
363 performed, in particular on measures to avoid risks to the product, to the environment, and
364 health risks.

365 Training can be provided in-house. The effectiveness of training should be periodically
366 assessed. Records of training should be kept.

367 **3.3. Hygiene**

368 High standards of personal hygiene and cleanliness are essential. Hygiene programs should
369 be established.

370 Eating, drinking, chewing or smoking, as well as the storage of food or personal medication
371 should be prohibited in the production and storage area.

372 Every person entering the manufacturing areas should wear clean clothing suitable for the
373 manufacturing activity with which they are involved and this clothing should be changed
374 when appropriate. Additional protective garments appropriate to the operations to be carried
375 out (*e.g.* head, face, hand and/or arm coverings) should be worn when necessary.

376 The clothing and its quality should be appropriate for the process and the grade of the
377 working area. It should be worn in such a way as to protect the product from contamination.

378 The description of clothing required for each grade is as follows:

379 • Grade D: Hair and, where relevant, beard should be covered. A general protective
380 suit and appropriate shoes or overshoes should be worn. Appropriate
381 measures should be taken to avoid any contamination coming from
382 outside the clean area.

383 • Grade C: Hair and where relevant beard and moustache should be covered. A
384 single or two-piece trouser suit, gathered at the wrists and with high neck
385 and appropriate shoes or overshoes should be worn. They should shed
386 virtually no fibres or particulate matter.

387 • Grade A/B: Headgear should totally enclose hair and, where relevant, beard and
388 moustache; it should be tucked into the neck of the suit; a face mask
389 should be worn to prevent the shedding of droplets. Appropriate
390 sterilised, non-powdered rubber or plastic gloves and sterilised or
391 disinfected footwear should be worn. Trouser-legs should be tucked
392 inside the footwear and garment sleeves into the gloves. The protective
393 clothing should shed virtually no fibres or particulate matter and retain
394 particles shed by the body.

395 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms.
396 For every worker in a grade A/B area, clean (sterilised) protective garments should be
397 provided at each work session. Gloves should be regularly disinfected during operations.
398 Masks and gloves should be changed at least for every working session. Clean area clothing
399 should be cleaned and handled in such a way that it does not gather additional contaminants
400 which can later be shed. Wristwatches, make-up and jewellery should not be worn in clean
401 areas.

402 Where required to minimise the risk for cross-contamination, restrictions on the movement of
403 all personnel should be applied. In general, personnel (or any other person) should not pass
404 directly from areas where there is exposure to live micro-organisms, genetically modified
405 organisms, toxins or animals to areas where other products, inactivated products or different
406 organisms are handled. If such passage is unavoidable, appropriate control measures (having
407 regard to the risks) should be applied. When a person moves from one clean room to another
408 clean room appropriate disinfection measures should be applied.

409 Only the minimum number of personnel should be present in clean areas. Inspections and
410 controls should be conducted outside the clean areas as far as possible.

411 Steps should be taken to ensure that health conditions of the personnel that may be relevant to
412 the quality of the ATMP are declared. As far as possible, no person affected by an infectious

413 disease which could adversely affect the quality of the product or having open lesions on the
414 exposed surface of the body should be involved in the manufacture of ATMPs.

415 Health monitoring of staff should be proportional to the risks. Where necessary having regard
416 to the specific risks of the product, personnel engaged in production, maintenance, testing and
417 internal controls, and animal care should be vaccinated. Other measures may need to be put
418 in place to protect the personnel according to the known risks of the product.

419 **3.4. Key personnel**

420 Because of their essential role in the quality system, the person responsible for production, the
421 person responsible for quality control and the Qualified Person (“QP”) should be appointed
422 by senior management.

423 The roles and responsibilities of key personnel should be clearly defined and communicated
424 within the organisation. As a minimum, the person responsible for production should take
425 responsibility for ensuring that manufacturing is done in accordance with the relevant
426 specifications/instructions, while the person responsible for quality control should take
427 responsibility for the control of raw materials, starting materials, packaging materials,
428 intermediate, bulk and finished products (including approval/rejection thereof).

429 Responsibility for production and for quality control cannot be assumed by the same person.
430 In small organisations, where teams are multi-skilled and trained in both QC and production
431 activities, it is acceptable that the same person is responsible for both roles (production and
432 quality control) with respect to different batches. In those cases, it becomes particularly
433 important that the independency of the QC activities from the production activities for the
434 same batch is clearly established through appropriate written procedures.

435 **4. Premises**

436 **4.1. General principles**

437 Premises must be suitable for the operations to be carried out. In particular, they should be
438 designed to minimise the opportunity for extraneous contamination, cross-contamination, the
439 risk of errors and, in general, any adverse effect on the quality of products.

440 It is important that the following general principles are implemented:

- 441 (a) Premises should be kept clean (disinfection to be applied as appropriate).
- 442 (b) Premises should be carefully maintained, ensuring that repair and maintenance
443 operations do not present any hazard to the quality of products.
- 444 (c) Lighting, temperature, humidity and ventilation should be appropriate for the
445 activities performed and should not adversely affect the ATMPs or the
446 functioning of equipment.

- 447 (d) Appropriate measures to monitor key environmental parameters should be
448 applied.
- 449 (e) Steps should be taken to prevent the entry of unauthorised people. Production,
450 storage and quality control areas should not be used as a transit area by
451 personnel who do not work in them. When such passage is unavoidable,
452 appropriate control measures should be applied.
- 453 (f) The manufacture of technical poisons, such as pesticides and herbicides, should
454 not be allowed in premises used for the manufacture of ATMPs.

455 For production of ATMPs, the premises should be qualified (*see* Section 10.1).

456 4.2. Production areas

457 4.2.1. Design and construction

458 Manufacture in a multi-product facility is acceptable when appropriate risk-mitigation
459 measures commensurate with the risks are implemented to prevent cross-contamination.
460 Further explanations can be found in Section 9.4.

461 If the manufacturing site produces medicinal products other than ATMPs, the manufacture of
462 ATMPs should take place in a dedicated area of the facility. In the case of manufacturing of
463 investigational ATMPs, it is accepted that the same area is used for multiple purposes,
464 provided that appropriate cleaning and procedural controls are in place to ensure that there is
465 no carry-over of materials or products, or mix-ups.

466 Segregated production areas (*see* Section 9.4(i)) should be used for the manufacturing of
467 ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical
468 measures. Specifically, manufacturing activities involving infectious viral vectors (*e.g.*
469 oncolytic viruses) or materials from infected donors⁴ should be done in a segregated area. The
470 arrangements for the segregation of the area should be demonstrated to be effective. Closed
471 systems should be used wherever possible.

472 In the case of investigational ATMPs, where there are no separate production suites, a
473 thorough cleaning and decontamination procedure should take place before any subsequent
474 manufacturing in the same area can occur.

475 It is recommended that the design of the premises permits the production to take place in
476 areas connected in a logical order corresponding to the sequence of the operations and
477 required level of cleanliness. Likewise, the arrangement of the working environment and of
478 the equipment and materials should be adequate to minimise the risk of confusion between
479 different products or their components, to avoid cross-contamination, and to minimise the risk
480 of omission or wrong application of any of the manufacturing or control steps.

⁴Donors that have tested positively for HIV 1 and 2, Hepatitis B, Hepatitis C or Syphilis.

481 The lay out of the premises should permit the separation of flows of contaminated materials
482 and equipment from those sterilized/non-contaminated. Where this is not possible, the
483 handling of contaminated materials/equipment should be separated in time.

484 Production areas should be effectively ventilated, with air control systems (including
485 temperature and, where necessary, humidity and filtration of air) appropriate both to the
486 products handled, to the operations undertaken within them, and to the external environment.

487 Air handling units should be designed, constructed, and maintained to prevent the risk of
488 cross-contamination between different areas in the manufacturing site and may need to be
489 specific for an area. Depending on specific risks of the product, the use of single pass air
490 systems should be considered.

491 *4.2.2. Aseptic environment*

492 Premises should be suitable for the intended operations and they should be adequately
493 controlled to ensure an aseptic environment. The measures implemented to ensure an aseptic
494 environment should be adequate having regard to all the specific risks of the product and the
495 manufacturing process. Special attention should be paid to products for which there is no
496 sterilisation of the finished product.

497 Clean areas

498 A critical clean area is an area where the product is exposed to environmental conditions and
499 the design thereof should therefore be designed to ensure sterility. The air in the immediate
500 vicinity of the critical clean area should be adequately controlled also (background clean
501 area).

502 Clean areas should be supplied with air which has passed through filters of an appropriate
503 efficiency. The appropriate level of air classification should be determined having regard to
504 the specific risks taking into account the nature of the product and the manufacturing process,
505 in particular whether processing takes place in an open or closed system.

506

- Production in a closed system⁵ or in an isolator: a background clean area of D grade is
507 acceptable.

508 Isolators should be introduced only after appropriate validation. Validation should take
509 into account all critical factors of isolator technology, for example the quality of the
510 air inside and outside (background) the isolator, sanitisation of the isolator, the transfer
511 process and the isolator's integrity.

512 Monitoring should be carried out routinely and should include frequent leak testing of
513 the isolator and glove/sleeve system. The transfer of materials into and out of the

⁵A closed system ensures that, during the manufacturing process, the product is not exposed to the environment.

514 isolator is one of the greatest potential sources of contamination and appropriate
515 control measures should be put in place.

516 ■ Production in an open system: In general, when the product is exposed to the
517 environment (*e.g.* working under laminar air flow), a critical clean area of grade A
518 with a background clean area of grade B (or similarly controlled environment) is
519 required.

520 In the case of production in an open system, the following considerations apply:

- Preparation of solutions which are to be sterile filtered during the process can be done in a grade C environment.

521 - For the manufacturing process of viral vectors, two steps should be considered:
522 ○ The expansion phase before the sterilizing filtration can be performed
523 in a critical clean area of grade A with a background clean area of
524 grade C.
525 ○ The sterilizing filtration and filling need to be performed in a critical
526 clean room of grade A with a background clean room of grade B.

527 The classification of clean rooms/clean air devices should be done according to ISO 14644-1.
528 For qualification, the airborne particles equal to or greater than 0.5 µm should be measured.
529 This measurement should be performed both at rest⁶ and in operation⁷. The maximum
530 permitted airborne particle concentration for each grade is as follows:

Maximum permitted number of particles equal or greater than 0.5 µm			
	At rest (per m ³)	In operation (per m ³)	ISO classification (At rest/in operation)
Grade			
A	3 520	3 520	5/5
B	3 520	352 000	5/7
C	352 000	3 520 000	7/8
D	3 520 000	Not defined	8

⁶ Room with all HVAC systems and installations functioning but without personnel and with equipment static. The particle limits should be measured after a short “clean up period” of approximately 15-20 minutes after completion of operations.

⁷ All equipment and installations are functioning and personnel is working in accordance with the manufacturing procedure.

531 The presence of containers and/or materials liable to generate fibres should be minimised in
532 the clean areas.

533 Appropriate cleaning/sanitation of clean areas is essential. Fumigation may be useful to
534 reduce microbiological contamination in inaccessible places. Where disinfectants are used, it
535 is advisable that more than one type is used to avoid the development of resistant strains.

536 Clean/contained areas should be accessed through an air lock with interlocked doors or by
537 appropriate procedural controls to ensure that both doors are not opened simultaneously.

538 4.2.3. Environmental monitoring

539 Environmental monitoring programs are an important part of the strategy to minimise the risk
540 of contamination. The environmental monitoring program should include the following
541 parameters: particulate matter/microbiological contamination, air pressure differentials,
542 airflow direction, temperature and relative humidity.

543 The monitoring locations should be determined having regard to the risks (*i.e.* at locations
544 posing the highest risk of contamination) and the results obtained during the qualification of
545 the premises.

546 Monitoring of clean rooms should be performed “in operation”. Additionally, monitoring “at
547 rest” should be performed as appropriate in order to identify potential incidents (*e.g.* prior to
548 the start of manufacturing and post sanitization).

549 The number of samples and frequency of monitoring should be appropriate taking into
550 account the risks and the overall control strategy.

551 Non-viable particulate monitoring

552 Airborne particle monitoring systems should be established to obtain data for assessing
553 potential contamination risks and to ensure an aseptic environment. The degree of
554 environmental control of non-viable particulate and the selection of the monitoring system
555 should be adapted to the specific risks of the product and of the manufacturing process. The
556 frequency, sampling volume or duration, alert limits and corrective actions should be
557 established case by case having regard to the risks. It is not necessary for the sample volume
558 to be the same as that used for qualification of the clean room.

559 The monitoring system should ensure that when alert limits are exceeded, the event is rapidly
560 identified (*e.g.* alarm settings). The recommended action limits are as follows:

	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
Grade	At rest		In operation	
	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900

C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Limit to be set according to the risks.	Limit to be set according to the risks.

561 For Grade A zones, particle monitoring should be undertaken for the full duration of critical
562 processing, including equipment assembly, except where duly justified (*e.g.* contaminants in
563 the process that would damage the particle counter or when this would present a hazard, *e.g.*
564 live pathogenic organisms). In such cases, monitoring during equipment set-up operations
565 should take place (*i.e.* prior to exposure of the product to the risk). Monitoring should also be
566 performed during simulated operations. The effectiveness of the segregation between the
567 Grade A and B zones is an important consideration when designing the monitoring system of
568 the grade B.

569 When there is no critical operations on-going (*i.e.* at rest), sampling at appropriate intervals
570 should be conducted. While at rest, the HVAC system should not be interrupted, as this may
571 trigger the need for re-qualification.

572 When ‘closed’ systems are used for the manufacture of ATMPs, it may be justified not to
573 conduct continued particle monitoring, for example when there is intrinsic particle generation
574 by the process (*e.g.* spraying of disinfectants). A rationale for not utilising continuous particle
575 monitoring should be documented, considering the risk to product and the source(s) of
576 particles generated. Validation should demonstrate that in the absence of identified particle
577 generating sources (such as spraying of sanitising agents under normal operating conditions),
578 the Grade A zone will conform to the environmental requirements. A periodic monitoring
579 exercise should demonstrate continued compliance with the requirements.

580 In Grade A and B zones, the monitoring of the $\geq 5.0 \mu\text{m}$ particle concentration is an important
581 diagnostic tool for early detection of failures. While the occasional indication of $\geq 5.0 \mu\text{m}$
582 particle counts may be false counts, consecutive or regular counting of low levels is an
583 indicator of a possible contamination and it should be investigated. Such events may indicate
584 early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor
585 practices during machine set-up and routine operation.

586 Viable particle monitoring

587 Checks to detect the presence of specific microorganisms in the environment (*e.g.* host
588 organism, yeast, moulds, anaerobes, *etc.*) should be performed as appropriate.

589 Where aseptic operations are performed, monitoring should be frequent using methods such
590 as settle plates, volumetric air and surface sampling (*e.g.* swabs and contact plates). Rapid
591 microbial monitoring methods should be considered and may be adapted after validation of
592 the premises. Sampling methods used in operation should not interfere with zone protection.

593 The frequency of monitoring should be determined according to the contamination risks
 594 associated with the characteristics of the product and of the manufacturing process (*e.g.* in a
 595 closed production system the risk of contamination from operators can be reduced and
 596 therefore the frequency of monitoring can also be reduced).

597 Surfaces and personnel should be monitored after critical operations. Additional
 598 microbiological monitoring is also required outside production operations, *e.g.* after
 599 validation of systems, cleaning and sanitisation.

600 The following recommended maximum limits for microbiological monitoring of clean areas
 601 apply (average values):

Grade	Air sample cfu/m ³	Settle plates (diameter 90mm) cfu/4 hours*	Contact plates (diameter 55 mm)	Cfu plate glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

602 *Individual settle plates may be exposed for less than 4 hours.

603 If these limits are exceeded, appropriate corrective actions should be taken. These should be
 604 documented.

605 Air pressure

606 An essential part of contamination prevention is the adequate separation of areas of operation.
 607 To maintain air quality, it is important to achieve a proper airflow from areas of higher
 608 cleanliness to adjacent less clean areas. It is fundamental for rooms of higher air cleanliness
 609 to have a substantial positive pressure differential relative to adjacent rooms of lower air
 610 cleanliness. These pressure cascades should be clearly defined and continuously monitored
 611 with appropriate methods (*e.g.* alarm settings). Adjacent rooms of different grades should
 612 have a pressure differential of 10-15 Pa.

613 However, negative pressure in specific areas may be required in for containment reasons (*e.g.*
 614 when replication competent vectors or infectious materials are used). In such cases, the
 615 negative pressure areas should be surrounded by a positive pressure clean zone of appropriate
 616 grade.

617 4.2.4. Drains

618 Drains should be of adequate size, and have trapped gullies. Drainage systems must be
 619 designed so that effluents can be effectively neutralised or decontaminated to minimise the
 620 risk of cross-contamination. Open channels should be avoided where possible, but if
 621 necessary, they should be shallow to facilitate cleaning and disinfection. Manufacturers are
 622 reminded that, for risks relating to biohazard waste, local regulations should be followed.

623 Clean areas Grade A/B should not have drains installed.

624 **4.3. Storage areas**

625 Storage areas should be of sufficient capacity to allow orderly storage of the various
626 categories of materials and products: starting and packaging materials, intermediate, bulk and
627 finished products, products in quarantine, released, rejected, returned or recalled.

628 Storage areas should be clean and dry and maintained within acceptable temperature limits.
629 Where special storage conditions are required (*e.g.* temperature, humidity) these should be
630 specified and monitored.

631 Where quarantine status is ensured by storage in separate areas, these areas should be clearly
632 marked and their access restricted to authorised personnel. Any system replacing the physical
633 quarantine should give equivalent security.

634 Separated areas should be provided for the storage of rejected, recalled or returned materials
635 or products, unless control of these materials/products is ensured through electronic means.

636 Highly reactive materials or products should be stored in safe and secure areas.

637 **4.4. Quality control areas**

638 Control laboratories should be designed to suit the operations to be carried out in them.
639 Sufficient space should be given to avoid mix-ups and cross-contamination. There should be
640 adequate suitable storage space for samples and records.

641 Quality control laboratories should normally be separated from production areas. However,
642 in-process controls may be carried out within the production area provided that they do not
643 carry any risk for the products. Further details are available in Section 12.1.

644 **4.5. Ancillary areas**

645 Rest and refreshment rooms should be separate from production, storage and quality control
646 areas. Toilets and washrooms should not directly communicate with production, storage and
647 quality control areas.

648 Premises where laboratory animals are kept should be isolated from production, storage and
649 quality control areas with separate entrance and air handling facilities.

650 **5. Equipment**

651 **5.1. General principles**

652 Equipment used in production or control operations should be suitable for its intended
653 purpose and it should not present any hazard to the product. Parts of production equipment
654 that come into contact with the product should not have unwanted reactive, additive,
655 adsorptive or absorptive properties that may affect the quality of the product.

656 The integrity of the components should be verified as appropriate having regard to the
657 specific risk of the product and the intended manufacturing process (*e.g.* ensuring structural
658 integrity during freeze and thawing).

659 The location and installation of the equipment should be adequate to minimise risks of errors
660 or contamination. Aseptic connections should be performed in a critical clean area of grade A
661 with a background clean area of grade B.

662 Balances and measurement equipment should be of appropriate range and precision to ensure
663 the accuracy of weighing operations.

664 Qualification of relevant equipment should be done in accordance with the principles in
665 Section 10.1.

666 Defective equipment should, if possible, be removed from production and quality control
667 areas, or at least be clearly labelled as defective.

668 **5.2. Maintenance, cleaning, repair**

669 Equipment should be adequately maintained:

670 - Equipment shall be calibrated, inspected or checked (as appropriate) at defined
671 intervals to ensure adequate performance. In the case of computerised systems, the
672 checks should include an evaluation of the ability of the system to ensure data
673 integrity. Appropriate records of those checks shall be maintained.

674 - Air vent filters should be hydrophobic and validated with integrity testing at
675 appropriate intervals taking into account the specific risks.

676 Adequate cleaning and storage of the equipment is essential in order to avoid the risk of
677 contamination for the products. Whenever possible, single-use cleaning materials should be
678 used, preferably pre-sterilized/sterile. The cleaning/decontamination procedures applied to
679 multi-use equipment coming into contact with the product should be validated (*see* Section
680 10.2).

681 Repair and maintenance operations should not present any hazard to the quality of the
682 products. As far as possible, maintenance and repair operations should be done outside the
683 clean area. When repair or cleaning operations occur in a clean area, production should not
684 be restarted until it has been verified that the area has been adequately cleaned.

685 Where required to minimise the risk of cross-contamination, restrictions on the movement of
686 equipment should be applied. In general, equipment should not be moved from high risk
687 areas to other areas or between high risk areas (*e.g.* equipment used for the handling of cells
688 from infected donors or the handling of oncolytic viruses). When this happens, appropriate
689 measures need to be applied to avoid the risk of cross-contamination. The qualification status
690 of the equipment moved should also be reconsidered.

691 **6. Documentation**

692 **6.1. General principles**

693 Good documentation is an essential part of the quality system and is a key element of GMP.
694 The main objective of the system of documentation utilized must be to establish, control,
695 monitor and record all activities which directly or indirectly may affect the quality of
696 medicinal products. Records required to ensure traceability should also be kept.

697 There are two primary types of documentation relevant for the quality assurance system:
698 specifications/instructions (including -as appropriate- technical requirements, SOPs, and
699 contracts) and records/reports.

700 Documentation may exist in a variety of forms, including paper-based, electronic or
701 photographic media. Irrespective of the form in which data is kept, suitable controls should
702 be implemented to ensure data integrity, including:

- 703 - Implementation of measures to protect data against accidental loss or damage, *e.g.* by
704 methods such as duplication or back-up and transfer to another storage system.
- 705 - Implementation of measures to protect the data against tampering or unauthorised
706 manipulation.
- 707 - Implementation of measures to ensure the accuracy, completeness, availability and
708 legibility of documents throughout the retention period.

709 **6.2. Specifications and Instructions**

710 The specifications for the materials and the finished product and the manufacturing
711 instructions are intended to ensure compliance with the terms of the marketing
712 authorisation/clinical trial authorisation, product consistency (appropriate to the relevant stage
713 of development), and the required level of quality. Therefore, it is important that
714 specifications and instructions are documented appropriately and that they are clear and
715 detailed enough.

716 Documents containing specifications and instructions (including changes thereto) should be
717 approved, signed and dated by appropriate and authorised persons and the date of entry into
718 operation should be defined.

719 Specifications and instructions should be periodically re-assessed during development and
720 post-authorisation and be updated as necessary. Each new version should take into account
721 the latest data, current technology used, as well as the terms of the marketing
722 authorisation/clinical trial authorisation. It should also allow traceability to the previous
723 document.

724 Rationales for changes should be recorded and the consequences of a change on product
725 quality, safety or efficacy and, where applicable, on any on-going non-clinical study or
726 clinical trials should be investigated and documented. It is recalled that changes into the

727 manufacturing requirements approved as part of the marketing authorisation must be
728 submitted to the competent authorities (variation procedure),⁸ and that substantial
729 modifications in the manufacturing process of an investigational ATMP require approval by
730 the competent authorities.⁹

731 As a minimum, the following should be documented:

- 732 (i) Specifications for raw materials, including:
- 733 - Description of the raw materials, including reference to designated name and
734 any other information required to avoid risks of error (*e.g.* use of internal
735 codes). For raw materials of biological origin, the identification of the supplier
736 and anatomical environment from which materials originate should also be
737 described.
 - 738 - For critical raw materials, quality requirements to ensure suitability for
739 intended use, as well as acceptance criteria. Quality requirements agreed with
740 suppliers should be kept (*see* Section 7.2).
 - 741 - Instructions for sampling and testing, as appropriate (*see* Section 7.2, 12.2 and
742 12.3).
 - 743 - Storage conditions and maximum period of storage.
 - 744 - Transport conditions and precautions.
- 745 (ii) Specifications for starting materials, including:
- 746 - Description of the starting materials, including any relevant information
747 required to avoid risks of error (*e.g.* use of internal codes). For starting
748 materials of human origin, the identification of the supplier and the anatomical
749 environment from which the cells/tissues/virus originate (or, as appropriate,
750 the identification of the cell-line, master cell bank, seed lot) should also be
751 described.
 - 752 - Quality requirements to ensure suitability for intended use, as well as
753 acceptance criteria. Contracts and quality requirements agreed with the
754 suppliers should be kept (*see* Section 7.3).
 - 755 - Sampling and testing instructions (*see* Sections 7.3, 12.2 and 12.3).
 - 756 - Storage conditions and maximum period of storage.
 - 757 - Transport conditions and precautions.
- 758 (iii) Specifications for intermediate and bulk products should be available where
759 applicable, including release and rejection criteria.
- 760 (iv) Specifications for primary packaging materials, including release and rejection
761 criteria.

⁸Commission Regulation (EC) No 1234/2008 of 24 of November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L334, 12.12.2008, p.7), as amended.

⁹The definition of substantial modification is provided for under Article 2.2(13) of the Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

- 762 (v) Specifications for other materials that are used in the manufacturing process and that
763 can have a critical impact on quality, where appropriate (*e.g.* medical devices used in a
764 combined ATMP).
- 765 (vi) Batch definition. For autologous products, each unit should be considered a distinct
766 batch.
- 767 (vii) Manufacturing instructions, including description of principal equipment to be used.
- 768 (viii) Specifications for finished products, in particular:
- 769 - Name/identification of the product.
- 770 - Description of the pharmaceutical form.
- 771 - Instructions for sampling and testing (*see* Sections 12.2 and 12.3).
- 772 - Qualitative and quantitative requirements with acceptance limits.
- 773 - Storage and transport conditions and precautions. Where applicable, particular
774 attention should be paid to the requirements at cryopreservation stage (*e.g.* rate
775 of temperature change during freezing) to ensure the quality of the product.
- 776 - The shelf-life.
- 777 (ix) Where applicable, the control strategy to address cases when test results for starting
778 materials, intermediates and/or finished product are not available prior to product
779 release (*see* Section 11.3.2).
- 780 (x) Packaging instructions for each product. Particular attention should be paid to ensuring
781 the traceability of the product. It is recalled that, for authorised ATMPs, the
782 identification code received from the tissue establishment/blood establishment, should
783 be included in the outer packaging or, where there is no outer packaging, on the
784 immediate packaging.¹⁰
- 785

786 Investigational ATMPs: the Product Specification File

787 In the case of investigational ATMPs, the level of detail of the specifications and instructions
788 should be adapted to the type of product and to the stage of development. Given the
789 evolution/refinement of the manufacturing process and quality controls that is typical of
790 investigational products, it is important that the level of documentation is sufficient to enable
791 the identification of the specific characteristics of each batch. It is also noted that a deficient
792 characterization of the product may hinder the acceptability of the results of the clinical trial
793 for the purposes of obtaining a marketing authorisation.

794 In addition to the specifications and instructions, the Product Specification File should contain
795 appropriate documentation of the system used to ensure the blinding while allowing for
796 identification of the product when necessary. The effectiveness of the blinding procedures
797 should be verified.

798 A copy of the manufacturing order and a copy of the approved label should also be kept as
799 part of the Product Specification File.

¹⁰See Article 11 of Regulation (EC) No. 1394/2007 on advanced therapy medicinal products.

800 **6.3. Records/reports**

801 Records provide evidence that the relevant specifications/instructions have been complied
802 with. Records should be made or completed at the time each action is taken. Any change to a
803 record should be approved, signed and dated by authorised persons.

804 The level of documentation will vary depending on the product and stage of development.
805 The records should enable the entire history of a batch to be traced. Additionally, the
806 records/reports should form the basis for assessment of the suitability for certification and
807 release of a particular batch. Where different manufacturing steps are carried out at different
808 locations under the responsibility of different QPs, it is acceptable to maintain separate files
809 limited to information of relevance to the activities at the respective locations. As a
810 minimum, the following should be documented:

811 (i) Receipt records for each delivery of raw materials, starting material, bulk,
812 intermediate as well as primary packaging materials. The receipt records should
813 include:

- 814 - name of the material on the delivery note and the containers as well as any “in-
815 house name” and or code if appropriate;
- 816 - supplier’s name and manufacturer’s name;
- 817 - supplier’s batch or reference number;
- 818 - total quantity received;
- 819 - date of receipt;
- 820 - unique receipt number assigned after receipt; and
- 821 - any relevant comment.

822 (ii) A batch processing record should be kept for each batch processed; it should contain
823 the following information:

- 824 - name of the product and batch number;
- 825 - dates and times of commencement, of critical intermediate stages and of
826 completion of production;
- 827 - quantities and batch number of each starting material;
- 828 - quantities and batch number of critical raw materials;
- 829 - identification (*e.g.* by means of initials or another suitable system) of the
830 operator who performed each significant step and, where appropriate, of the
831 person that checked these operations;
- 832 - a record of the in-process controls (*see* Section 12.3);
- 833 - the product yield obtained at relevant stages of manufacture;
- 834 - notes on special problems including details, with signed authorisation for any
835 deviation from the manufacturing instructions.

836 (iii) Results of release testing.

837 (iv) Environmental monitoring records.

838 (v) On-going stability program in accordance with Section 12.4 (for authorised ATMPs).

839 Any deviations should be recorded and investigated, and appropriate corrective measures
840 should be taken.

841 **6.4. Other documentation**

842 There should be appropriate documentation of policies and procedures to be applied by the
843 manufacturer with a view to safeguard the quality of the product, including:

- 844 (i) Qualification of premises and equipment.
- 845 (ii) Validation of manufacturing process.
- 846 (iii) Validation of relevant analytical methods.
- 847 (iv) Maintenance and calibration of equipment.
- 848 (v) Cleaning procedures.
- 849 (vi) Environmental monitoring.
- 850 (vii) Investigations into deviations and non-conformances.
- 851 (viii) Outcome of self-inspections should be recorded. Reports should contain all the
852 observations made during the inspections and, where applicable, proposals for
853 corrective measures. Statements on the actions subsequently taken should also be
854 recorded.
- 855 (ix) Procedure for recall of products.

856 Logbooks should be kept for equipment used for critical manufacturing and testing
857 operations.

858 The documentation of the above policies and procedures should be adjusted to the stage of
859 development. The documentation for Phase I/II clinical trials can be more limited but it is
860 expected that it becomes more comprehensive in later phases of development.

861 A site master file should be prepared for every site involved in manufacturing of authorised
862 ATMPs. The site master file should provide a high level description of the premises, activities
863 conducted at the site and of the quality system implemented.¹¹

864 **6.5. Retention of documents**

865 Batch documentation (*i.e.* documents in the batch processing record, results of release testing,
866 as well as -where applicable- any data on product related deviations) should be kept for one
867 year after expiry of the batch to which it relates or at least five years after certification of the
868 batch by the QP, whichever is the longest. For investigational medicinal products, the batch
869 documentation must be kept for at least five years after the completion or formal
870 discontinuation of the last clinical trial in which the batch was used.

¹¹ ATMPs manufacturers may follow the principles laid down in http://ec.europa.eu/health/files/eudralex/vol-4/2011_site_master_file_en.pdf

871 It is acceptable that some of the data pertaining to the batch documentation is kept in a
872 separate file, provided that they are readily available and are unequivocally linked to the
873 relevant batch.

874 Critical documentation, including raw data (for example relating to validation or stability) that
875 supports information in the marketing authorisation, should be retained whilst the
876 authorization remains in force. However, it is acceptable to retire certain documentation (*e.g.*
877 raw data supporting validation reports or stability reports) where the data has been superseded
878 by a full set of new data. Justification for this should be documented and should take into
879 account the requirements for retention of batch documentation.

880 **6.6. Traceability**

881 The traceability of the cells/tissues contained in ATMPs should be ensured so that the donor
882 of the cells and tissues used as starting materials can be identified, through the entire
883 manufacturing process, storage and transport, up to the delivery of the finished product to the
884 recipient.

885 In accordance with Article 15 of Regulation 1394/2007, traceability information should also
886 cover raw materials and all substances coming into contact with the cells or tissues. This
887 Section develops the type and amount of data that must be generated and kept by
888 manufacturers of ATMPs.

889 The manufacturer should ensure that the following data is retained for a minimum of 30 years
890 after the expiry date of the product, unless a longer period is provided for in the marketing
891 authorisation:

- 892 (i) Donor identification code received from the tissue establishment/blood establishment.
893 For cells and tissues that are not covered by Directive 2004/23 or Directive 2002/98¹²,
894 such as cell-lines or cell-banks established outside the EU, information permitting the
895 identification of the donor should be kept.
- 896 (ii) Internal code (or other identification system) that is generated by the manufacturer to
897 unequivocally identify the tissues/cells used as starting materials throughout the entire
898 manufacturing process up to the point of batch release. The manufacturer must ensure
899 that the link between the internal code and the donor identification code can always be
900 established. For starting materials not covered by Directive 2004/23 or Directive
901 2002/98, it should be ensured that a link between the internal code and the donor
902 identification can always be established.
- 903 (iii) Identification (including batch number) of critical raw materials and other substances
904 that come into contact with the cells or tissues used as starting materials that may have

¹²Directive 2002/98 of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

905 a significant impact on the safety of the finished ATMP (*e.g.* reagents of biological
906 origin, scaffolds, matrixes). For biological materials, the identification of the supplier
907 and anatomical environment from which materials originate should also be described.

908 (iv) Where applicable, identification (including batch number) of all other active
909 substances that are contained in the ATMPs.

910 When xenogeneic cells are used as starting materials for ATMPs, information permitting the
911 identification of the donor should be kept for 30 years.

912 Traceability data should be kept as auditable documents. It is acceptable that it is kept outside
913 the batch processing record, provided that they are readily available and are unequivocally
914 linked to the relevant medicinal product.

915 **7. Starting and raw materials¹³**

916 **7.1. General principles**

917 The quality of starting and raw materials is a key factor to consider in the production of
918 ATMPs. Particular attention should be paid to avoiding contamination and to minimising as
919 much as possible the variability of the starting and raw materials. Prior to introduction in the
920 manufacturing process, the conformity to the relevant requirements should be checked.

921 The use of antimicrobials may be necessary to reduce bioburden associated with the
922 procurement of living tissues and cells. However, it is stressed that the use of antimicrobials
923 does not replace the requirement for aseptic manufacturing. When antimicrobials are used,
924 they should be removed as soon as possible, unless the presence thereof in the finished
925 product is specifically foreseen in the marketing authorisation/clinical trials authorisation (*e.g.*
926 antibiotics that are part of the matrix of the finished product). Additionally, it is important to
927 ensure that antibiotics do not interfere with the sterility testing, and that they are not present in
928 the finished product (unless specifically foreseen in the marketing authorisation/clinical trial
929 authorisation).¹⁴

930 **7.2. Raw Materials**

931 Raw materials should be of suitable quality having regard to the intended use. In particular,
932 the growth promoting properties of culture media should be demonstrated to be suitable for its
933 intended use.

934 Where possible, raw materials used in the manufacturing of ATMPs should take into
935 consideration the *Ph. Eur* 5.2.12 *general chapter on raw materials of biological origin for the*
936 *production of cell based and gene therapy medicinal products*. While raw materials should be
937 of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research

¹³The definition of “raw materials” and “starting materials” is provided for in Part IV of the Annex to Directive 2001/83/EC on the Community code relating to medicinal products for human use.

¹⁴Ph.Eur. chapter 2.6.12 on sterility testing describes the use of neutralising substances for products containing antibiotics.

938 grade are available. The risks of using research grade materials should be understood
939 (including the risks to the continuity of supply when larger amounts of product are
940 manufactured). Additionally, the manufacturer should ensure the suitability of such raw
941 materials for the intended use, including –where appropriate– by means of testing (*e.g.*
942 functional test). The ATMP manufacturer should put in place appropriate measures to ensure
943 that raw materials can be traced in order to facilitate recall of products if necessary.

944 The ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder)
945 should establish quality requirements for critical raw materials (specifications) which -where
946 applicable- should be agreed with the supplier(s). The assessment whether a specific raw
947 materials is critical should be done by the manufacturer having regard to the specific risks.
948 The decisions taken should be documented. These specifications should cover aspects of the
949 production, testing and control, and other aspects of handling and distribution as appropriate.
950 The specifications set should be in compliance with the terms of the marketing authorisation
951 or clinical trial authorisation.

952 The ATMP manufacturer should verify compliance of the supplier’s materials with the agreed
953 specifications. The level of supervision and further testing by the ATMP manufacturer should
954 be proportionate to the risks posed by the individual materials. Reliance on the certificate of
955 analysis of the supplier is acceptable if all the risks are duly understood and measures are put
956 in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of
957 suppliers). For raw materials that are authorised as medicinal products (*e.g.* cytokines, human
958 serum albumin, recombinant proteins) the certificate of analysis of the supplier is not
959 required.

960 The risk of contamination of raw materials of biological origin during their passage along the
961 supply chain must be assessed, with particular emphasis on viral and microbial safety and
962 Transmissible Spongiform Encephalopathy (“TSE”). Compliance with the latest version of
963 the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform
964 Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required.¹⁵

965 The risk of contamination from other raw materials that come into direct contact with
966 manufacturing equipment or the product (such as media used for process simulation tests and
967 lubricants that may contact the product) should also be taken into account.

968 Critical raw materials in the storage area should be appropriately labelled. Labels should bear
969 at least the following information:

- 970 - the designated name of the product and the internal code reference (if applicable);
- 971 - a batch number given at receipt;
- 972 - storage conditions;
- 973 - the status of the contents (*e.g.* in quarantine, on test, released, rejected);
- 974 - an expiry date or a date beyond which retesting is necessary.

¹⁵http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf
(updated as appropriately).

975 When fully computerised storage systems are used, all the above information need not
976 necessarily be in a legible form on the label. The use of automated systems (*e.g.* use of
977 barcodes) is permissible.

978 Only raw materials that have been released by the person/department responsible for quality
979 control should be used.

980 **7.3. Starting Materials**

981 The donation, procurement and testing of human tissues and cells used as starting materials
982 should be in accordance with Directive 2004/23/EC.¹⁶ When the cells/tissues used are outside
983 the scope of the Directive (*e.g.* cell-lines/cell banks established outside the EU, or cells
984 procured before the entry into force of the Directive), the ATMP manufacturer should take
985 appropriate steps to ensure the quality, safety and traceability thereof, in accordance with the
986 terms of the marketing authorization/clinical trial authorisation.

987 The ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder)
988 should establish quality requirements for the starting materials (specifications) which should
989 be agreed with the supplier(s). These specifications should cover aspects of the production,
990 testing and control, and other aspects of handling and distribution as appropriate. Depending
991 on the product's characteristics, testing in addition to that foreseen in the Directive 2004/23
992 may be required. The specifications set should be in compliance with the terms of the
993 marketing authorisation or clinical trial authorisation.

994 The ATMP manufacturer should verify compliance of the supplier's materials with the agreed
995 specifications. The level of supervision and further testing by the ATMP manufacturer should
996 be proportionate to the risks posed by the individual materials. Blood establishments and
997 tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23
998 do not require additional audits by the ATMP manufacturer regarding compliance with the
999 requirements on donation, procurement and testing.

1000 In addition to the specifications for the starting materials, the agreement between the ATMP
1001 manufacturer and the supplier (including blood and tissue establishments) should contain
1002 clear provisions about the transfer of information regarding the starting materials, in
1003 particular, on tests results performed by the supplier, traceability data, and transmission of
1004 health donor information that may become available after the supply of the starting material
1005 and which may have an impact on the quality or safety of the ATMPs manufactured
1006 therefrom.

1007 The risk of contamination of the starting materials during their passage along the supply chain
1008 must be assessed, with particular emphasis on viral and microbial safety and Transmissible
1009 Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for

¹⁶ For blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing is likewise acceptable.

1010 Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE)
1011 Agents via Human and Veterinary Medicinal Products is required.

1012 Only starting materials that have been released by the person/department responsible for
1013 quality control should be used.

1014 Where the test(s) required to release the starting materials take a long time (*e.g.* sterility test),
1015 it may be permissible to process starting materials before the results of the test(s) are
1016 available. The risk of using a potentially failed material and its potential impact on other
1017 batches should be clearly assessed and understood. In such cases, the finished product can
1018 only be released if the results of these tests are satisfactory, unless appropriate risk mitigation
1019 measures are possible (*see* also section 11.3.2).

1020 Starting materials in the storage area should be appropriately labelled. Labels should bear at
1021 least the following information:

- 1022 - the designated name of the product and the internal code reference (if applicable);
- 1023 - a batch number given at receipt;
- 1024 - storage conditions;
- 1025 - the status of the contents (*e.g.* in quarantine, on test, released, rejected);
- 1026 - an expiry date or a date beyond which retesting is necessary.

1027 When fully computerised storage systems are used, all the above information need not
1028 necessarily be in a legible form on the label. The use of automated systems (*e.g.* use of
1029 barcodes) is permissible.

1030 The initial processing steps of the starting materials (*e.g.* isolation, purification) are
1031 manufacturing activities that should be conducted in accordance with the manufacturing
1032 requirements for pharmaceuticals,¹⁷ even if it is done by a third party (*e.g.* a tissue
1033 establishment). The use of cells that have been separated/isolated and preserved outside a
1034 GMP environment for the manufacture of an ATMP should remain exceptional and it is only
1035 possible if a risk analysis is performed to identify the testing requirements necessary to ensure
1036 the quality of the starting material. The overall responsibility for the quality – as well as the
1037 impact thereof on the safety and efficacy profile of the product- lies with the ATMP
1038 manufacturer, even if the activities have been outsourced, and their release for use in the
1039 manufacturing process should be done by the QC after verifying the quality and safety
1040 thereof. Additionally, the competent authorities should agree to the control strategy in the
1041 context of the assessment of the marketing authorisation application/clinical trial authorisation
1042 application.

1043 Additional considerations for xenogeneic cells and tissues:

¹⁷Donation, procurement and testing of cells and tissues are governed by Directive 2004/23/EC . These activities are not to be considered as processing of starting materials.

1044 The use of xenogeneic cells/tissues in the manufacture of ATMPs poses additional risks of
1045 transmitting known and unknown pathogens to humans, including the potential risk of
1046 introducing new infectious diseases. The selection of donor animals must therefore be strictly
1047 controlled. Source/donor animals should be healthy and should be specific pathogen free
1048 (SPF)¹⁸ and be raised in SPF conditions, including health monitoring. The donor/source
1049 animal should have been bred in captivity (barrier facility) specifically designed for this
1050 purpose. In the manufacture of ATMPs, it is not acceptable to use xenogeneic cells and
1051 tissues from wild animals or from abattoirs. Cells and tissues of founder animals¹⁹ similarly
1052 should not be used.

1053 Appropriate measures should be implemented to identify and prevent incidents that negatively
1054 affect the health of the source/donor animals or that could negatively impact on the barrier
1055 facility or the SPF status of the source/donor animals. In addition to compliance with TSE
1056 regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of
1057 source animals) should be monitored and recorded. Specialist advice should be obtained in
1058 establishing the monitoring program.

1059 Instances of ill-health occurring in the herd should be investigated with respect to the
1060 suitability of in-contact animals for continued use (in manufacture, as sources of starting and
1061 raw materials, in quality control and safety testing). The decisions taken must be
1062 documented. A look-back procedure should be in place which informs the decision-making
1063 process on the continued suitability of the biological active substance or medicinal product in
1064 which the animal sourced cells/tissues have been used or incorporated. This decision-making
1065 process may include the re-testing of retained samples from previous collections from the
1066 same donor animal (where applicable) to establish the last negative donation. The withdrawal
1067 period of therapeutic agents used to treat source/donor animals must be documented and used
1068 to determine the removal of those animals from the programme for defined periods.

1069 **8. Seed lot and cell bank system**

1070 It is recommended that the system of master and working seed lots/cell banks is used for
1071 allogeneic products which do not require a match between the donor and the patient.
1072 However, the establishment of seed lots/cell banks is not mandatory.

1073 When seed lots and cell banks, including master and working generations are used, they
1074 should be established under appropriate conditions, including compliance with GMP as
1075 provided for in these Guidelines. This should include an appropriately controlled environment
1076 to protect the seed lot and the cell bank and the personnel handling it. During the
1077 establishment of the seed lot and cell bank, no other living or infectious material (*e.g.* virus,
1078 cell lines or cell strains) should be handled simultaneously in the same area.

¹⁸Specific pathogen free means that the animals are derived from groups (*e.g.* flocks or herds) of animals free from specified pathogens. Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

¹⁹Founder animals are the animals from which the source animals are initially bred.

1079 The number of generations (doublings, passages) should be consistent with specifications in
1080 the marketing authorisation/clinical trial authorisation.

1081 For stages prior to the master seed or cell bank generation, documentation should be available
1082 to support traceability including issues related to components used during development with
1083 potential impact on product safety (*e.g.* reagents of biological origin) from initial sourcing and
1084 genetic development if applicable.

1085 However, it is acknowledged that comprehensive information may not be available for seed
1086 lots and cell banks established in the past. The use of starting materials coming from such
1087 seed lots/cell banks can only be accepted in exceptional cases and provided that there is
1088 extensive characterisation to compensate for the missing information. Additionally, the
1089 competent authorities should agree to the strategy in the context of the assessment of the
1090 marketing authorisation application/clinical trial authorisation application.

1091 Cell bank safety testing and characterisation are important for batch-to-batch consistency and
1092 to prevent contamination with adventitious agents. Seed lots and cell banks should be stored
1093 and used in such a way as to minimize the risks of contamination (*e.g.* stored in the vapour
1094 phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage
1095 of different seeds/cells in the same area or equipment should prevent mix-up and take account
1096 the infectious nature of the materials to prevent cross-contamination.

1097 Storage containers should be sealed, clearly labelled and kept at an appropriate temperature.
1098 A stock inventory must be kept. The storage temperature should be recorded continuously
1099 and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective
1100 and preventive action taken should be recorded.

1101 It is desirable to split stocks and to store the split stocks at different locations so as to
1102 minimize the risks of total loss. The controls at such locations should provide the assurances
1103 outlined in the preceding paragraphs.

1104 Following the establishment of cell banks and master and viral seed lots, quarantine and
1105 release procedures should be followed. Evidence of the stability and recovery of seeds and
1106 banks should be documented and records should be kept in a manner permitting trend
1107 evaluation. In the case of investigational ATMPs, a gradual approach is acceptable. Thus,
1108 preliminary stability data (*e.g.* from earlier phases of development or from suitable cell
1109 models) should be available before the product is used in a clinical trial, and the stability data
1110 should be built-up with real-life data as the clinical trial progresses.

1111 Containers removed from the cryostorage unit, can only be returned to storage if it can be
1112 documented that adequate conditions have been maintained.

1113 Cell Stock

1114 Cell-based products are often generated from a cell stock obtained from a limited number of
1115 passages. In contrast with the two tiered system of master and working cell banks, the
1116 number of production runs from a cell stock is limited by the number of aliquots obtained
1117 after expansion and does not cover the entire life cycle of the product. Cell stock changes
1118 (including introduction of cells from new donors) should be addressed in the marketing
1119 authorisation/clinical trial authorisation and the conditions therein should be complied with.

1120 When cell stocks are used, the handling, storage and release of cells should be done in
1121 accordance with the principles outlined above for cell banks.

1122 Cell stocks/banks and viral seed stocks established in the past outside of GMP conditions

1123 The establishment of new cell stocks/banks and viral seed stocks should be done in
1124 accordance with GMP. In exceptional and justified cases, it might be possible to accept the
1125 use of cell stocks/cell banks and viral seed stocks that were generated in the past without full
1126 GMP compliance. In these cases, a risk analysis should be conducted to identify the testing
1127 requirements necessary to ensure the quality of the starting material. In all cases, the overall
1128 responsibility for the quality – as well as the impact thereof on the safety and efficacy profile
1129 of the product- lies with the ATMP manufacturer.

1130 The use of starting materials from cell stocks/cell banks and viral seed stocks generated (in
1131 the past) without full GMP in the manufacture of an ATMP should be approved by the
1132 competent authorities in the context of the assessment of the marketing authorisation
1133 application/clinical trial authorisation application.

1134 **9. Production**

1135 **9.1. General principles**

1136 Production operations, including filling, packaging and -as applicable- cryopreservation
1137 should follow clearly defined procedures designed to ensure the quality of the product,
1138 consistent production (appropriate to the relevant stage of development), and to comply with
1139 the requirements set in the relevant manufacturing and marketing/clinical trial authorization.

1140 In case of investigational ATMPs, the knowledge and understanding of the product may be
1141 limited, particularly for early phases of clinical trials (phase I and I/II). It is therefore
1142 acknowledged that the manufacturing process (including quality controls) may need to be
1143 adapted as the knowledge of the process increases. In the early phases of development, it is
1144 critical to carefully control and record the manufacturing process. It is expected that the
1145 manufacturing process and quality controls become more refined as development progresses.

1146 Manufacturing processes and their control strategies should be reviewed regularly, and they
1147 should be improved as appropriate. While this is especially relevant during the early phases
1148 of clinical trials, it is also important to consider steps necessary to reduce process variability
1149 and to enhance reproducibility at the different stages of the lifecycle.

1150 When any new manufacturing formula or manufacturing process is adopted, steps should be
1151 taken to demonstrate its suitability. The effects of changes in the production in relation to the
1152 quality of the finished product and consistent production (appropriate to the relevant stage of
1153 development) should be considered prior to implementation. Significant changes, which may
1154 affect the quality, safety or efficacy of the product or the reproducibility of the process,
1155 should be assessed through a comparability study to assess the impact thereof on the quality
1156 profile of the product and, based on that, to evaluate the potential impact on the safety and
1157 efficacy of the product. Any change to the manufacturing formula or manufacturing method
1158 should be managed in accordance with the principles set out in Section 6(2).

1159 Any deviation from instructions or procedures should be avoided as far as possible. If a
1160 deviation occurs, it should be approved in writing by the person responsible for
1161 manufacturing, with the involvement of the person/department responsible for quality control
1162 when appropriate.

1163 **9.2. Handling of incoming materials and products**

1164 All handling of materials and products (such as receipt and quarantine, sampling, storage,
1165 labelling and packaging) should be done in accordance with written procedures or instructions
1166 and recorded as appropriate. The control strategy should be adequate having regard to the
1167 risks.

1168 All incoming materials should be checked to ensure that the consignment corresponds to the
1169 order. Reliance on the documentation provided by third parties (*e.g.* supplier) is acceptable
1170 provided that all risks are duly understood and that appropriate measures are put in place to
1171 eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers).
1172 Where necessary, identity testing should be considered.

1173 Incoming materials and finished products should be physically or administratively
1174 quarantined immediately after receipt or processing, until they have been released for use or
1175 distribution.

1176 Intermediate and bulk products²⁰ purchased as such should be released by the
1177 person/department responsible for quality control before they can be used in production, after
1178 verification of compliance with the relevant specifications.

1179 All materials and products should be stored under appropriate conditions to ensure the quality.

1180 At all times during processing, all materials, bulk containers, major items of equipment and,
1181 where appropriate, rooms used should be labelled or otherwise identified with an indication of
1182 the product or material being processed, its strength (where applicable) and batch number.
1183 Where applicable, this indication should also mention the stage of production.

²⁰ “Bulk Product” is any product which has completed all processing stages up to, but not including, final packaging.

1184 Labels applied to containers, equipment or premises should be clear and unambiguous. It is
1185 often helpful, in addition to the wording on the labels, to use colours to indicate status (for
1186 example, quarantined, accepted, rejected, clean). The compatibility of labels with (*e.g.* ultra-
1187 low storage temperatures, waterbath) should be verified.

1188 Containers should be cleaned where necessary. Damage to containers and any other problem
1189 which might adversely affect the quality of a material should be investigated, recorded and
1190 reported to the person/department responsible for quality control.

1191 **9.3. Utilities**

1192 *9.3.1. Water*

1193 Water used in the manufacturing of ATMPs should be of appropriate quality and regular
1194 checks should be carried out to verify the absence of contamination (chemical and biological
1195 and, as appropriate, from endotoxins). In the case of water for injection, special attention
1196 should be paid to prevention of microbial growth, for example by constant circulation at a
1197 temperature above 70°C. Water for injection pipes, purified water piping and, where
1198 appropriate, other water pipes should be sanitised according to written procedures that detail
1199 the action limits for microbiological contamination and the measures to be taken.

1200 The use of pre-packaged water for injection compliant with the European Pharmacopeia
1201 removes the need for demonstrating the appropriateness of the quality of the water for
1202 injection as provided for in the previous paragraph.

1203 *9.3.2. Medical gases*

1204 Gasses that come into contact with the product during processing should be of suitable
1205 quality. Where possible, gasses compliant with the European Pharmacopoeia should be used.

1206 Gasses taken into the aseptic work place or that come into contact with the product should be
1207 passed through micro-organism retentive filters.

1208 *9.3.3. Clean steam*

1209 Steam used for sterilisation should be of suitable quality and free from additives at a level that
1210 could cause contamination of the product or equipment.

1211 **9.4. Prevention of cross-contamination in production**

1212 Before any manufacturing operation starts, steps should be taken to ensure that the work area
1213 and equipment are clean and free from any starting materials, products, product residues or
1214 documents not required for the current operation.

1215 At every stage of production, products and materials should be protected from microbial and
1216 other contamination. Mix-ups of materials should be prevented; special precautions should be
1217 taken to avoid the mixing of autologous materials or other dedicated materials. Appropriate
1218 measures should also be put in place to protect the preparation of solutions, buffers and other

- 1219 additions from the risk of contamination (or within the accepted bioburden level foreseen in
1220 the marketing authorisation/clinical trial authorisation).
- 1221 The risks of cross-contamination should be assessed having regard to the characteristics of the
1222 product (*e.g.* biological characteristics of the starting materials, possibility to withstand
1223 purification techniques) and manufacturing process (*e.g.* the use of processes that provide
1224 extraneous microbial contaminants the opportunity to grow). If sterilisation of the finished
1225 product is not possible, particular attention should be paid to the manufacturing steps where
1226 there is exposure to the environment (*e.g.* filling).
- 1227 Measures to prevent cross-contamination appropriate to the risks identified should be put in
1228 place. Measures that can be considered to prevent cross-contamination include, among
1229 others:
- 1230 (i) Segregated premises (*i.e.* separate cryostorage, separate production suite with separate
1231 HVAC, restrictions on the movement of personnel and equipment without appropriate
1232 decontamination measures) and dedicated equipment reserved solely for the
1233 production of one type of product with a specific risk profile.
- 1234 (ii) Dedicating the whole manufacturing facility or a self-contained production area on a
1235 campaign basis (separation in time) followed by a cleaning process of validated
1236 effectiveness.
- 1237 (iii) Use of “closed systems” for processing and material/product transfer between
1238 equipment.
- 1239 (iv) Use of air-locks and pressure cascade to confine potential airborne contaminant within
1240 a specified area.
- 1241 (v) Utilisation of single use disposable technologies.
- 1242 (vi) Adequate cleaning procedures. A risk-assessment should be used to determine the
1243 cleaning/decontamination procedures that are necessary, including the frequency
1244 thereof. For autologous products, there should be appropriate
1245 cleaning/decontamination between each batch. The cleaning/decontamination
1246 procedures should be validated (*see* Section 10.2).
- 1247 (vii) Other suitable technical measures, such as the dedication of certain parts of equipment
1248 (*e.g.* filters) to a given type of product with a specific risk profile.
- 1249 (viii) Other suitable organizational measures, such as keeping specific protective clothing
1250 inside areas where products with high-risk of contamination are processed,
1251 implementing adequate measures to handling waste, contaminated rinsing water and
1252 soiled gowning, or imposing restrictions on the movement of personnel.

1253 The effectiveness of the measures implemented to avoid cross-contamination should be
1254 reviewed periodically according to set procedures.

1255 Accidental spillages, especially of live organisms, must be dealt with quickly and safely.
1256 Qualified decontamination measures should be available taking into consideration the
1257 organism used in production, as well as the risks attached to the relevant biological materials.

1258 **9.5. Aseptic manufacturing**

1259 *9.5.1. General principles*

1260 The majority of ATMPs cannot be terminally sterilized. Therefore, the manufacturing
1261 process should be conducted aseptically (*i.e.* under conditions which prevent microbial
1262 contamination). In particular, this requires that, for any manufacturing activity that may
1263 expose the product to a risk of contamination, the following measures should be implemented:

- 1264 (i) The premises should comply with the requirements in Section 4.2.2 and 4.2.3.
- 1265 (ii) Manufacturing activities concerning different starting materials and/or finished
1266 products should be separated, either in place or in time.

1267 - Separation in place: “Closed systems” may be used to separate activities within the
1268 same room (each closed system is to be regarded as an area). Thus, the use of
1269 more than one isolator (or other closed systems) in the same room at the same time
1270 is acceptable, provided that there is separated expulsion of the exhausted air from
1271 the isolators and regular integrity checks of the isolator. Likewise, it is acceptable
1272 to conduct a manufacturing activity in a clean room which hosts an incubator which
1273 is used for a different batch/product if there is separated expulsion of exhausted air
1274 from the isolator and regular integrity checks of the isolator.

1275 The simultaneous incubation/storage of different batches within the same incubator
1276 is only acceptable if they are physically separated (*e.g.* distinct cell cultures in
1277 closed vessels). When simultaneous incubation/storage of different batches takes
1278 place as described above, the manufacturer should evaluate the possible risks and
1279 implement appropriate measures to avoid mix-ups of materials. However, the
1280 simultaneous incubation/storage of replication competent vectors/products based on
1281 them, or infected material/products based on them with other materials/products is
1282 not acceptable.

1283 Concurrent manufacture of different viral vectors in the same area is also not
1284 acceptable. However, it is possible to use two isolators to process different viral
1285 vectors within the same room if appropriate mitigation measures are taken to avoid
1286 cross-contamination or mix-ups of materials (*i.e.* regular integrity checks of the
1287 isolator; close, separate and unidirectional waste handling, separate expulsion of
1288 exhausted air from the isolators). Concurrent production of non-viral vectors in the
1289 same area is possible, provided that effective controls are put in place.

1290 - Separation in time: The whole manufacturing facility or a self-contained production
1291 area may be dedicated to the manufacturing of a specific product on a campaign basis
1292 followed by a cleaning process of validated effectiveness.

1293 (iii) Materials, equipment and other articles that are introduced in a clean area should not
1294 introduce contamination. To this end, the use of double-ended sterilisers sealed into a
1295 wall or other effective procedures may be used.

1296 Sterilisation of articles and materials elsewhere is acceptable provided that there are
1297 multiple wrappings, as appropriate to the number of stages of entry to the clean area,
1298 and enter through an airlock with the appropriate surface sanitization precautions.
1299 Unless culture media is delivered ready-to-use (*i.e.* already sterilised by the supplier),
1300 it is recommended that media is sterilized in situ.

1301 When sterilisation of articles, materials or equipment is not possible, a strictly
1302 controlled process should be implemented to minimise the risks (*e.g.* treatment of
1303 biopsy with antibiotics, sterile filtration of raw materials). The effectiveness of the
1304 process should be checked at appropriate intervals.

1305 (iv) Addition of materials or cultures to fermenters and other vessels and sampling should
1306 be carried out under carefully controlled conditions to prevent contamination. Care
1307 should be taken to ensure that vessels are correctly connected when addition or
1308 sampling takes place. In-line sterilizing filters for routine addition of gases, media,
1309 acids or alkalis, anti-foaming agents, etc. to bioreactors should be used where possible.

1310 The conditions for sample collection, additions and transfers involving replication
1311 competent vectors or materials from infected donors should prevent the release of
1312 viral/infected material.

1313 9.5.2. Sterilisation

1314 The sterilization processes applied should be suitable having regard to the specific
1315 characteristics of the product. In particular, where sterilization of starting materials (*e.g.*
1316 chemical matrixes) and raw materials and excipients is required, it should be ensured that the
1317 sterilisation process applied (*e.g.* heat, irradiation filtration, or chemical inactivation) is
1318 effective in terms of removing/reducing the contaminants while preserving the activity of
1319 starting/raw materials and excipients.

1320 The sterilisation process(es) applied should be validated. Particular attention should be paid
1321 when the adopted sterilization method is not in accordance with the European Pharmacopoeia.

1322 Solutions or liquids that cannot be sterilised in the final container, should be filtered through a
1323 sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-
1324 organism retaining properties, into a previously sterilised container.

1325 The filter should not have a negative impact on the product (*e.g.* by removing components or
1326 by releasing substances into it). The integrity of the sterilised filter should be verified before
1327 use and should also be confirmed after use by an appropriate method (*e.g.* bubble point,
1328 diffusive flow or pressure hold test).

1329 The same filter should not be used for different batches. Additionally, the same filter should
1330 not be used for more than one working day, unless such use has been validated.

1331 9.5.3. *Aseptic processing validation*

1332 The validation of aseptic processing should include a process simulation test using a nutrient
1333 medium (so-called “media fill”). A media fill process simulation is the performance of the
1334 manufacturing process using a sterile microbiological growth medium to test whether the
1335 manufacturing procedures are adequate to prevent contamination during production. Results
1336 and conclusions should be recorded.

1337 If the validation of aseptic processing cannot be done by means of a media fill process
1338 simulation, an appropriate simulated model may be used, provided that this is duly justified.

1339 The process simulation tests should follow as closely as possible the routine manufacturing
1340 process and it should be conducted in the same locations where the production occurs.
1341 However, alternative approaches may be developed for steps that take a long time. The
1342 simulation of reduced times for certain activities (*e.g.* centrifugation, incubation) should be
1343 justified having regard to the risks. In some cases, it may also be acceptable to split the
1344 process into key stages which are simulated separately provided that the transitions between
1345 each stage are also evaluated.

1346 After the final product container is filled, it should be incubated for the time and under the
1347 temperature specified in the protocol/media fill procedure. All contaminants from the media
1348 fill containers should be identified. The results should be assessed, in particular in relation to
1349 the overall quality of the product and the suitability of the production process. The target
1350 should be zero growth. Any growth detected should be investigated. If the growth detected is
1351 indicative of potential systemic failure, the potential impact on batches manufactured since
1352 the last successful media fill simulation test should be assessed.

1353 Process simulation test should be performed as initial validation with three consecutive
1354 satisfactory simulation tests per shift.

1355 It is generally expected that the process simulation test with media fill test is run every six
1356 months per shift, as well as when there is any significant change to the process (*e.g.*
1357 modification of HVAC system, equipment, *etc*). A reduced frequency in cases of infrequent
1358 production may be justified. Thus, if the interval between the production of two batches is
1359 more than six months the process simulation test can be done just before the manufacturing of
1360 the second batch (three consecutive runs should be performed).

1361 When considering the frequency of the simulation test, the manufacturer is required to
1362 consider also the relevance of the media fill test for the training of operators and their ability
1363 to operate in an aseptic environment. A reduced frequency is not acceptable when the product
1364 should be administered to the patient prior to having the results of the sterility tests.

1365 In case of manufacturing of various types of ATMPs, consideration can be given to the matrix
1366 approach (combined media fills for different ATMPs but based on identical handling of the
1367 product), provided that worst-case scenario is covered by the matrix approach.

1368 **9.6. Other operating principles**

1369 Critical process parameters and other input parameters that affect product quality (as
1370 identified in the marketing authorisation/clinical trial authorisation) should be monitored at
1371 appropriate intervals. When technically possible, continuous monitoring of key process
1372 parameters is expected (*e.g.* in bioreactors). Any deviations should be recorded and
1373 investigated, and the measures taken should also be documented.

1374 Any necessary environmental controls (*see* Section 4.2.3) should be carried out and recorded.

1375 Where chromatography equipment is used, a suitable control strategy for matrices, the
1376 housings and associated equipment (adapted to the risks) should be implemented when used
1377 in campaign manufacture and in multi-product environments. The re-use of the same matrix at
1378 different stages of processing is discouraged. Acceptance criteria, operating conditions,
1379 regeneration methods, life span and sanitization or sterilization methods of chromatography
1380 columns should be defined.

1381 Where ionizing radiation is used in the manufacturing of ATMPs, Annex 12 to EudraLex,
1382 Volume 4, should be consulted for further guidance.

1383 **9.7. Packaging**

1384 The suitability of primary packaging materials shall be ensured having regard to the
1385 characteristics of the product and the storage conditions (*e.g.* products that should be stored at
1386 ultra-low temperature). The specifications provided for in the marketing authorisation or the
1387 clinical trial authorisation should be complied with.

1388 The level of documentation regarding the demonstration of suitability of the primary
1389 packaging material for Phase I/II clinical trials may be more limited but it is expected that it
1390 becomes more detailed in later phases of development. For production of authorised ATMPs,
1391 selection, qualification, approval and maintenance of suppliers of primary packaging
1392 materials shall be documented.

1393 ATMPs should be suitably packaged to maintain the quality of the product during storage,
1394 handling, and shipping. Particular attention should be paid to the closure of containers so as
1395 to ensure the integrity and quality of the product. For authorised ATMPs, the closure

1396 procedures should be validated. Validation with surrogate materials is acceptable when
1397 materials are scarce.

1398 Checks should be made to ensure that any electronic code readers, label counters or similar
1399 devices are operating correctly. Labels should be compatible with transport and storage
1400 conditions (*e.g.* ultra-low temperatures).

1401 Prior to product labelling operations, the work area and any equipment used should be clean
1402 and free from any product, material or document that is not required for the current operation.
1403 Precautions should be taken to avoid mix-ups of products and to protect the product from the
1404 risk of contamination.

1405 **9.8. Finished products**

1406 As a general principle, finished products should be held in quarantine until their release under
1407 conditions established by the manufacturer in accordance with the terms of the marketing
1408 authorization or the clinical trial authorisation. It is acknowledged, however, that due to the
1409 short shelf-life, physical or administrative quarantine of ATMPs may not always be possible.
1410 The release of products before completion of all QC tests is addressed under Section 11.3.2.

1411 **9.9. Rejected, recovered and returned materials**

1412 Rejected materials should be clearly marked as such and stored separately in restricted areas.
1413 Starting and raw materials should either be returned to the suppliers or, removed from the
1414 production environment. Whatever action is taken, it should be approved and recorded by
1415 authorized personnel.

1416 The reprocessing of rejected products should be exceptional. For authorised ATMPs,
1417 reprocessing is only permissible if this possibility is contemplated in the marketing
1418 authorisation. In the case of investigational ATMPs, the competent authorities should be
1419 informed²¹ when, exceptionally, there is reprocessing.

1420 Additionally, the use of reprocessed materials is only possible if the quality of the final
1421 product is not affected and the specifications are met. The need for additional testing of any
1422 finished product which has been reprocessed, or into which a reprocessed product has been
1423 incorporated, should be evaluated by the person/department responsible for quality control.
1424 Records should be kept of the reprocessing.

1425 Returned products, which have left the control of the manufacturer, should be marked as such
1426 and be segregated so that they are not available for further clinical use, unless without doubt
1427 their quality is satisfactory after they have been critically assessed by the person/department
1428 responsible for quality control.

²¹Article 54 of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

1429 **10. Qualification and Validation**

1430 **10.1. Qualification of premises and equipment**

1431 *10.1.1 General principles*

1432 Premises and equipment used in the manufacture of ATMPs should be qualified. Through the
1433 qualification of premises and equipment, the manufacturer establishes that the premises and
1434 equipment are adequate for the intended operations.

1435 Decisions on the scope and extent of the qualification should be based on a risk-assessment,
1436 which should be documented. The following should be considered when defining the strategy
1437 to the qualification of premises and equipment:

1438 - Clean rooms should be qualified in accordance with ISO 14644-1 and re-qualified at
1439 appropriate intervals in accordance with ISO 14644-2.

1440 - If computerized systems are used, their validation should be proportionate to the
1441 impact thereof on the quality of the product.

1442 - For investigational ATMPs, it is expected that at least the suitability of the air quality
1443 system (in accordance with ISO 14644) and the suitability of the premises to
1444 adequately control the risk of microbial and non-viable particle contamination is
1445 verified. Any other aspect of the premises that is critical having regard to the specific
1446 risks of the intended manufacturing process should be qualified (*e.g.* containment
1447 measures when viral replicating vectors are used). Critical equipment should be
1448 qualified also.

1449 Before starting the manufacturing of a new type of ATMP in premises that have already been
1450 qualified, the manufacturer should assess if there is a need for re-qualification having regard
1451 to the specific risks and characteristics of the new manufacturing process/new product. For
1452 example, if the premises have been qualified for open processing and a closed system is
1453 introduced, it can be assumed that the (existing) qualification of the premises covers a worst
1454 case scenario and therefore no re-qualification is needed. In contrast, when the premises have
1455 been qualified for a simple manufacturing process and a more complex process is introduced
1456 that *e.g.* may require an additional level of containment, requalification is required.

1457 Facilities and equipment should be re-evaluated at appropriate intervals to confirm that they
1458 remain suitable for the intended operations. Requalification should be done in accordance
1459 with ISO 14644-2. In general, for clean rooms of grade A, requalification is expected every
1460 six months, while for B, C and D grades requalification is expected on a yearly basis. A
1461 different frequency may, however, be justified in case of very small production.

1462 *10.1.2. Steps of the qualification process*

1463 The qualification strategy should follow the following steps:

1464 (a) Setting the user requirement specifications: The manufacturer should define the
1465 specifications for the premises and equipment. The user requirement specifications
1466 should ensure that the critical quality attributes of the product and the identified risks
1467 linked to the manufacturing processes are adequately addressed (*e.g.* measures to avoid
1468 cross-contamination in a multi-product facility).

1469 (b) Verifying compliance with the user requirement specifications: The manufacturer
1470 should verify that the premises/equipment comply with the user specifications.
1471 Typically, this involves the following steps:

1472 (i) *Installation Qualification (IQ)*: As a minimum, it should be verified that:

1473 - components, equipment, pipe work and other installations have been installed
1474 in conformity with the user specifications,

1475 - operating and maintenance instructions are provided (as appropriate),

1476 - instruments are appropriately calibrated, and

1477 - the materials of parts of the equipment that come into contact with the product
1478 are suitable.

1479 (ii) *Operational Qualification (OQ)*: The suitability of the premises and equipment
1480 to operate as designed (including under “worse case” conditions) should be
1481 tested.

1482 (iii) *Performance Qualification (PQ)*: The suitability of the premises and
1483 equipment to operate consistently in accordance with the requirements of the
1484 intended manufacturing process (assuming worse case conditions) should be
1485 tested. A test with surrogate materials or simulated product is acceptable.

1486 Any deviations identified should be addressed before moving to the next qualification
1487 step. However, it is acknowledged that, in some cases, it may be appropriate to
1488 concurrently perform IQ, OQ and PQ. It may also be acceptable to perform the process
1489 validation concurrently with the PQ.

1490 Where functionality of the equipment is not affected by transport and installation, the
1491 documentation review and some tests should be performed at the vendor’s site (*e.g.*
1492 through factory acceptance testing), without the need to repeat the relevant elements of
1493 IQ/OQ at the manufacturer’s site.

1494 (c) Documentation: A report should be written summarizing the results and conclusions
1495 reached. When qualification documentation is supplied by a third party (*e.g.* vendor,
1496 installers), the manufacturer should assess whether the documentation provided is
1497 sufficient or if additional tests should be performed at the site to confirm suitability of

1498 the equipment (*e.g.* information gaps exist having regard to the intended manufacturing
1499 process, equipment to be used differently than as intended by the manufacturer, *etc.*)

1500 Where the qualification of the premises/equipment is outsourced to a third party, the
1501 principles laid down in Section 13 apply.

1502 **10.2. Cleaning validation**

1503 The cleaning procedures applied to re-usable tools and parts of equipment that enter into
1504 contact with the product should be validated.

1505 Cleaning validation is the documented evidence that a given cleaning procedure effectively
1506 and reproducibly removes contaminants, residues from previous product and cleaning agents
1507 below a given threshold. There may be more than one way to perform cleaning validation.
1508 The objective is to demonstrate that the cleaning process consistently meets the predefined
1509 acceptance criteria. The risk of microbial and endotoxin contamination should be duly
1510 assessed.

1511 The following considerations apply when designing the cleaning validation strategy:

1512 - Factors that influence the effectiveness of the cleaning process (*e.g.* operators, rinsing
1513 times, cleaning equipment and cleaning agents used) should be identified. If variable
1514 factors have been identified, the worst case situations should be used as the basis for
1515 cleaning validation studies.

1516 - The influence of the time between manufacture and cleaning, and between cleaning
1517 and use should be taken into account when designing the cleaning procedure.

1518 - When justified due to the scarcity of the starting materials, simulating agents may be
1519 used.

1520 Cleaning procedures for closely related ATMPs do not need to be individually validated. A
1521 single validation study which considers worst case scenario is acceptable.

1522 Cleaning validation should be described in a document, which should cover:

1523 (i) *Detailed cleaning procedure for each piece of equipment:* Grouping
1524 approaches²² are acceptable if appropriately justified (*e.g.* cleaning of
1525 processing vessels of the same design but with different capacity). Where
1526 similar types of equipment are grouped together, a justification of the specific
1527 equipment selected for cleaning validation is expected. The selection of the
1528 equipment should be representative of the worst case scenario (for example, the
1529 higher capacity vessel).

²² The design assumes that validation of any intermediate levels is represented by validation of the extremes.

1530 (ii) *Sampling procedures*: Sampling may be carried out by swabbing and/or rinsing
1531 or by other means depending on the production equipment. The sampling
1532 materials and method should not influence the result. Recovery should be
1533 shown to be possible from all product contact materials sampled in the
1534 equipment with all the sampling methods used.

1535 (iii) *Validated analytical methods to be used.*

1536 (iv) *Acceptance criteria*, including the scientific rationale for setting the specific
1537 limits.

1538 The cleaning procedure should be performed an appropriate number of times based on a risk
1539 assessment and meet the acceptance criteria in order to prove that the cleaning method is
1540 validated (usually three consecutive batches). Cleaning validation may be reduced or not
1541 required if only disposables are used in the manufacturing process.

1542 A visual check for cleanliness is an important part of the acceptance criteria for cleaning
1543 validation. However, it is not generally acceptable for this criterion alone to be used.
1544 Repeated cleaning and retesting until acceptable residue results are obtained is not considered
1545 an acceptable approach either.

1546 Approach for investigational ATMPs

1547 For investigational ATMPs, cleaning verification is acceptable when the volume of
1548 production is small (less than three batches). In such cases, there should be sufficient data
1549 from the verification to support a conclusion that the equipment is clean and available for
1550 further use.

1551 **10.3. Process validation**

1552 Process validation is the documented evidence that the manufacturing process can
1553 consistently produce a result within specific parameters. While it is acknowledged that some
1554 degree of variability of the finished product due to the characteristics of the starting materials
1555 is intrinsic to ATMPs, the aim of the process validation for ATMPs is to demonstrate that the
1556 finished product characteristics are within a given range (in compliance with the terms of the
1557 marketing authorisation).

1558 The strategy to process validation should be laid down in a document (“validation protocol”).
1559 The protocol should define the critical process parameters, critical quality attributes and the
1560 associated acceptance criteria based on development data or documented process knowledge.
1561 The approach retained should be justified. As appropriate, the protocol should identify other
1562 (non-critical) attributes and parameters which will be investigated or monitored during the
1563 validation activity, and the reasons for their inclusion.

1564 The following should also be specified in the protocol:

- 1565 - List of the equipment/facilities to be used (including measuring/monitoring/recording
1566 equipment) together with the calibration status.
- 1567 - List of analytical methods and validation method, as appropriate.
- 1568 - Proposed in-process controls with acceptance criteria and the reason(s) why each in-
1569 process control is selected.
- 1570 - Where required, additional testing to be carried out with acceptance criteria.
- 1571 - Sampling plan and the rationale behind it.
- 1572 - Methods for recording and evaluating results.
- 1573 - Process for release and certification of batches (if applicable).
- 1574 - Specifications for the finished product.
- 1575 It is generally accepted that three consecutive batches manufactured under routine conditions
1576 constitute a validation of the process. An alternative number of batches may be justified
1577 taking into account whether standard methods of manufacture are used, whether similar
1578 products or processes are already used at the site, the variability of starting material
1579 (autologous v. allogenic), clinical indication (rare disease: only few batches will be
1580 produced).
- 1581 The limited availability of the cells/tissues which is typical for most ATMPs requires the
1582 development of pragmatic approaches. The approach to process validation should take into
1583 account the quantities of tissue/cells available and should focus on gaining maximum
1584 experience of the process from each batch processed. Reduced process validation should,
1585 where possible, be offset by additional in-process testing to demonstrate consistency of
1586 production.
- 1587 - Validation with surrogate materials: The use of surrogate material may be acceptable
1588 when there is shortage of the starting materials (*e.g.* autologous ATMPs, allogeneic
1589 1:1, allogeneic where there is no expansion of cells to MCB). The representativeness
1590 of surrogate starting material should be evaluated, including -for example- donor age,
1591 use of materials from healthy donors, anatomical source (*e.g.* femur vs iliac crest) or
1592 other different characteristics (*e.g.* use of representative cell-types or use of cells at a
1593 higher passage number than that foreseen in the product specifications).
- 1594 Where possible, consideration should be given to complementing the use of surrogate
1595 materials with samples from the actual starting materials for key aspects of the
1596 manufacturing process. For instance, in the case of an ATMP based on modification
1597 of autologous cells to treat a genetic disorder, process validation using the autologous
1598 cells (affected by the condition) may be limited to those parts of the process that focus
1599 on the genetic modification itself. Other aspects could be validated using a
1600 representative surrogate cell type.

1601 - Concurrent validation approaches: Due to the limited availability of the starting
1602 materials and/or where there is a strong benefit-risk ration for the patient, a concurrent
1603 validation may be acceptable. The decision to carry out concurrent validation should
1604 be justified, having regard also to the possibility to use surrogate starting materials.
1605 Regular reviews of data from the manufacture of batches should be subsequently used
1606 to confirm that the manufacturing process is able to ensure that the specifications in
1607 the clinical trial/marketing authorization are complied with.

1608 Where a concurrent validation approach has been adopted, there should be sufficient
1609 data to support the conclusion that the batch meets the defined criteria. The results and
1610 conclusion should be formally documented and available to the Qualified Person prior
1611 to the certification of the batch.

1612 - Use of quality markers as an alternative to process validation: The process validation
1613 may be replaced by the continuous monitoring of surrogate markers reflecting critical
1614 quality attributes either as part of the control strategy (analogous to PAT) or the
1615 release process. This does not preclude the qualification of individual steps.

1616 - Retrospective validation where time to manufacture, batch size, or other factors make
1617 prospective validation unethical (*e.g.* performing a biopsy only for validation
1618 purposes) or disproportionate having regard to the anticipated benefits for patients.

1619 - Process validation for a class of products: where the same manufacturing process is
1620 used for a class of products (*i.e.* autologous T-cell based ATMPs), the validation of the
1621 process does not need to be repeated for each of the products, in so far as the
1622 manufacturing process remains the same.

1623 Investigational ATMPs

1624 The manufacturing process for investigational ATMPs is not expected to be validated but
1625 appropriate monitoring and control measures should be implemented to ensure compliance
1626 with the requirements in the clinical trial authorisation. Additionally, it is expected the
1627 aseptic conditions of the manufacturing process have been validated.

1628 Process validation/evaluation data should be collected throughout the development. It is
1629 recalled that for the clinical trial to be used in support of a marketing authorisation application
1630 it is important to demonstrate that the manufacturing process of the investigational ATMP
1631 ensures consistent production.

1632 **10.4. Validation of test methods.**

1633 The validation of analytical methods is intended to ensure the suitability of the analytical
1634 methods for the intended purpose. Validation of test methods can follow a gradual approach
1635 during clinical development:

1636 - Safety and microbial assay should be validated before first-in-man clinical trials.

1637 - The suitability of analytical methods should be demonstrated for phase II and III
1638 clinical trials but a full validation report is not required.

1639 - Potency assays should be validated throughout clinical development (*i.e.* typically
1640 validation finalized before phase III clinical trials).

1641 Analytical procedures, which are either described in the European Pharmacopoeia, the
1642 pharmacopoeia of a Member State, USP or JP general chapter, or are linked to a product
1643 specific monograph, and are performed according to the monograph, are normally considered
1644 as validated.

1645 **11. Qualified person and batch release**

1646 **11.1. General principles**

1647 Each manufacturing site in the EEA must have at least one Qualified Person (“QP”).²³ It is
1648 not excluded that two or more sites may have the same QP, provided that this does not impair
1649 the ability of the QP to provide his services to each of the sites in a continuous fashion.

1650 Without prejudice to Section 11.3.3, batches of medicinal products should only be released
1651 for sale, supply to the market, or for use in clinical trial after certification by a QP. Until a
1652 batch is released, it should remain at the site of manufacture or be shipped under quarantine to
1653 another authorised site. Safeguards to ensure that uncertified batches are not released should
1654 be in place. These safeguards may be physical (via the use of segregation and labelling) or
1655 electronic (via the use of computerized systems). When uncertified batches are moved from
1656 one authorised site to another, the safeguards to prevent premature release should remain.

1657 **11.2. Qualified person**

1658 In addition to having the qualification requirements provided for under Article 49 of Directive
1659 2001/83, QPs responsible for ATMPs should have training and experience relevant to the
1660 specific characteristics of these products, including cell and tissue biology, biotechnological
1661 techniques, cell processing, characterization and potency testing. QPs should have detailed
1662 knowledge of the product type and manufacturing steps for which they are taking
1663 responsibility.

1664 The QP’s main responsibility is to verify and certify that each batch produced in the EU has
1665 been manufactured and checked in accordance with:

- 1666 - the requirements of the marketing authorisation or clinical trial authorisation,
- 1667 - relevant regulations governing the manufacture of medicinal products, including
1668 GMP, and

²³Article 48(1) of Directive 2001/83/EC on the Community code relating to medicinal products for human use, (OJ L311, 28.11.2001, p.67), as amended. *See also* Article 61(2)(b) of Regulation (EU) No 536/2014.

1669 - relevant product specifications in the destination country (in the case of exports).

1670 In case of imports of investigational ATMPs from third countries, the QP should ensure that
1671 the quality of the batch is in accordance with the terms of the clinical trial authorisation and
1672 that it has been manufactured in accordance with quality standards at least equivalent to the
1673 GMP requirements applied in the EU.²⁴

1674 In case of imports of authorised ATMPs from third countries, the QP should ensure that the
1675 quality of the batch is in accordance with the terms of the marketing authorisation, including
1676 by means of a full qualitative and quantitative analysis of the active substance(s) as well as
1677 any other necessary checks.²⁵ However, it is acknowledged that for ATMPs it is not always
1678 possible to separate the testing of the active substance from the testing of the finished product.
1679 Additionally, it may be justified to rely on testing performed in the third country in cases
1680 where the limited amount of material available (*e.g.* autologous products) or the short shelf-
1681 life impedes double release testing. In such cases, the testing in the third country should be
1682 conducted under conditions equivalent to those applicable in the EU. The re-testing strategy
1683 should be in accordance with the terms of the marketing authorisation.

1684 When the QP wishes to rely on testing of samples taken in a third country, transport and
1685 storage conditions should be adequate, so as to ensure the samples taken in the third country
1686 are still representative of the batch.

1687 In all cases, the conditions of storage and transport should be checked before certifying any
1688 batch; these conditions must be in accordance with the terms of the marketing
1689 authorisation/clinical trials authorisation.

1690 QPs should have access to:

1691 - the necessary details of the marketing authorisation, or clinical trial authorisation to
1692 assess if the relevant requirements have been complied with, and

1693 - relevant data about the entire manufacturing process of the ATMP, including
1694 importation activities if any.

1695 Relying on GMP assessments by third parties *e.g.* audits

1696 In some cases the QP may rely on audits conducted by third parties attesting the general
1697 compliance with GMP in sites involved in the manufacture of the product. In these cases,
1698 there should be a clear delimitation of responsibilities and the general requirements in Section
1699 13 apply.

1700 The QP should have access to all documentation which facilitates review of the audit outcome
1701 and continued reliance on the outsourced activity.

²⁴Article 62 and 63(3) of Regulation (EU) No 536/2014.

²⁵Article 51(1)(b) of Directive 2001/83/EC.

1702 Involvement of more than one QP

1703 The QP who performs certification of the finished product batch may assume full
1704 responsibility for all stages of manufacture of the batch, or this responsibility may be shared
1705 with other QPs who have confirmed compliance of specific steps in the manufacture and
1706 control of a batch.

1707 If a site only undertakes partial manufacturing operations, the QP at that site must (as a
1708 minimum) confirm that the operations undertaken by the site have been performed in
1709 accordance with GMP and the terms of the written agreement detailing the operations for
1710 which the site is responsible.

1711 Where more than one QP is involved in the assessment of one batch, the division of
1712 responsibilities amongst QPs in relation to compliance of the finished batch (including details
1713 on the responsibility for assessment of any deviations) should be clearly laid down in writing.

1714 **11.3. Batch release**

1715 *11.3.1. Batch release process*

1716 The process of batch release includes the following steps:

1717 (i) Checking that the manufacture and testing of the batch has been done in accordance
1718 with applicable requirements, including that:

1719 - all manufacturing steps (including controls and testing) have been done in
1720 accordance with the marketing authorisation or clinical trial authorisation,

1721 - the specifications of raw materials, starting materials (including matrixes or
1722 devices that are a component of the ATMP) and packaging materials comply
1723 with the terms of the marketing authorisation or clinical trial authorisation,

1724 - the excipients used in the manufacturing of the finished product are of suitable
1725 quality and that they have been manufactured under adequate conditions,

1726 - for combined ATMPs, the medical device(s) used comply with the relevant
1727 essential requirements provided for under the EU legislation on medical
1728 devices, and are adequate for the use in the combined ATMP,

1729 - where relevant, the viral and microbial safety and TSE status of all materials
1730 used in batch manufacture is compliant with the terms of the marketing
1731 authorisation or clinical trial authorisation.

1732 - all required in-process controls and checks (including environmental
1733 monitoring) have been made and appropriate records exists,

1734 - finished product quality control (QC) test data complies with the relevant
1735 specifications,

- 1736 - on-going stability data continues to support certification,
- 1737 - the impact of any change to product manufacturing or testing has been
- 1738 evaluated and any additional checks and tests are complete,
- 1739 - all investigations related to the batch being certified has been completed and
- 1740 supports the certification of the batch,
- 1741 - the self-inspection programme is active,
- 1742 - appropriate arrangements for storage and transport exist,
- 1743 - the presence of the safety features referred to in Article 54 of Directive
- 1744 2001/83/EC have been verified, where applicable.²⁶

1745 It is acknowledged that, in the case of investigational ATMPs, the amount of relevant
 1746 information will depend on the stage of development (*e.g.* medical devices used in an
 1747 investigational combined ATMP may be in an investigational phase as well and, in
 1748 such cases, the role of the QP is to ensure that the quality specifications set by the
 1749 manufacturer are respected). For investigational ATMPs, the assessment of the QP
 1750 should be based on all existing data and information relevant to the quality of the
 1751 investigational ATMP.

1752 (ii) Certification of the finished product batch by the QP. The QP must certify that each
 1753 production batch has been manufactured and checked in accordance with the
 1754 requirements of the marketing authorisation or clinical trial authorisation, and all other
 1755 relevant regulatory requirements.

1756 The certification should be recorded by the QP in a register or equivalent document
 1757 provided for that purpose, which must be kept up to date. The register or equivalent
 1758 document must remain at the disposal of the competent authority for one year after
 1759 expiry of the batch to which it relates or at least five years after certification of the
 1760 batch by the QP, whichever is the longest.

1761 For investigational ATMPs, the certification must be kept for at least five years after
 1762 the completion or formal discontinuation of the last clinical trial in which the batch
 1763 was used, whichever is the longest.

1764 (iii) Assigning the release status to the batch. This is the step that effectively releases the
 1765 batch for sale, export, or (in case of an investigational ATMP) use in a clinical study.
 1766 This step can be done by the QP as an integral part of certification or it can be done

²⁶ ATMPs that contain or consist of tissues or cells are exempted from the safety feature in accordance with Commission delegated Regulation (EU) 2016/161 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use, (OJ L32, 9.2.2016, p. 1).

1767 afterwards by another person. In this case, this arrangement should be delegated by the
1768 QP in a SOP or a contract.

1769 The notification by a QP to the releasing site that certification has taken place should
1770 be formal and unambiguous.

1771 Additional considerations for investigational ATMPs

1772 Investigational ATMPs should remain under the control of the sponsor until after completion
1773 of a two-step procedure: certification by the QP and release by the sponsor for use in a
1774 clinical trial. Both steps should be documented.

1775 Transfers of the investigational ATMPs from one trial site to another should remain the
1776 exception. When they occur, the QP is responsible to establish the specific conditions under
1777 which the transfers should take place.

1778 *11.3.2. Batch release prior to obtaining the results of quality control tests*

1779 Due to short shelf-life, some ATMPs may have to be released before completion of all quality
1780 control tests. In this case, it is possible to organise the procedure for batch certification and
1781 release in various stages, for example:

1782 - Assessment by a designated person(s) of the batch processing records, results from
1783 environmental monitoring (where available) and the available analytical results for
1784 review in preparation for the initial certification by the QP, which allows release for
1785 administration.

1786 - Assessment of the final analytical tests and other information available for final
1787 certification by the QP.

1788 The delegation of tasks to the designated person(s) and the description of the batch
1789 certification and release procedure should be laid down in writing.

1790 A procedure should be in place to describe the measures to be taken (including liaison with
1791 clinical staff) where out of specification test results are obtained after the release of the
1792 product.

1793 It is acknowledged that, in the case of ATMPs, out of specification products are not always
1794 attributable to failures in the manufacturing process (*e.g.* idiopathic factors of the patient).
1795 All instances of out of specification products should be investigated and, where a failure in
1796 the manufacturing process is identified, the relevant corrective and preventive actions taken to
1797 prevent recurrence documented. In case of recurrent deviations, the need for changes to the
1798 manufacturing process should be assessed.

1799 **11.4. Handling of unplanned deviations**

1800 As long as the specifications for the finished product are met, a QP may confirm
1801 compliance/certify a batch where an unexpected deviation related to the manufacturing
1802 process and/or the analytical control methods has occurred provided that:

- 1803 - there is an in-depth assessment of the impact of the deviation which supports a
1804 conclusion that the occurrence does not have a negative effect on quality, safety or
1805 efficacy of the product, and
- 1806 - the need for inclusion of the affected batch/ batches in the on-going stability
1807 programme has been evaluated, where appropriate.

1808 **11.5. Administration of out of specification products**

1809 In cases where, for imperative reasons linked to the health of the patient, an out of
1810 specification product needs to be administered to the patient, the manufacturer should provide
1811 the treating physician with its evaluation of the risks (the possibility of reprocessing may be
1812 considered as appropriate). The agreement of the treating physician to use the product should
1813 be recorded by the manufacturer.

1814 In addition to the above, when the out of specification product is administered to a trial
1815 subject, the impact of the use of an out-of-specification product in the clinical trial should be
1816 determined and notified to the sponsor. Instances of administration of an out-of-specification
1817 product to a clinical trial subject should be notified to the relevant competent authorities.

1818 **12. Quality control**

1819 **12.1. General principles**

1820 Quality control is intended to ensure that the necessary and relevant tests are carried out, and
1821 that materials are not released for use, nor products released for sale or supply, until their
1822 quality has been judged satisfactory. Quality control is not confined to laboratory operations,
1823 but must be involved in all decisions which may affect the quality of the product.

1824 The person responsible for quality control should ensure that the premises and equipment
1825 where quality control operations are carried out are appropriate and maintained under suitable
1826 conditions and that the personnel working under his/her responsibility is adequately trained.
1827 In-process controls may be carried out within the production area provided they do not carry
1828 any risk for the product.

1829 The person responsible for quality control supervises all quality control procedures. In
1830 particular, it assumes responsibility for the following tasks:

- 1831 (i) Approval of specifications, sampling instructions, test methods and other quality
1832 control procedures.
- 1833 (ii) Approval of conditions for outsourced testing.

- 1834 (iii) Control of raw materials, starting materials, medical devices that are used in combined
1835 ATMPs, packaging materials, intermediate, bulk and finished products (including
1836 approval or rejection thereof). In case of autologous products or donor-match
1837 situation, a control should be carried out to verify the match between the origin of the
1838 starting material and the recipient.
- 1839 (iv) Supervision of the control of the reference and/or retention samples of materials and
1840 products, as appropriate.
- 1841 (v) Ensuring that all necessary testing is carried out and the associated records are
1842 evaluated.
- 1843 (vi) Ensuring the monitoring of the stability of the products.
- 1844 (vii) Ensuring that the appropriate qualifications/validations are done.
- 1845 (viii) Ensuring the correct labelling of containers of materials and products.
- 1846 (ix) Participation in investigations related to the quality of the product.
- 1847 Appropriate records in connection with the above-referred activities should be kept. Written
1848 procedures should be put in place in connection with the activities listed in (iii) to (viii).
- 1849 Quality control personnel should have access to production areas for sampling and
1850 investigation as appropriate. All documents that are needed for the assessment of quality
1851 control (*e.g.* procedure description or records from the manufacturing process and testing)
1852 should also be accessible.

1853 **12.2. Sampling**

1854 *12.2.1. General principles*

1855 Samples should be representative of the batch of materials or products from which they are
1856 taken. Bulk containers from which samples have been drawn should be identified.

1857 The sample taking should be done and recorded in accordance with written procedures that
1858 describe the method of sampling, including the amount of sample to be taken, precautions to
1859 be observed, storage conditions, *etc.* Containers should bear a label indicating, as a minimum,
1860 the content, batch number and date of sampling. When containers are too small, the use of
1861 bar-codes or other means that permit access to this information should be considered.

1862 *12.2.2. Retention of samples*

1863 Samples are generally retained for analytical purposes should the need arise during the shelf
1864 life of the batch concerned (reference samples) and for identification purposes (retention
1865 samples of a fully packaged unit from a batch of finished product).

1866 As a general principle, a reference sample should be of sufficient size to permit the carrying
1867 out on at least two occasions of the full analytical controls on the batch foreseen in the

1868 marketing authorisation/clinical trial authorisation. However, it is acknowledged that this
1869 may not always be possible due to scarcity of the starting materials or limited size of the
1870 batches (*e.g.* autologous products, ATMPs for ultra-rare diseases).

1871 The retention sample should be contained in its finished primary packaging or in packaging
1872 composed of the same material as the primary container in which the product is marketed

1873 Samples should normally be stored under the conditions foreseen in the product information.
1874 However, for products/materials with a short shelf-life, it should be carefully considered if
1875 other storage conditions that maximise stability can be used (*see* below).

1876 The sampling plan should be documented. The sampling plan should be adapted to the
1877 specific characteristics of the product. In designing the sampling strategy, the manufacturer
1878 should take into account the risks, the practical limitations that may exist, and possible
1879 mitigation measures (*e.g.* increased reliance on in-process testing). The sampling strategy of
1880 the manufacturer should be duly justified.

1881 In particular, the following considerations apply:

1882 - Samples of raw materials: Reference samples of critical raw materials (*e.g.* cytokines,
1883 growth factors) are important to investigate possible quality problems with the
1884 product. The assessment whether a specific raw materials is critical should be done by
1885 the manufacturer having regard to the specific risks and possible mitigation measures
1886 (*e.g.* increased QC controls). The decisions taken should be documented. Samples of
1887 critical raw materials should be retained for two years after the batch release or one
1888 year after the expiry date of the relevant batch, whichever is the longest.

1889 - Samples of the starting materials should generally be kept for two years after the batch
1890 release or one year after the expiry date of the relevant batch, whichever is the longest.
1891 However, it is acknowledged that the retention of samples may be challenging due to
1892 scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep
1893 reference samples of the cells/tissues used as starting materials in the case of
1894 autologous ATMPs and certain allogeneic ATMPs (matched donor scenario).

1895 - Samples of active substances and intermediate products should generally be kept for
1896 two years after the batch release or one year after the expiry date of the relevant batch,
1897 whichever is the longest. However, it is acknowledged that for ATMPs it is not
1898 always possible to separate the sampling of the starting materials, active substance,
1899 intermediate and finished product. The considerations regarding scarcity of starting
1900 materials apply -adapted as necessary- to the expectations on the retention of samples
1901 of active substances and intermediate products.

1902
1903 - Samples of primary packaging material: Samples of primary packaging material
1904 should generally be retained for the duration of the shelf-life of the finished product
1905 concerned. The retention of samples of primary packaging material may not be

1906 necessary in certain cases, having regard to the risks of the materials and/or other
1907 relevant consideration (*e.g.* increased QC controls, primary packaging material is
1908 certified as a medical device). A decision not to keep samples of primary packaging
1909 materials should be based on an analysis of the risks and should be duly justified and
1910 documented.

1911 - A sample of a fully packaged unit (retention sample) should be kept per batch for at
1912 least one year after the expiry date. A retention sample is, however, not expected in
1913 the case of autologous products or allogeneic products in a matched donor scenario as
1914 the unit produced with the patient's tissues/cells constitutes should be administered to
1915 the patient. When it is not possible to keep a retention sample, photographs or copies
1916 of the label are acceptable for inclusion in the batch records.

1917 The reference samples and the retention sample may be identical in some cases (*i.e.* a fully
1918 packaged unit).

1919 In all cases, the retention period should be adapted to the stability and shelf-life of the product
1920 and, therefore, shorter periods may be justified. In cases of short shelf-life, the manufacturer
1921 should consider if the retention of the sample under conditions that prolong the shelf-life
1922 (such as cryopreservation) is representative for the intended purpose. For instance,
1923 cryopreservation of fresh-cells may render the sample inadequate for characterisation purposes
1924 but the sample may be adequate for sterility or viral safety controls (the volume of the
1925 samples can be reduced according to the intended purpose). When the cryostorage of a
1926 sample is considered inadequate for the intended purpose, the manufacturer should consider
1927 alternative approaches (*e.g.* sample of intermediate product such as differentiated cells.)

1928 **12.3. Testing**

1929 Testing is important to ensure that each batch meets the relevant specification. In-process
1930 controls testing should be performed at appropriate stages of production to control those
1931 conditions that are important for the quality of the product.

1932 Testing of critical raw materials, starting materials, active substance/intermediates/finished
1933 products, and stability testing should be performed in accordance with the terms defined in
1934 the marketing authorisation/clinical trial authorisation.

1935 Testing methods should be validated and reference materials should be established (where
1936 available) for qualification and routine testing. For investigational ATMPs, the level of
1937 validation should be commensurate with the development phase and the criticality of the test
1938 results considering the risks for the patient (*see* Section 10.4).

1939 The following records should be kept:

1940 (i) Name of the material or product and, where applicable, dosage form.

1941 (ii) Batch number and, where appropriate, the manufacturer and/or supplier.

- 1942 (iii) References to the relevant specifications and testing procedures.
- 1943 (iv) Test results, including observations and calculations, and reference to any
1944 certificates of analysis.
- 1945 (v) Dates of testing.
- 1946 (vi) Initials of the persons who performed the testing (or another suitable
1947 identification system).
- 1948 (vii) Initials of the persons who verified the testing and the calculations, where
1949 appropriate (or another suitable identification system).
- 1950 (viii) A clear statement of approval or rejection (or other status decision) and the
1951 dated signature of the responsible person.
- 1952 (ix) Reference to the equipment used.
- 1953 A continuous assessment of the effectiveness of the quality assurance system is important.
1954 Results of parameters identified as a quality attribute or as critical should be trended and
1955 checked to make sure that they are consistent with each other. Any calculations should be
1956 critically examined. No trending is however required in connection with an investigational
1957 ATMP.
- 1958 Technical transfer of testing methods
- 1959 The transfer of testing methods from one laboratory (transferring laboratory) to another
1960 laboratory (receiving laboratory) should be described in a detailed protocol.
- 1961 The transfer protocol should include, among others, the following parameters:
- 1962 (i) Identification of the testing to be performed and the relevant test method(s)
1963 undergoing transfer.
- 1964 (ii) Identification of any additional training requirements.
- 1965 (iii) Identification of standards and samples to be tested.
- 1966 (iv) Identification of any special transport and storage conditions of test items.
- 1967 (v) The acceptance criteria.
- 1968 Deviations from the protocol should be investigated prior to closure of the technical transfer
1969 process. The technical transfer report should document the comparative outcome of the
1970 process and should identify areas requiring further test method revalidation, if applicable.

1971 **12.4. Stability monitoring program**

1972 After the marketing authorisation is granted, a program should be implemented to verify that,
1973 under the relevant storage conditions (as foreseen in the marketing authorisation), the product
1974 remains within the specifications during the shelf-life (so called- “on-going stability
1975 program”). The methodology in the on-going stability programme can differ from the
1976 approach followed to obtain the stability data submitted in the marketing authorisation
1977 application (*e.g.* different frequency of testing), provided that it is justified.

1978 The on-going stability studies should generally be performed on the finished product (*i.e.* as
1979 released by the manufacturer). When intermediates can be stored for extended periods of
1980 time, consideration should be given to include in the stability program those batches that have
1981 been manufactured from materials stored for longer periods of time. Stability studies on the
1982 reconstituted product are performed during product development and need not be monitored
1983 on an on-going basis.

1984 The number of batches and frequency of testing should be adequate to allow for trend
1985 analysis. It is generally expected that at least one batch of the product is included per year in
1986 the stability program, unless none are produced in a given year or a different frequency is
1987 otherwise justified. Out of specifications and significant atypical trends should be
1988 investigated and their possible impact on the batches on the market should be assessed and
1989 discussed with the competent authorities as appropriate.

1990 **13. Outsourced activities**

1991 **13.1. General principles**

1992 Activities that are outsourced to a third party (including consultancy work) should be
1993 governed by a written contract that establishes the responsibilities of each party. As
1994 appropriate, the role and responsibilities in the event of detection of quality defects should be
1995 clearly established in the contract, as well as the obligations of each party regarding
1996 traceability.

1997 **13.2. Obligations of the contract giver**

1998 Prior to outsourcing any activity, the manufacturer (“contract giver”) should assess the
1999 suitability of the contractor (“contract acceptor”) to carry out the outsourced activities in
2000 accordance with the terms of the marketing authorisation/clinical trial authorisation and other
2001 applicable regulations, including compliance with GMP.

2002 When the outsourced activity is a highly specialised test (*e.g.* karyotype test), it is however
2003 acceptable that the contract acceptor does not operate under GMP, provided that it complies
2004 with suitable quality standards relevant to the outsourced activity (*e.g.* ISO or OCL).

2005 The contract giver should provide the contract acceptor with detailed information on the
2006 product/manufacturing process, as well as any other data that is necessary to carry out the
2007 contacted operations correctly.

2008 The contract giver should review and assess the records and the results related to the
2009 outsourced activities.

2010 **13.3. Obligations of the contract acceptor**

2011 The contract acceptor should take all necessary measures (*e.g.* adequate premises, equipment,
2012 trained personnel, *etc.*) to carry out satisfactorily the outsourced activities. Special
2013 consideration should be given to the prevention of cross-contamination and to maintaining
2014 traceability.

2015 The contract acceptor should not introduce changes in the process, premises, equipment, test
2016 methods, specifications or any other element related to the outsourced activity without the
2017 prior approval of the contract giver.

2018 All records related to the outsourced activities as well as reference samples should be kept by,
2019 or made available to, the contract giver.

2020 Subcontract to a third party is not permissible without the approval of the contract giver.

2021 The contract acceptor should permit inspections by the contract giver in connection with the
2022 outsourced activities.

2023 **14. Quality defects and product recalls**

2024 **14.1. Quality defects**

2025 A system should be put in place to ensure that all quality related complaints, whether received
2026 orally or in writing, are recorded and that they are thoroughly investigated, including the
2027 identification of the potential root cause(s) of the quality defect, the assessment of the risk(s)
2028 posed by the quality defect, the need for appropriate corrective or preventive measures, and
2029 the assessment of the impact that any recall action may have on the availability of the
2030 medicinal product to patients. Where the root cause cannot be ascertained, the most probable
2031 reasons should be identified.

2032 If additional donor (human or animal) health information becomes available after
2033 procurement, which affects product quality, an analysis of the risk(s) and of the need for
2034 corrective or prevented measures is also required.

2035 When a quality defect is discovered or suspected in a batch, consideration should be given to
2036 the need of checking other batches (or, as appropriate, other products) in order to determine if
2037 they are also affected.

2038 Quality defect investigations should include a review of previous quality defect reports or any
2039 other relevant information for any indication of specific or recurring problems.

2040 The priority during an investigation should be to ensure that appropriate risk-managements
2041 measures are taken to ensure patients safety. All decisions and measures adopted should be
2042 documented. The authorities should be informed in accordance with the relevant regulations.

2043 The effectiveness of the corrective or preventive measures implemented should be monitored.

2044 Quality defect records should be retained and used to evaluate the possible existence of
2045 recurring problems.

2046 **14.2. Product recalls**

2047 There should be established written procedures for recall of products, including how a recall
2048 should be initiated, who should be informed in the event of a recall (including relevant
2049 authorities and clinical sites), and how the recalled material should be treated.

2050 The documented destruction of a defective product at the clinical site is an acceptable
2051 alternative to the return of the product.

2052 An action plan should be established for cases where the product cannot be recalled because it
2053 has already been administered to the patient(s).

2054 **15. Environmental control measures for ATMPs containing or consisting of GMO's**

2055 The handling of ATMPs containing or consisting of GMO's may pose a risk for the
2056 environment, requiring the implementation of additional control measures. As a first step, an
2057 assessment of the risks should be performed taking into account the risk of the isolated
2058 ATMP, as well as the risk in case of expansion inside a permissive cell host. The risk
2059 assessment should result in a categorization of the products as having a negligible, low,
2060 moderate or high risk for the environment.

2061 Containment measures should be established according to the risk of the product that is
2062 handled, including measures regarding the design of the premises, organizational and
2063 technical measures, and measures regarding the treatment of residues.

2064 Where replication limited vectors are used, measures should be in place to prevent the
2065 introduction of wild-type viruses, which may lead to the formation of replication competent
2066 recombinant vectors.

2067 Emergency plans should also be in place covering the actions to be taken in case of accidental
2068 release into the environment. The plan should foresee measures/procedures for containment,
2069 protection of personnel, cleaning, and decontamination.

2070 In the case of authorised ATMPs, the risk assessment, the containment measures and the
2071 emergency plan(s) should be part of the Risk Management Plan. In the case of investigational
2072 ATMPs, the suitability of the containment measures and the emergency plan(s) is assessed as
2073 part of the authorisation by the competent authorities responsible for GMOs.

2074 **16. Reconstitution of product after batch release**

2075 **16.1. Reconstitution activities**

2076 Reconstitution activities can be performed at the administration site (*e.g.* in hospital
2077 pharmacies) outside a GMP environment.

2078 For the purposes of these Guidelines, the term “reconstitution” covers activities required after
2079 batch release and prior to the administration of the ATMP to the patient, and which cannot be
2080 considered as a manufacturing step.²⁷ No activity that entails substantial manipulation can,
2081 however, be considered reconstitution (*e.g.* cultivation). Substantial manipulations should be
2082 conducted under GMP.

2083 The following are examples of reconstitution activities relevant for ATMPs. It is stressed that
2084 these examples cannot be extrapolated to medicinal products other than ATMPs:

2085 - Thawing, washing, buffer exchange, centrifugation steps necessary to remove
2086 preservation solution (*e.g.* DMSO), removal of process related impurities (residual
2087 amount of preservation solution, dead cells) including filtering.

2088 - (Re)suspension, dissolution or dilution with solvent/buffer, dispersion.

2089 - Cell recovery after cryo-storage.

2090 - Mixing the product with patient’s own cells, with an adjuvant and/or with other
2091 substances added for the purposes of administration (including matrixes). However,
2092 the mixing of a gene therapy vector with autologous cells is a manufacturing activity
2093 that should be conducted under GMP.

2094 - Splitting the product into several aliquots and use in separate doses over a period of
2095 time, adaptation of dose (*e.g.* cell count).

2096 - Loading into delivery systems/surgical devices, transfer to an infusion bag/syringe.

2097 The above steps can only be part of the reconstitution process if it is appropriately justified
2098 that these steps cannot be performed as part of the manufacturing process before QP release
2099 without negative impact on the product. Additionally, the above activities can only be
2100 considered “reconstitution” when they are carried out at administration site (*i.e.* it is not
2101 acceptable to have these steps outsourced to a third party that is not GMP-compliant).

2102 **16.2. Obligations of the ATMP manufacturer in connection with reconstitution**
2103 **activities.**

2104 The manufacturer should validate the reconstitution processes to be followed from the point
2105 of batch release to the moment of administration to the patient; *i.e.* through appropriate
2106 studies it should be demonstrated that the specified reconstitution process is sufficiently

²⁷ Grinding and shaping are part of surgical procedures and therefore are neither manufacturing, nor reconstitution activities.

2107 robust and consistent so that the product can be administrated without negative impact on
2108 quality/safety/efficacy profile of the ATMP.

2109 The manufacturer should document the reconstitution process, including equipment to be used
2110 and requirements at the site of administration. The instructions should be detailed and clear
2111 enough so as to avoid negative impacts on the quality of the product (*e.g.* when the
2112 reconstitution involves thawing, the rate of temperature change during thawing should be
2113 described.)

2114 Likewise, when the constitution requires the use of solvents and/or other materials these
2115 should be specified or, as appropriate, provided.

2116 **17. Automated production of ATMPs**

2117 **17.1. General principles**

2118 If the output of an automated production system meets the definition of ATMP (either
2119 because the process amounts to substantial manipulation of the cells/tissues, or because the
2120 cells/tissues are used for a different essential function in the recipient as in the donor), the
2121 requirements of the Regulation (EU) No 1394/2007 apply. This means that the marketing of
2122 the ATMP requires authorisation by the European Commission, or by the national competent
2123 authorities in the context of the authorisation of the clinical trial or in application of the
2124 hospital exemption. Additionally, this also means that GMP requirements apply.

2125 The use of functionally closed manufacturing equipment may, however, ease compliance with
2126 certain GMP requirements and may also bring certain advantages in respect to product's
2127 quality. This section outlines some specific aspects relevant to the use of this technology for
2128 the manufacture of ATMPs but, unless stated otherwise, the remaining sections of these
2129 Guidelines are also applicable.

2130 **17.2. Automated equipment**

2131 The user of the automated production system (hereafter referred to as “automated equipment”
2132 (*i.e.* ATMP manufacturer) is responsible for the quality of the ATMP and, therefore, has to
2133 ensure the suitability of the automated equipment for the specific intended purpose.

2134 While the level of effort to demonstrate suitability may be reduced when the automated
2135 equipment is certified for the intended used according to the EU medical device legislation
2136 (CE mark), it is stressed that the CE mark may not be relevant (*i.e.* automated equipment that
2137 does not qualify as medical device) and that, in any case, the CE mark does not suffice to
2138 demonstrate suitability as required for under these Guidelines.

2139 Of particular relevance are the following obligations of the ATMP manufacturer:

2140 - Validation of the equipment: The validation process as described in Section 10.1
2141 applies. The user requirement specifications should be clear, unambiguous and

2142 detailed enough to ensure the suitability of the automated equipment for the intended
2143 operations.

2144 In turn, the amount of information received from the manufacturer of the automated
2145 equipment should be sufficient for the ATMP manufacturer to fully understand the
2146 functioning of the automated equipment and to identify the steps critical for the
2147 quality, safety and efficacy of the product. Additional tests and operating procedures
2148 should be developed by the ATMP manufacturer where appropriate (*e.g.* in case of
2149 information gaps in the information provided by the manufacturer of the automated
2150 equipment, or deviations from the operating instructions supplied).

2151 The automated equipment should not be used outside the recommendations of its
2152 manufacturer/supplier, unless the new operating mode has been fully validated.

2153 - Standard operating procedures should be developed. SOPs should be clear and
2154 detailed enough to ensure that the operators understand the manufacturing process and
2155 the associated risks. SOPs should also ensure that any deviation can be rapidly
2156 identified and that appropriate measures are taken.

2157 - Adequate maintenance: Maintenance of the automated equipment to ensure optimal
2158 conditions of use and to avoid unintended deviations/ instances of malfunctioning is
2159 essential.

2160 A program of services/calibration at regular intervals should be described and the split
2161 of responsibilities of the manufacturer of the automated equipment and the
2162 responsibilities of the manufacturer of ATMPs should be laid down in writing.

2163 - Asseptic processing: The automated equipment should be only used under conditions
2164 that ensure aseptic processing (*e.g.* validation of cleaning processes and sterilization of
2165 repeatedly used materials that are in contact with the product).

2166 - Batch and traceability records should be kept.

2167 **17.3. Personnel**

2168 Personnel involved in production should be adequately trained and the associated risks of the
2169 process should be duly understood (including risks to the efficacy of the product).

2170 **17.4. Premises**

2171 As explained in Section 4, the room where a closed system is used should be of at least D
2172 grade. The transfer of the material into/from the equipment is a critical step and a validated
2173 procedure should be put in place to preserve the product from the risk of contamination.

2174 If justified having regard to the risks and provided that the approach is supported by
2175 validation data (*e.g.* leak testing and pressure check of the equipment), a controlled but non-
2176 classified background environment could be acceptable if the time between the donation and

2177 administration of the material is very short and the manufacturing is performed at the
2178 operating room in the hospital (the patient is also in the operating room waiting for
2179 administration of the ATMP). The conditions of the operating room where the manufacturing
2180 activity takes place should be adequate and sufficient to ensure the quality and safety of the
2181 product.

2182 **17.5. Production and process validation**

2183 The definition of the moment when the manufacturing process starts and finishes should be
2184 defined and the role and responsibilities of all actors involved at the different time-points
2185 should be clearly established.

2186 Possibilities for in-process and release controls are limited due to the continuous closed
2187 processing, limited amount of material and usually very short shelf-life. Continuous
2188 monitoring of critical process parameters and other input parameters that affect product
2189 quality (as identified in the marketing authorisation/clinical trial authorisation) should be
2190 performed if technically possible. When continuous monitoring is not technically possible,
2191 monitoring at appropriate intervals having regard to the criticality of the parameter and the
2192 risks is required. Data on process parameters should be kept as part of the batch records.

2193 Lack of routine controls (due to continuous process in closed system and short shelf-life) of
2194 each individual batch must be compensated by a reinforced process validation.

2195 Validation of aseptic processing by media fill simulation should also be performed. The bi-
2196 annual frequency is recommended but it could be adapted having regard to the risks (*see*
2197 Section 9.5.3).

2198 **17.6. Qualified Person and Batch Release**

2199 Batch release is a fundamental requirement for all medicinal products, including ATMPs that
2200 are manufactured using automated equipment. Some specific elements described in Section
2201 may be considered in the context of automated production of ATMPs, such as the possibility
2202 that the same QP is responsible for more than one site, or the possibility to rely on audits
2203 conducted by third parties.