

## ANNEX 2A

# MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

## SCOPE

The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, genome editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this annex. In a medicinal product, the genetically modified cells can be presented alone or combined with medical devices. This annex provides additional and specific guidance on the full range (as defined in the glossary) of ATMPs and the active substances that are used in their manufacture. Although one of the objectives of this present revision was to prepare a document that would stand for several years the field is quickly changing; it is recognised that amendments may be necessary to accommodate technological change, to clarify uncertainty or to specifically recognise important alternatives. Comments are therefore invited at any stage of the life of this edition. Interpretation and necessary adjustments will be given as Q&A until a new revision will be necessary.

This annex is divided into two main parts:

- 1) Part A contains supplementary guidance and alternative provisions on the manufacture of ATMPs, from control over seed lots and cell banks through to finishing activities and testing.
- 2) Part B contains further guidance on selected types of ATMPs and its substances.

This annex, along with several other annexes of the Guide to GMP, provides guidance which supplements that in Part I and in Part II of the PIC/S GMP Guide.

Table 1 gives examples of where this Annex applies. It should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that in line with the corresponding table, the level of GMP increases in detail from early to later steps in the manufacture of ATMPs active substances but should always adhere to GMP principles. The inclusion of some early steps of manufacture within the scope of this annex does not imply that those steps will be routinely subject to inspection by the authorities.

In certain cases, other national laws may be applicable to the starting materials for ATMPs. For example,

- (a) Tissue and cells used as starting materials of ATMPs, donation, procurement, testing, processing, preservation, storage, and distribution of human tissue and cells may be covered by national law.

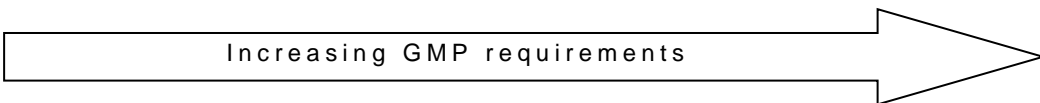
48 (b) Blood or blood components used as starting materials for ATMPs, national law  
 49 may provide the technical requirements for the selection of donors and the  
 50 collection and testing of blood and blood components<sup>1</sup>.

51 Additionally, the manufacture and control of genetically modified organisms needs  
 52 to comply with local and national requirements. Appropriate containment should  
 53 be established and maintained in facilities where any genetically modified micro-  
 54 organism is handled. Advice should be obtained according to national law in order  
 55 to establish and maintain the appropriate Biological Safety Level. There should be  
 56 no conflicts with GMP requirements.  
 57

58 **Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2A**

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells <sup>1</sup>	Vector manufacturing; cell isolation, culture and purification	Ex-vivo genetic modification of cells, Establishment of MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells <sup>1</sup>	Establishment of MCB, WCB or primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells <sup>1</sup>	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill
Non-Human and/or animal sources	Gene Therapy: in Vivo Viral Vectors by stable producer cell lines	Plasmid manufacturing <sup>1</sup>	Producer cell lines manufacturing	Vector Manufacturing	Formulation, filling
	Gene Therapy: in Vivo Viral Vectors by transient production system	Virus manufacturing <sup>1</sup>	Cell system manufacturing	Vector Manufacturing	Formulation, filling

59

60  Increasing GMP requirements

61

62 See Glossary for explanation of acronyms.

63

## 64 PRINCIPLE

65

66 The manufacture of ATMPs involves certain specific considerations arising from the  
 67 nature of the products and the processes. The ways in which biological medicinal  
 68 products are manufactured, controlled and administered make some particular  
 69 precautions necessary.

70

71 Since materials and processing conditions used in manufacturing processes are  
 72 designed to provide conditions for the growth of specific cells and microorganisms, this  
 73 provides extraneous microbial contaminants the opportunity to grow. In addition, some

<sup>1</sup> Separate GMP requirements may apply where required under national law.

74 products may be limited in their ability to withstand a wide range of purification  
75 techniques particularly those designed to inactivate or remove adventitious viral  
76 contaminants. The design of the processes, equipment, facilities, utilities, the  
77 conditions of preparation and addition of buffers and reagents, sampling and training  
78 of the operators are key considerations to minimise such contamination events.

79  
80 Specifications related to products (such as those in Pharmacopoeial monographs,  
81 Clinical Trial Authorisation (CTA), and Marketing Authorisation (MA) will dictate  
82 whether and to what stage ATMP substances and materials can have a defined level  
83 of bioburden or need to be sterile. Similarly, manufacturing must be consistent with  
84 other specifications set out in the CTA or MA (e.g. number of generations (doublings,  
85 passages) between the seed lot or cell bank).

86  
87 For biological materials that cannot be sterilized (e.g. by filtration), processing must be  
88 conducted aseptically to minimise the introduction of contaminants. Where they exist,  
89 other guidance documents should be consulted on the validation of specific  
90 manufacturing methods, e.g. virus removal or inactivation. The application of  
91 appropriate environmental controls and monitoring and, wherever feasible, in-situ  
92 cleaning and sterilisation systems together with the use of closed systems can  
93 significantly reduce the risk of accidental contamination and cross-contamination.

94  
95 Control usually involves biological analytical techniques, which typically have a greater  
96 variability than physico-chemical determinations. A robust manufacturing process is  
97 therefore crucial and in-process controls take on a particular importance in the  
98 manufacture of ATMP active substances and products.

99

100

## 101 **Part A: GENERAL GUIDANCE**

102

103

104

105

106

107

108

109

110

111

112

Part A provides alternative or supplementary provisions to respective sections in Part I, II and annexes of the PIC/S GMP Guide, where necessary. Where this annex provides specific guidance for the manufacture of ATMPs, (including modification, replacement or redundancy of other sections) this will be clearly indicated. In the absence of specific guidance for ATMPs, compliance with other sections in the PIC/S GMP Guide is expected.

Note: Where the term Marketing Authorisation Holder (MAH) is used, unless otherwise specified, it should be intended to signify the “Sponsor” for Investigational Medicinal Product that is used according to a CTA or equivalent.

## 113 **CHAPTER 1 PHARMACEUTICAL QUALITY SYSTEM**

114

### 115 **Pharmaceutical Quality System**

116

117 1.1 ATMPs are not sold or supplied before an Authorised Person has certified that each  
118 production batch has been produced and controlled in accordance with the  
119 requirements of the CTA, MA and any other regulations relevant to the production,  
120 control and release of medicinal products as applicable. Special provisions apply for  
121 the supply of products that do not meet release specifications where there is no  
122 alternative treatment available and these are described in 5.49 of this Annex.  
123 (Replaces PICS GMP Guide Part I Section 1.4, xv)

124

### 125 **Quality Control**

126

127 1.2 The finished products and active substances comply with the qualitative parameters  
128 and quantitative composition (including purity required and the correct gene sequence)  
129 approved in the CTA or MA are correctly labelled and are enclosed within their proper  
130 containers;

131

### 132 **Quality Risk Management**

133

134 1.3 GMP applies to the lifecycle stages from the manufacture of investigational medicinal  
135 products, technology transfer, and commercial manufacturing through to product  
136 discontinuation. Unlike conventional medicinal products, which are manufactured  
137 using chemical and physical techniques capable of a high degree of consistency, the  
138 manufacture of ATMP active substances and products involves biological processes  
139 and materials, such as cultivation of cells or extraction of material from living  
140 organisms. These biological processes may display inherent variability, so that the  
141 range and nature of by-products may be variable. As a result, Quality Risk  
142 Management (QRM) principles as detailed in Annex 20 are particularly important for  
143 this class of materials and should be used to develop their control strategy across all  
144 stages of manufacture so as to minimise variability and to reduce the opportunity for  
145 contamination and cross-contamination. (Replaces PICS GMP Guide Part I Section  
146 1.2)

147

## 148 **CHAPTER 2 PERSONNEL**

149

### 150 **Personnel Hygiene**

151

152 2.1 The health status of personnel should be taken into consideration for product safety.  
153 Where necessary, personnel engaged in production, maintenance, testing and  
154 inspections should be vaccinated with appropriate specific vaccines and have regular  
155 health checks.

156

157 2.2 Any changes in the health status of personnel, which could adversely affect the quality  
158 of the product, should preclude work in the production area and appropriate records  
159 kept. Health monitoring of staff should be commensurate with the risk; medical advice  
160 should be sought for personnel involved with hazardous organisms.

161

162 2.3 Every person entering the manufacturing areas should wear clean protective garments  
163 appropriate to the operations to be carried out.

164 Where required to minimise the opportunity for cross-contamination, restrictions on the  
165 movement of all personnel (including quality control (QC), maintenance and cleaning

166 staff) should be controlled on the basis of QRM principles. In general, personnel should  
167 not pass from areas where exposure to live micro-organisms, genetically modified  
168 organisms, toxins or animals to areas where other products, inactivated products or  
169 different organisms are handled. If such passage is unavoidable, the contamination  
170 control measures should be based on QRM principles. (Replaces PICS GMP Guide  
171 Part I Section 2.18)  
172

## 173 CHAPTER 3 PREMISES AND EQUIPMENT

### 174 PREMISES

#### 175 Production Areas

- 176
- 177
- 178
- 179 3.1 Cross-contamination should be prevented for all products by appropriate design and  
180 operation of manufacturing facilities. The measures to prevent cross-contamination  
181 should be commensurate with the risks. QRM principles should be used to assess and  
182 control the risks. Depending on the level of risk, it may be necessary to dedicate  
183 premises and equipment for manufacturing and/or packaging operations to control the  
184 risk presented by some ATMPs. Segregated production areas should be used for the  
185 manufacturing of ATMPs presenting a risk that cannot be adequately controlled by  
186 operational and/or technical measures. (Replaces PICS GMP Guide Part I Section 3.6)  
187
- 188 3.2 Manufacturing activities concerning different starting materials and/or finished  
189 products should be separated, either in place or in time.  
190
- 191 3.3 Concurrent production of two different ATMPs/batches in the same area is permitted  
192 under the following conditions:
- 193 (a) The use of more than one closed isolator (or other closed systems) in the same  
194 room at the same time is acceptable, provided that appropriate mitigation  
195 measures are taken to avoid cross-contamination or mix-ups of materials,  
196 including separated expulsion of the exhausted air from the isolators and regular  
197 integrity checks of the isolator.
- 198 (b) When two isolators are used to process different viral vectors within the same  
199 room there should be 100% air exhaustion from the room and the facility (i.e. no  
200 recirculation). In addition, in case of concurrent production of viral vectors, it is  
201 necessary to provide for closed, separate and unidirectional waste handling.
- 202 (c) The possibility of using more than one biosafety cabinet in the same room is only  
203 acceptable if effective technical and organisational measures are implemented to  
204 separate the activities (e.g. strict material and personal flows defined, no crossing  
205 lines in the use of equipment in the same room etc.). It is stressed that the  
206 simultaneous use of more than one biosafety cabinet entails additional risks and,  
207 therefore, it should be demonstrated that the measures implemented are effective  
208 to avoid risks to the quality of the product and mix-ups.
- 209 (d) It is acceptable to conduct a manufacturing activity in a clean room which hosts  
210 an incubator which is used for a different batch/product if there is separated  
211 expulsion of exhausted air from the incubator. Particular attention should be paid  
212 to prevent mix-ups.
- 213 (e) The simultaneous incubation/storage of different batches within the same  
214 incubator is only acceptable if they are physically separated (e.g. distinct cell  
215 cultures in closed vessels). When simultaneous incubation/storage of different  
216 batches takes place as described above, the manufacturer should evaluate the  
217 possible risks and implement appropriate measures to avoid mix-ups of materials.

- 218 (f) However, the simultaneous incubation/storage of replication competent  
219 vectors/products based on them, or infected material/products based on them with  
220 other materials/products is not acceptable.
- 221 (g) Given their lower risk profile, concurrent production of non-viral vectors in separate  
222 laminar flow hoods placed in the same room may be acceptable if appropriate  
223 measures are implemented to avoid mix-ups.  
224
- 225 3.4 The measures and procedures necessary for containment (i.e. for environment and  
226 operator safety) should not conflict with those for product quality.  
227
- 228 3.5 Special precautions should be taken in the case of manufacturing activities involving  
229 infectious viral vectors (e.g. oncolytic viruses): these activities should take place in a  
230 segregated area. Dedicated production area should be used for the manufacture of  
231 pathogenic organisms. (i.e. Biosafety level 3 or 4), in accordance with national law.  
232
- 233 3.6 Air handling units should be designed, constructed and maintained to minimise the risk  
234 of cross-contamination between different manufacturing areas and may need to be  
235 specific for an area. Consideration, based on QRM principles, should be given to the  
236 use of single pass air systems.  
237
- 238 3.7 Due to the variability of biological products or manufacturing processes,  
239 relevant/critical raw materials (such as culture media and buffers) have to be measured  
240 or weighed during the production process. In these cases, small stocks of these raw  
241 materials may be kept in the production area for a specified duration based on defined  
242 criteria such as for the duration of manufacture of the batch or of the campaign.  
243 (Replaces PICS GMP Guide Part I Section 3.13)  
244
- 245 3.8 Positive pressure areas should be used to process sterile products but negative  
246 pressure in specific areas at the point of exposure of pathogens is acceptable for  
247 containment reasons. Where negative pressure areas or safety cabinets are used for  
248 aseptic processing of materials with particular risks (e.g. pathogens), they should be  
249 surrounded by a positive pressure clean zone of appropriate grade. These pressure  
250 cascades should be clearly defined and continuously monitored with appropriate alarm  
251 settings.  
252
- 253 3.9 Air vent filters should be hydrophobic and validated for their scheduled life span with  
254 integrity testing at appropriate intervals based on appropriate QRM principles.  
255
- 256 3.10 Drainage systems must be designed so that effluents can be effectively neutralised or  
257 decontaminated to minimise the risk of cross-contamination. Local regulation must be  
258 complied with to minimize the risk of contamination of the external environment  
259 according to the risk associated with the biohazardous nature of waste materials.  
260 (Replaces PICS GMP Guide Part I Section 3.11)  
261
- 262 3.11 The degree of environmental control of particulate and microbial contamination of the  
263 production premises should be adapted to the product and the production step, bearing  
264 in mind the potential level of contamination of the starting materials and the risks to the  
265 product. The environmental monitoring programme should be supplemented by the  
266 inclusion of methods to detect the presence of specific microorganisms (e.g. host  
267 organism, yeasts, moulds, anaerobes, etc.) where indicated by the QRM process.  
268 (Replaces PICS GMP Guide Part I Section 3.1)  
269
- 270 3.12 Where processes are not closed and there is exposure of the product to the immediate  
271 room environment without a subsequent microbial inactivation process, (e.g. during

272 additions of supplements, media, buffers, gasses, manipulations) then this must be in  
273 a working environment with air particle counts, microbial colony counts and other clean  
274 room parameters equivalent to those defined in Annex 1. The appropriate level of air  
275 classification should be determined having regard to the specific risks, considering the  
276 nature of the product and the manufacturing process. (Replaces PICS GMP Guide Part  
277 I Section 3.1)

278  
279 3.13 A less stringent environment than specified in 3.12 above may be acceptable where  
280 approved by the competent authority. This should be considered only when a product  
281 is intended to treat a life-threatening condition where circumstances necessitate a less  
282 stringent environment and manufacturing alternatives do not exist or are not suitable.  
283 In this case, the environment must be specified and justified to provide patient benefit  
284 that outweighs the significant risk created by manufacturing under less stringent  
285 environments. It must be demonstrated that the chosen environment is suitable for  
286 maintaining critical quality and safety attributes, taking into account the intended  
287 purpose, the mode of application and the health status of the recipient. (Replaces PICS  
288 GMP Guide Part I Section 3.1)

289  
290 3.14 Performing a manufacturing step in premises that are not under direct control of the  
291 MAH or Sponsor, (including for example placing equipment used to perform  
292 manufacturing steps in hospital wards or theatre), is permissible provided that the MAH  
293 or Sponsor demonstrates that the process maintains its validated status utilising the  
294 provisions of Annex 15 and any derogation from the mandated standards in this Annex  
295 are justified utilising QRM principles described Annex 20, and subject to approval by  
296 the competent authority.

297

## 298 EQUIPMENT

299

300 3.15 Production equipment should not present any hazard to the products. The parts of the  
301 production equipment that come into contact with the product must not be reactive,  
302 additive or absorptive to such an extent that it will affect the quality of the product and  
303 thus present any hazard. In addition to that, if single use systems are used, the  
304 manufacturer should take in account and verify the impact on the product from  
305 extractable, leachable, insoluble particulate and insoluble matter derived from such  
306 systems. (Replaces PICS GMP Guide Part I Section 3.39)

307

308 3.16 Where required to minimise the risk of cross-contamination, restrictions on the  
309 movement of equipment should be applied. In general, equipment should not be  
310 moved from high risk areas to other areas, or between high risk areas (e.g. equipment  
311 used for the handling of cells from infected donors or the handling of oncolytic viruses).  
312 When this happens, appropriate measures need to be applied to avoid the risk of cross-  
313 contamination. The qualification status of the equipment moved should also be  
314 reconsidered.

315

316 3.17 Equipment used during handling of live organisms and cells, including those for  
317 sampling, should be designed to prevent any contamination during processing.

318

319 3.18 Primary containment<sup>2</sup> should be designed and periodically tested to ensure the  
320 prevention of escape of biological agents into the immediate working environment.

321

322 3.19 Bioinformatics systems used to support manufacturing must be qualified in accordance  
323 with Annex 11 and 15. Any analytical testing performed on materials not used in

---

<sup>2</sup> See main GMP Glossary on 'Containment'.

324 manufacturing but that support bioinformatics informing the manufacturing process  
325 (e.g. patient gene sequencing) must be validated. Such analytical equipment is  
326 expected to be qualified prior to use.  
327

## 328 **CHAPTER 4 DOCUMENTATION**

### 329 **Retention of Documents**

330  
331  
332 4.1 Traceability records must be retained 30 years after the expiry date of the product  
333 unless otherwise specified in the MA or national law. Particular care should be taken  
334 to maintain the traceability of products for special use cases, such as donor-matched  
335 cells. National requirements apply to blood components in regards to traceability  
336 requirements and notification of serious adverse reactions and events apply to blood  
337 components when they are used as starting or raw materials in the manufacturing  
338 process of medicinal products. Human cells including haematopoietic cells must  
339 comply with the principles laid down in national law with regards to traceability.  
340 (Replaces PICS GMP Guide Part I Section 4.11)  
341

342 4.2 When xenogeneic cells are used as starting materials for ATMPs, information  
343 permitting the identification of the donor animal should be kept for 30 years unless  
344 otherwise specified in the MA or national law. (Replaces PICS GMP Guide Part I  
345 Section 4.11)  
346

### 347 **Specifications & Traceability**

348  
349 4.3 Specifications for ATMP starting and raw materials may need additional documentation  
350 on the source, origin, distribution chain, method of manufacture, and controls applied,  
351 to assure an appropriate level of control including their microbiological quality.  
352

353 4.4 Some products may require specific definition of what materials constitutes a batch.  
354 For autologous and donor-matched situations, the manufactured product should be  
355 viewed as a batch.  
356

357 4.5 Where human cell or tissue is used, full traceability is required from starting and raw  
358 materials, including all substances coming into contact with the cells or tissues through  
359 to confirmation of the receipt of the products at the point of use whilst maintaining the  
360 privacy of individuals and confidentiality of health-related information.  
361

362 4.6 For starting materials of human origin, the identification of the supplier and the  
363 anatomical environment from which the cells/tissues/virus originates (or, as  
364 appropriate, the identification of the cell-line, master cell bank, seed lot) should also be  
365 described.  
366

367 4.7 A system that enables the bidirectional tracking of cells/tissues contained in ATMPs  
368 from the point of donation, through manufacturing, to the delivery of the finished  
369 product to the recipient should be created. Such system, which can be manual or  
370 automated, should be established since the beginning of the manufacture of batches  
371 for clinical use.  
372

373 4.8 Traceability data should be kept as auditable documents. It is acceptable that it is kept  
374 outside the batch processing record, provided that they are readily available and are  
375 unequivocally linked to the relevant medicinal product. The storage system should  
376 ensure that traceability data may be accessed rapidly in case of an adverse reaction  
377 from the patient.



## 378 CHAPTER 5 PRODUCTION

379

### 380 General

381

382 5.1 ATMPs must comply with the applicable national requirements on minimising the risk  
383 of transmitting animal spongiform encephalopathy agents via human and veterinary  
384 medicinal products.

385

386 5.2 The conditions for sample collection, additions and transfers involving replication  
387 competent vectors or materials from infected donors should prevent the release of  
388 viral/infected material.

389

390 5.3 All incoming materials should be checked to ensure that the consignment corresponds  
391 to the order. Containers should be cleaned where necessary and labelled with the  
392 prescribed information. Material of biological origin with unknown adventitious agent  
393 status should be treated in a way to avoid mix-up and cross-contamination. (Replaces  
394 PICS GMP Guide Part I Section 5.3)

395

396 5.4 At every stage of processing, materials and products should be protected from  
397 microbial and other contamination. Appropriate cross-contamination control measures  
398 and monitoring strategies should be implemented. Particular consideration should be  
399 given to the risk of cross-contamination between cell preparations from different donors  
400 with various health statuses. (Replaces PICS GMP Guide Part I Section 5.10)

401

402 5.5 PICS GMP Guide Part I Section 5.11 is not applicable to this class of products

403

404 5.6 Labels applied to containers, equipment or premises should be clear, unambiguous  
405 and in the manufacturer's agreed format. For products containing cells derived from  
406 human cell or tissue, donor's labels should contain all relevant information that is  
407 needed to provide full traceability. In the case of products for autologous use, the  
408 unique patient identifier and the statement "for autologous use only" should be  
409 indicated on the immediate label. Alternative approaches/ measures are permitted as  
410 long as the risk of erroneous administration of the product is adequately mitigated.  
411 (Replaces PICS GMP Guide Part I Section 5.13)

412

413 5.7 If closed systems are used for the production of ATMPs, checks should be carried out  
414 to ensure that all pieces of the equipment are connected in a correct manner to assure  
415 the closed state. Special attention should be given to apply these tests to automated  
416 systems. The integrity of single use equipment should be verified prior to every use.  
417 The integrity of reused equipment should be verified prior to and after cleaning and  
418 sterilisation.

419

420 5.8 When materials are added/withdrawn from the closed system without an aseptic  
421 connection (e.g. use of sterile connectors, use of filters), the system can no longer be  
422 considered closed.

423

424 5.9 Where chromatography equipment is used, a suitable control strategy for matrices, the  
425 housings and associated equipment (adapted to the risks) should be implemented  
426 when used in campaign manufacture and in multi-product environments. The re-use  
427 of the same matrix at different stages of processing is discouraged. Any such re-usage  
428 should be supported by appropriate validation data. Acceptance criteria, operating  
429 conditions, regeneration methods, life span, and sanitization or sterilisation methods  
430 of chromatography columns should be defined.

431

432 5.10 The use of technologies (e.g. processing inside sterile disposable kits, or processing  
433 using closed, automated, manufacturing platform or incubation in closed flasks, bags  
434 or fermenters) in a grade C environment may be acceptable if adequate control  
435 measures are implemented to avoid the risk of cross-contamination (e.g. appropriate  
436 control of materials, personnel flows and cleanness). Particular attention should be  
437 paid if the materials are subsequently moved to a clean area of higher grade.  
438

439 5.11 The compatibility of labels with ultra-low storage temperatures, where such  
440 temperatures are used, should be verified.  
441

## 442 **Prevention of Cross-contamination in Production**

443  
444 5.12 An evidence-based QRM process should be used to assess and control the cross-  
445 contamination risks presented by the products manufactured. Factors including:  
446 vectors used and the risk of occurrence of replication competent virus (including  
447 different level of risk derived from the use of replication limited, replication defective,  
448 conditional replication and replication incompetent vector), facility/equipment design  
449 and use, personnel and material flow, microbiological and other adventitious agent  
450 controls, characteristics of the critical starting materials/active substance and raw  
451 materials, process characteristics, clean room conditions, cleaning processes and  
452 analytical capabilities relative to the relevant limits established from the evaluation of  
453 the products should also be taken into account. The outcome of the QRM process  
454 should be the basis for determining the process workflow and necessity for and extent  
455 to which premises and equipment should be dedicated or single-use equipment should  
456 be used for a particular product. This may include dedicating specific product contact  
457 parts or dedication of the entire manufacturing facility. It may be acceptable to confine  
458 manufacturing activities to a segregated, self-contained production area within a  
459 multiproduct facility, where justified. (Replaces PICS GMP Guide Part I Section 5.20)  
460

461 5.13 In cases where a virus inactivation or removal process is performed during  
462 manufacture, measures should be taken to avoid the risk of recontamination of treated  
463 products by non-treated products.  
464

465 5.14 Accidental spillages, especially of live organisms, must be dealt with quickly and safely.  
466 Validated decontamination measures should be available for each organism or groups  
467 of related organisms.  
468

469 5.15 If obviously contaminated, such as by spills or aerosols, or if a potential hazardous  
470 organism is involved, production and control materials, including paperwork, must be  
471 adequately disinfected, or the information transferred out by other means.  
472

473 5.16 The use of antimicrobials may be necessary to reduce bioburden associated with the  
474 procurement of living tissues and cells. However, the use of antimicrobials does not  
475 replace the requirement for aseptic manufacturing. When antimicrobials are used, their  
476 use should be recorded, they should be removed as soon as possible, unless the  
477 presence thereof in the finished product is specifically foreseen in the CTA or MA (e.g.  
478 antibiotics that are part of the matrix of the finished product). Additionally, it is important  
479 to ensure that antibiotics or antimicrobials do not interfere with the sterility testing, and  
480 that they are not present in the finished product (unless specifically foreseen in the  
481 CTA or MA).  
482

483 5.17 The risks of cross-contamination should be assessed having regard to the  
484 characteristics of the product (e.g. biological characteristics of the starting materials,  
485 possibility to withstand purification techniques) and manufacturing process (e.g. the

486 use of processes that provide extraneous microbial contaminants the opportunity to  
487 grow). If sterilisation of the finished product is not possible, particular attention should  
488 be paid to the manufacturing steps where there is exposure to the environment (e.g.  
489 filling).

490  
491 5.18 In all manufacturing steps that may lead to unwanted formation of aerosols (e.g.  
492 centrifugation, working under vacuum, homogenisation, and sonication) appropriate  
493 mitigation measures should be implemented to avoid cross-contamination. Special  
494 precautions should be taken when working with infectious materials.

495  
496 5.19 Measures to prevent cross-contamination appropriate to the risks identified should be  
497 put in place. Measures that can be considered to prevent cross-contamination include,  
498 among others:

- 499 (a) Segregated premises.  
500 (b) Dedicating the whole manufacturing facility or a self-contained production area on  
501 a campaign basis (separation in time) followed by a cleaning process of validated  
502 effectiveness.  
503 (c) Use of “closed systems” for processing and material/product transfer between  
504 equipment.  
505 (d) Use of air-locks and pressure cascade to confine potential airborne contaminant  
506 within a specified area.  
507 (e) Utilisation of single use disposable technologies.  
508 (f) Adequate cleaning procedures. The cleaning procedure (technique, number of  
509 sanitation steps, etc.) should be adapted to the specific characteristics of the  
510 product and of the manufacturing process. A risk-assessment should be used to  
511 determine the cleaning/decontamination procedures that are necessary, including  
512 the frequency thereof. As a minimum, there should be appropriate  
513 cleaning/decontamination between each batch. The cleaning/decontamination  
514 procedures should be validated  
515 (g) Other suitable technical measures, such as the dedication of certain parts of  
516 equipment (e.g. filters) to a given type of product with a specific risk profile. Other  
517 suitable organizational measures, such as keeping specific protective clothing  
518 inside areas where products with high-risk of contamination are processed,  
519 implementing adequate measures to handling waste, contaminated rinsing water  
520 and soiled gowning, or imposing restrictions on the movement of personnel.  
521 (Replaces PICS GMP Guide Part I Section 5.21)

## 522 523 **Validation**

524  
525 5.20 Validation studies should reinforce GMP and be conducted in accordance with defined  
526 procedures. Results and conclusions should be recorded, in particular:

- 527 (a) All aseptic and sterilisation processes for investigational and authorized ATMPs  
528 are expected to be validated to the extent of routine production.  
529 (b) Viral clearance or the removal of any biological contamination that might be a risk  
530 for patient safety should be validated.  
531 (c) The methods used for disinfection, should be validated.  
532 (d) For all aseptic processes, aseptic process simulations should be performed as  
533 part of initial validation and normally repeated every six months. See Annex 1 for  
534 more information. In the case of infrequent production (i.e. if the interval between  
535 the production of two batches is more than six months but less than a year), it is  
536 acceptable that the process simulation test is done just before the manufacturing  
537 of the next batch, provided that the results of the process simulation test are  
538 available prior to the starting of production.

539 (e) If the ATMP is not produced on a routine basis (i.e. over a year) the aseptic  
540 process simulation should be conducted in triplicate prior to the start of  
541 manufacturing, involving all relevant operators. (Replaces PICS GMP Guide Part  
542 I Section 5.23)

543  
544 5.21 The limited availability of the cells/tissues which is typical for most ATMPs requires the  
545 development of approaches to process validation that take into account the quantities  
546 of tissue/cells available and that focus on gaining maximum experience of the process  
547 from each batch processed. Additional in-process testing to demonstrate consistency  
548 of production should where possible offset reduced process validation. ATMPs  
549 manufactured for early phase clinical trials (phase I and phase I/II), are not expected  
550 to be validated to the extent necessary for routine production

551  
552 5.22 The use of surrogate material may be acceptable when there is shortage of the starting  
553 materials (e.g. autologous ATMPs, allogeneic in a matched-donor scenario, allogeneic  
554 where there is no expansion of cells to MCB). The representativeness of surrogate  
555 starting material should be evaluated, including -for example- donor age, use of  
556 materials from healthy donors, anatomical source (e.g. femur vs. iliac crest) or other  
557 different characteristics (e.g. use of representative cell-types or use of cells at a higher  
558 passage number than that foreseen in the product specifications).

559  
560 5.23 Where possible, consideration should be given to complementing the use of surrogate  
561 materials with samples from the actual starting materials for key aspects of the  
562 manufacturing process. For instance, in the case of an ATMP based on modification  
563 of autologous cells to treat a genetic disorder, process validation using the autologous  
564 cells (affected by the condition) may be limited to those parts of the process that focus  
565 on the genetic modification itself. Other aspects could be validated using a  
566 representative surrogate cell type.

567

## 568 **Control of Starting Materials and Raw Materials**

569

570 5.24 The quality of starting and raw materials is a key factor to consider in the production of  
571 ATMPs. Particular attention should be paid to avoiding contamination and to  
572 minimizing as much as possible the variability of the starting and raw materials.  
573 Specifications related to the product (such as those in Pharmacopoeia monographs,  
574 CTA, or MA), will dictate whether and to what stage substances and materials can  
575 have a defined level of bioburden or need to be sterile. Prior to introduction in the  
576 manufacturing process, the conformity to the relevant requirements should be  
577 checked.

578

579 5.25 The controls required for the quality of starting materials and on the aseptic  
580 manufacturing process, particularly for cell-based products, where final sterilisation is  
581 generally not possible and the ability to remove microbial by-products is limited,  
582 assume greater importance. For autologous cell therapies, the maintenance of the  
583 aseptic processing from time of collection through manufacturing and administration  
584 back into the patient should be ensured. Where a CTA or MA provides for an allowable  
585 type and level of bioburden, for example at active substance stage, the control strategy  
586 should address the means by which this is maintained within the specified limits.

587

588 5.26 The ATMP manufacturer should verify compliance of the supplier's materials with the  
589 agreed specifications. The level of oversight and further testing by the ATMP  
590 manufacturer should be proportionate to the risks posed by the individual materials.  
591 (Replaces PICS GMP Guide Part I Section 5.35).

592

593 5.27 In addition to the specifications for the starting materials, the agreement between the  
594 ATMP manufacturer (or, as appropriate, the sponsor or MAH) and the supplier  
595 (including blood and tissue establishments) should contain clear provisions about the  
596 transfer of information regarding the starting materials, in particular, on tests results  
597 performed by the supplier, traceability data, and transmission of health donor  
598 information that may become available after the supply of the starting material and  
599 which may have an impact on the quality or safety of the ATMPs manufactured  
600 therefrom. (Replaces PICS GMP Guide Part I Section 5.28)  
601

602 5.28 The MAH should define critical materials, for the process based on process knowledge  
603 and QRM process.  
604

605 5.29 The selection, qualification, approval and maintenance of suppliers of starting  
606 materials, raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media,  
607 buffers, serum, enzymes, cytokines, growth factors) and materials that come in direct  
608 contact with the products during manufacture and storage (e.g. single use equipment)  
609 together with their purchase and acceptance, should be documented as part of the  
610 pharmaceutical quality system. The level of oversight should be proportionate to the  
611 risks posed by the individual materials, taking account of their source, manufacturing  
612 process, supply chain complexity and the final use to which the material is put in the  
613 medicinal product. The supporting evidence for each supplier / material approval  
614 should be maintained. Staff involved in these activities should have a current  
615 knowledge of the suppliers, the supply chain and the associated risks involved. Where  
616 possible, these materials should be purchased directly from the manufacturer.  
617 (Replaces PICS GMP Guide Part I Section 5.27)  
618

619 5.30 The quality requirements established by the manufacturer for the starting materials and  
620 materials, defined to be critical during QRM process, should be discussed and agreed  
621 with the suppliers. Appropriate aspects of the production, testing and control, including  
622 handling, labelling, packaging and distribution requirements, complaints, recalls and  
623 rejection procedures should be documented in a formal quality agreement or  
624 specification. (Replaces PICS GMP Guide Part I Section 5.28)  
625

626 5.31 For the approval and maintenance of suppliers of critical materials, the following is  
627 required: (Replaces PICS GMP Guide Part I Section 5.29)  
628

#### 629 ATMP Active substances

630 The supply chain traceability should be established and the associated risks, from  
631 active substance starting materials to the finished medicinal product, should be  
632 formally assessed and periodically verified. Appropriate measures should be put in  
633 place to reduce risks to the quality of the active substance.

634 The supply chain and traceability records for each active substance should be  
635 available and be retained by the manufacturer of the medicinal product.  
636

#### 637 Raw materials

638 The risk of contamination from the relevant raw materials should be assessed by a  
639 QRM process prior to setting up the manufacturing process and whenever a change  
640 of the respective raw material is implemented.

641 Appropriate measures should be put in place to reduce risks to the quality of the raw  
642 materials.  
643  
644

645 Material directly in contact with product during manufacture and storage

646  
647 All material that comes in direct contact with the medicinal product should be of  
648 sufficient quality. The risk for cross-contamination due to microbiological  
649 contamination, extractable and leachable should be assessed especially for single use  
650 material (e.g. cell cultivation vessels, cryostorage containers).

651 A regular qualification of the manufacturers and distributors of all materials to confirm  
652 that they comply with the relevant GMP requirements should be performed. Whether  
653 an on-site audit needs to be performed at a manufacturer's or distributor's premises  
654 should be defined based on QRM process. Generally, audits need to be performed at  
655 vendors of all critical materials. Refer to provisions detailed in Chapter 7 as modified  
656 by this Annex.

657  
658 5.32 Only critical materials which have been released by the Quality Control department  
659 and which are within their retest date should be used. Where the necessary tests take  
660 a long time, it may be permissible to process critical materials before the results of the  
661 tests are available, the risk of using a potentially failed material and its potential impact  
662 on other batches should be clearly understood and assessed under the principles of  
663 QRM. In such cases, release of a finished product is conditional on satisfactory results  
664 of these tests. (Replaces PICS GMP Guide Part I Section 5.34)

665  
666 5.33 PICS GMP Guide Part I Section 5.39 is not applicable to these products

667  
668 **Human Tissues and Cells Used as Critical Starting Materials**

669  
670 5.34 The donation, procurement and testing of human tissues and cells used as critical  
671 starting materials for ATMPs should be in accordance with national law.

672 (a) Their procurement, donation and testing is regulated in some countries. Such  
673 supply sites must hold appropriate approvals from the national competent  
674 authority(ies) which should be verified as part of starting material supplier  
675 management.

676 (b) Where such human cells or tissues are imported they must meet equivalent  
677 national standards of quality and safety. The traceability and serious adverse  
678 reaction and serious adverse event notification requirements may be set out in  
679 national law.

680 (c) There may be some instances where processing of cells and tissues used as  
681 starting materials for ATMPs will be conducted at tissue establishments. This is  
682 permissible only when the material would be otherwise compromised and  
683 processing involves only minimal manipulation.

684 (d) Tissue and cells are released by the Responsible Person (RP) in the tissue  
685 establishment before shipment to the medicinal product manufacturer, after  
686 which normal medicinal product starting material controls apply. The test results  
687 of all tissues / cells supplied by the tissue establishment should be available to  
688 the manufacturer of the medicinal product. Such information must be used to  
689 make appropriate material segregation and storage decisions. In cases where  
690 manufacturing must be initiated prior to receiving test results from the tissue  
691 establishment, tissue and cells may be shipped to the medicinal product  
692 manufacturer provided controls are in place to prevent cross-contamination with  
693 tissue and cells that have been released by the RP in the tissue establishment.

694 (e) The transport of human tissues and cells to the manufacturing site must be  
695 controlled by a written agreement between the responsible parties. The

696 manufacturing sites should have documentary evidence of adherence to the  
697 specified storage and transport conditions.

698 (f) Continuation of traceability requirements started at tissue establishments  
699 through to the recipient(s), and vice versa, including materials in contact with the  
700 cells or tissues, should be maintained.

701 (g) A technical agreement should be in place between the responsible parties (e.g.  
702 manufacturers, tissue establishment, Sponsors, MAH) which defines the tasks  
703 of each party.  
704

### 705 **Seed Lot and Cell Bank System**

706

707 5.35 If the production of ATMP involves cell culture or propagation in embryos and animals,  
708 in order to prevent the unwanted drift of properties which might ensue from repeated  
709 subcultures or multiple generations, it should be based on a system of master and  
710 working virus seed lots and/or cell banks.

711

712 5.36 The number of generations (doublings, passages) between the seed lot or cell bank,  
713 the ATMPs active substance and finished product should be consistent with  
714 specifications in the MA or CTA.  
715

716

717 5.37 As part of product lifecycle management, establishment of seed lots and cell banks,  
718 including master and working generations, should be performed under circumstances  
719 which are demonstrably appropriate. This should include an appropriately controlled  
720 environment to protect the seed lot and the cell bank and the personnel handling it.  
721 During the establishment of the seed lot and cell bank, no other living or infectious  
722 material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the  
723 same area or by the same persons. For stages prior to the master seed or cell bank  
724 generation, where only the principles of GMP may be applied, documentation should  
725 be available to support traceability including issues related to components used during  
726 development with potential impact on product safety (e.g. reagents of biological origin)  
727 from initial sourcing and genetic development if applicable.

728

729 5.38 Following the establishment of master and working cell banks and master and working  
730 seed lots, quarantine and release procedures should be followed. This should include  
731 adequate characterization and testing for contaminants. Their on-going suitability for  
732 use should be further demonstrated by the consistency of the characteristics and  
733 quality of the successive batches of product. Evidence of the stability and recovery of  
734 the seeds and banks should be documented and records should be kept in a manner  
735 permitting trend evaluation.

736

737 5.39 Seed lots and cell banks should be stored and used in such a way as to minimize the  
738 risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed  
739 containers) or alteration. Control measures, based on QRM principles, for the storage  
740 of different seeds and/or cells in the same area or equipment should prevent mix-up  
741 and take into account the infectious nature of the materials to prevent cross-  
742 contamination.

743

744 5.40 Cell based medicinal products are often generated from a cell stock obtained from  
745 limited number of passages. In contrast with the two-tiered system of Master and  
746 Working cell banks, the number of production runs from a cell stock is limited by the  
747 number of aliquots obtained after expansion and does not cover the entire life cycle of  
748 the product. Cell stock changes should be covered by a validation protocol.

749 5.41 Storage containers should be sealed, clearly labelled and kept at an appropriate  
750 temperature. A stock inventory must be kept. The storage temperature should be  
751 recorded, with frequency based on QRM principles, and, where used, the liquid  
752 nitrogen level monitored. Deviation from set limits and corrective and preventive action  
753 taken should be recorded.

754  
755 5.42 It is desirable to split stocks and to store the split stocks at different locations so as to  
756 minimize the risks of total loss. The controls at such locations should provide the  
757 assurances outlined in the preceding paragraphs.

758  
759 5.43 The storage and handling conditions for stocks should be managed according to the  
760 same procedures and parameters. Once containers are removed from the seed lot /  
761 cell bank management system, the containers should not be returned to stock.

## 762 763 **Packaging Operations**

764  
765 5.44 When setting up a programme for the packaging operations, particular attention should  
766 be given to minimising the risk of cross-contamination, mix-ups or substitutions.  
767 Sterility and/or low bioburden requirements should be adhered to. Different products  
768 should not be packaged in close proximity unless there is physical segregation.  
769 (Replaces PICS GMP Guide Part I Section 5.49)

## 770 771 **Release**

772  
773 5.45 Batches of medicinal products should only be released for sale or supply to the market  
774 after certification by an Authorised Person. Until a batch is certified, it should remain  
775 at the site of manufacture or be shipped under quarantine to another site which has  
776 been approved for that purpose by the relevant national competent authority.  
777 Generally, a finished product that does not meet release specification should not be  
778 administered to a patient unless the provisions given below in 5.46 are met;

779  
780 5.46 Where authorised by national law, the administration of a product that does not meet  
781 the release specification, might be performed in exceptional circumstances (such as  
782 when there is no alternative treatment available that would provide the same  
783 therapeutic outcome and the administration of the failed products could be lifesaving).

784  
785 The responsibility and the decision of the patient treatment are solely of the treating  
786 physician and is beyond the remit of this PIC/S Annex. The Authorised Person, the  
787 MAH and or the Sponsor of clinical trial should consider the following in making the  
788 product available:

789  
790 (a) The batch manufacturing records and the documentation provided to the treating  
791 physician should clearly state that the batch has failed the release specifications  
792 and describe the parameters that have not been met;

793 (b) The Authorised Person may provide a less technical description of the failed  
794 parameters upon request to the treating physician and where possible a  
795 description of potential consequences; and

796 (c) The Authorised Person (or delegate) should report within 48 hours the supply of  
797 the product to the relevant competent authorities, on behalf of the MAH in  
798 accordance with their legal obligations.

799



**800 Batch release process in cases of decentralised /point of care manufacturing**

801  
802 5.47 There may be cases where manufacturing of the ATMP takes place in sites close to  
803 the patient (e.g. ATMPs with short shelf-life, clinical advantage of using fresh cells as  
804 opposed to freezing the starting materials/finished product, advantages of using  
805 automated equipment, etc.). This includes manufacturing models where partial  
806 manufacturing occurs at a central site and finishing occurs at a local site. It also  
807 includes manufacturing models where there are no steps occurring at a central site  
808 and the active substance is provided to a number of local sites where full manufacture  
809 occurs. In such cases, steps in the manufacturing of the ATMPs may occur in multiple  
810 sites that may be also located in treatment centres (point of care) including hospitals.

811  
812 5.48 The batch certification and release process become particularly important in the case  
813 of ATMPs manufactured under a decentralised system as manufacturing in multiple  
814 sites increases the risk of variability for the product. In particular, through the batch  
815 certification and release process it must be ensured that each batch released at any  
816 of the sites has been manufactured and checked in accordance with the requirements  
817 of the CTA or MA and other relevant regulatory requirements including compliance  
818 with GMP. The steps of the batch certification and release process should be laid down  
819 in a standard operating procedure (SOP). The following conditions need to be  
820 respected:  
821

822 (a) A "responsible site", should be identified. The responsible site is responsible for  
823 the oversight of the decentralised sites. The responsible site:

- 824
- 825 i. must have availability of an Authorised Person,
  - 826 ii. must ensure that those involved in the batch certification and release process  
827 are adequately qualified and trained for their tasks,
  - 828 iii. should perform audits to confirm compliance with the batch certification and  
829 release process (as described in SOP),
  - 830 iv. must ensure that there is a written contract/technical agreement between the  
831 responsible site and the decentralised sites establishing the responsibilities of  
832 each party, and
  - 833 v. must ensure that there are written arrangements to:
    - 834 • timely report quality defects, deviations or non-conformity to the central  
835 site,
    - 836 • ensure deviations are investigated to identify root causes and implement  
837 corrective and preventive measures as appropriate, and
    - 838 • ensure deviations are approved by a responsible person (after having  
839 assessed the impact on quality, safety and efficacy), with the involvement  
840 of the Authorised Person as appropriate.

- 841 (b) The Authorised Person should have ultimate responsibility for the batch  
842 certification (responsibility cannot be delegated). However, it should be possible  
843 for the Authorised Person of the responsible site to rely on data/information that is  
844 transmitted to him by qualified and trained personnel at the decentralised sites. In  
845 certain exceptional cases (for example, different time zones or unexpected release  
846 that has to occur at night time) and when permissible according to national law,  
847 when the release of the product is needed to address life threatening conditions,  
848 the Authorised Person may delegate the release to personnel at the decentralised  
849 site that act under the direction of the authorised person, under the following  
850 conditions:
- 851 i. There is a detailed algorithm that determines the cases when the product can  
852 be released at the local site without the preliminary approval of the Authorised  
853 Person, including deviations that do not require the intervention of the  
854 Authorised Person. If technology permits this step can be performed by a  
855 validated computer system;
  - 856 ii. The Authorised Person reviews all releases that have occurred at the sites  
857 within an appropriate timeframe (i.e. no longer than a monthly interval) to  
858 confirm the adequacy of the releases including:
    - 859 • determining that the local sites can continue release
    - 860 • if any product needs to be recalled or going through hazard alert
    - 861 • if any provision in the release procedure and /or technical agreement  
862 needs modification; and
    - 863 • the product has not been released without Authorised Person  
864 authorisation when required.
- 865

## 866 CHAPTER 6 QUALITY CONTROL

867

- 868 6.1 In-process controls have a greater importance in ensuring the consistency of the  
869 quality of ATMPs than for conventional products. In-process control testing should be  
870 performed at appropriate stages of production to control those conditions that are  
871 important for the quality of the finished product.
- 872

### 873 General

874

- 875 6.2 The person responsible for quality control should assume responsibility for control of  
876 raw materials, starting materials, medical devices that are used in combined ATMPs,  
877 packaging materials, intermediate, bulk and finished products (including approval or  
878 rejection thereof). In case of autologous products or allogeneic products in a donor-  
879 matched scenario, the match between the origin of the starting material and the  
880 recipient should be verified (information on the origin of the cells/tissues should be  
881 checked).
- 882

- 883 6.3 Samples should be representative of the batch of materials or products from which  
884 they are taken. Other samples may also be taken to monitor the most stressed part of  
885 a process (e.g. beginning or end of a process). The sampling plan used should be  
886 appropriately justified and based on a risk management approach. Certain types of  
887 cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and,  
888 where allowed in the MA or CTA, a modified testing and sample retention strategy may  
889 be developed and documented. (Replaces PICS GMP Guide Part I Section 6.12)
- 890

- 891 6.4 Sample containers should bear a label indicating the contents, with the batch number,  
892 the date of sampling and the containers from which samples have been drawn. They  
893 should be managed in a manner to minimize the risk of mix-up and to protect the  
894 samples from adverse storage conditions. When containers are too small, the use of  
895 bar-codes or other means that permit access to this information should be considered.  
896 (Replaces PICS GMP Guide Part I Section 6.13)  
897
- 898 6.5 As a general principle, a reference sample should be of sufficient size to permit the  
899 carrying out on at least two occasions of the full analytical controls on the batch  
900 foreseen in the CTA or MA. However, it is acknowledged that this may not always be  
901 feasible due to scarcity of the materials or limited size of the batches (e.g. autologous  
902 products, allogeneic products in a matched donor scenario, products for ultra-rare  
903 diseases, and products for use in first-in-man clinical trial with a very small scale  
904 production).  
905
- 906 6.6 Samples of the starting materials should generally be kept for two years after the batch  
907 release. However, it is acknowledged that the retention of samples may be challenging  
908 due to scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep  
909 reference samples of the cells/tissues used as starting materials in the case of  
910 autologous ATMPs and certain allogeneic ATMPs (matched donor scenario). In other  
911 cases, where the scarcity of the materials is also a concern, the sampling strategy may  
912 be adapted provided that this is justified and appropriate mitigation measures are  
913 implemented.  
914
- 915 6.7 A sample of a fully packaged unit (retention sample) should be kept per batch for at  
916 least two years after the expiry date. A retention sample is, however, not expected in  
917 the case of autologous products or allogeneic products in a matched donor scenario  
918 as the unit produced with the patient's tissues/cells constitutes what should be  
919 administered to the patient. When it is not possible to keep a retention sample,  
920 photographs or copies of the label are acceptable for inclusion in the batch records.  
921
- 922 6.8 The retention period of samples of starting materials, active substance and  
923 intermediate product should be adapted to the stability and shelf-life of the product  
924 and, therefore, shorter periods may be justified. In cases of short shelf-life, the  
925 manufacturer should consider if the retention of the sample under conditions that  
926 prolong the shelf-life (such as cryopreservation) is representative for the intended  
927 purpose. For instance, cryopreservation of fresh-cells may render the sample  
928 inadequate for characterisation purposes but the sample may be adequate for sterility  
929 or viral safety controls (the volume of the samples can be reduced according to the  
930 intended purpose). When the cryostorage of a sample is considered inadequate for the  
931 intended purpose, the manufacturer should consider alternative approaches (e.g.  
932 sample of intermediate product such as differentiated cells).  
933

## 934 Testing

- 935
- 936 6.9 For cell-based ATMPs, sterility tests should be conducted on antibiotic-free cultures of  
937 cells or cell banks to provide evidence for absence of bacterial and fungal  
938 contamination and to be able to detection fastidious organisms where appropriate.  
939
- 940 6.10 Batch certification of short shelf life products performed prior to completion of all end  
941 product quality control is permitted when the short shelf life, due to the testing timelines,  
942 would not allow for effective distribution to a patient. In this occurrence there must be  
943 a suitable control strategy in place. Such controls need to be built on enhanced  
944 understanding of product and process performance and take into account the controls

945 and attributes of starting and raw materials. The exact and detailed description of the  
946 entire release procedure, including the responsibilities of the different personnel  
947 involved in assessment of production and analytical data is essential. A continuous  
948 assessment of the effectiveness of the quality assurance system must be in place  
949 including records kept in a manner which permit trend evaluation.

950  
951 Where end product tests are not available due to their short shelf life, alternative  
952 methods of obtaining equivalent data to permit batch certification should be considered  
953 (e.g. rapid microbiological methods). The procedure for batch certification and release  
954 may be carried out in two or more stages:

955 (a) Assessment by designated person(s) of batch processing records, results from  
956 environmental monitoring (where available) which should cover production  
957 conditions, all deviations from normal procedures and the available analytical  
958 results for review in preparation for the initial certification by the Authorised  
959 Person.

960 (b) Assessment of the final analytical tests and other information available for final  
961 certification by the Authorised Person. A procedure should be in place to describe  
962 the measures to be taken (including liaison with clinical staff) where out of  
963 specification test results are obtained. Such events should be fully investigated  
964 and the relevant corrective and preventive actions taken to prevent recurrence  
965 documented.

966

## 967 **On-going stability programme**

968

969 6.11 The methodology in the on-going stability programme can differ from the approach  
970 followed to obtain the stability data submitted in the MA application (e.g. different  
971 frequency of testing), provided that it is justified. Stability studies on the reconstituted  
972 product are performed during product development and need not be monitored on an  
973 on-going basis. The use of surrogate materials, (i.e. material derived from healthy  
974 volunteers) or alternative scientifically sound approaches, are acceptable in case of  
975 autologous products (or matched donor scenario) where the batch needs to be  
976 administered in its entirety to the patient. (Replaces PICS GMP Guide Part I Section  
977 6.31)

978

## 979 **CHAPTER 7 OUTSOURCED ACTIVITIES**

980

### 981 **OTHERS**

982

983 7.1 Collection of starting materials and highly specialised testing in the jurisdictions that  
984 are subject to licensing (e.g. karyotype testing, exome sequencing) can be outsourced  
985 to non GMP licensed third party, as allowed by national law, provided that:

986 (a) There is a rationale and a justification in the quality system

987 (b) The contract giver takes responsibility to ensure that the contract acceptor  
988 demonstrates an appropriate level of GMP commensurate to the risk to the  
989 product and the activities performed using the principles of Annex 20

990 (c) That proportionate qualifications/validations as appropriate are conducted (with  
991 reference to Annex 15 and Annex 20) to demonstrate that the activities are not  
992 detrimental to the quality of the product manufactured.

993

## CHAPTER 8 COMPLAINTS AND PRODUCT RECALL

### PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS

- 8.1 If additional donor (human or animal) health information becomes available after procurement, which affects product quality, an analysis of the risk(s) and of the need for corrective or preventive measures is also required.
- 8.2 A product defect alert should be issued, in the cases of single batch products or when there is no alternative product available at the time and/or for which a recall action will result in a significant interruption of patient treatment either of which would likely present greater adverse clinical sequelae than the defect itself. The product defect alert- allows for the informed, continued use of defective but critical ATMPs, raises awareness of the issue and describes the precautionary actions that clinicians or patients may take to mitigate any associated risk.
- 8.3 In order to test the robustness of the recall procedure, in the case of authorised ATMPs, consideration should be given to the possibility of performing mock-recall actions. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations. However, it is acknowledged that a mock-recall action may not be appropriate in certain settings, e.g. autologous ATMPs, allogeneic ATMPs in a matched donor scenario, ATMPs where the time between manufacturing and administration of the product to the patient is very short. (Replaces PICS GMP Guide Part I Section 8.30)

## PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

### B1. ANIMAL SOURCED PRODUCTS

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability<sup>3</sup> and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

- B 1.1 Monitoring programmes should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.
- B 1.2 Where abattoirs are used to source animal tissues; they should be shown to operate to stringent standards. Account should be taken of reports from national regulatory organisations which verify compliance with the requirements of food, safety, and quality veterinary and plant health legislation.

---

<sup>3</sup> See PIC/S GMP Chapter 5.

1046 B 1.3 Control measures for starting or raw materials at establishments such as abattoirs  
1047 should include appropriate elements of a Quality Management System to assure a  
1048 satisfactory level of operator training, materials traceability, control and consistency.  
1049 These measures may be drawn from sources outside PIC/S GMP but should be shown  
1050 to provide equivalent levels of control.

1051  
1052 B 1.4 Control measures for starting or raw materials should be in place which prevent  
1053 interventions which may affect the quality of materials, or which at least provides  
1054 evidence of such activities, during their progression through the manufacturing and  
1055 supply chain. This includes the movement of material between sites of initial collection,  
1056 partial and final purification(s), storage sites, hubs, consolidators and brokers. Details  
1057 of such arrangements should be recorded within the traceability system and any  
1058 breaches recorded, investigated and actions taken.

1059  
1060 B 1.5 Regular audits of the starting or raw material supplier should be undertaken which  
1061 verify compliance with controls for materials at the different stages of manufacture.  
1062 Issues must be investigated to a depth appropriate to their significance, for which full  
1063 documentation should be available. Systems should also be in place to ensure that  
1064 effective corrective and preventive actions are taken.

1065  
1066 B 1.6 The use of cells, tissues and organs from wild animals is not permitted.

1067

## 1068 **B2. GENE THERAPY PRODUCTS**

1069

1070 There are potentially 2 types of gene therapy products (vectors and genetically modified cells)  
1071 and both are within the scope of the guidance in this section. For cell-based gene therapy  
1072 products, some aspects of guidance in section B3 may be applicable.

1073

1074 B2.1 Starting material:

1075 (a) For genome editing approaches, the starting materials shall be, as appropriate,  
1076 the vector (viral or non-viral vector) carrying the DNA sequences encoding the  
1077 modifying enzyme, the mRNA expressing the modifying enzyme, the modifying  
1078 enzyme itself, the genetic sequence for modification of the cell genome (e.g. a  
1079 regulatory guide RNA) or a ribonucleoprotein (e.g. Cas9 protein pre-complexed  
1080 with gRNA), the repair template (e.g. linear DNA fragment or a plasmid), and the  
1081 components to produce them. When vectors, mRNA or proteins are used, the  
1082 principles of GMP shall apply from the bank system used to produce these  
1083 materials onwards.

1084 (b) For medicinal products based on induced pluripotent stem (iPS) cells generated  
1085 by genetic modification, the principles of GMP and the scientific  
1086 recommendations given in this guideline should apply after procurement of the  
1087 cells including the generation of iPS cells and the subsequent selection process.  
1088 It is acknowledged that at the early steps in iPS cells generation, cell material  
1089 may be limited and availability of samples may impact the extent of testing and  
1090 process qualification.

1091 (c) For products consisting of viral vectors, the starting materials are the  
1092 components from which the viral vector is obtained, i.e. the master virus seed or  
1093 the plasmids used to transfect the packaging cells and the MCB of the packaging  
1094 cell line.

1095 (d) For products consisting of plasmids, non-viral vectors and genetically modified  
1096 micro-organisms other than viruses or viral vectors, the starting materials are the  
1097 components used to generate the producing cell, i.e. the plasmid, the host  
1098 bacteria and the MCB of the recombinant microbial cells.

- 1099 (e) For genetically modified cells, the starting materials are the components used to  
1100 obtain the genetically modified cells, i.e. the starting materials to manufacture the  
1101 vector and the human or animal cell preparations.
- 1102 The principles of GMP apply from the bank system used to manufacture the vector or  
1103 plasmid used for gene transfer.  
1104
- 1105 B2.2 Since the cells used in the manufacture of gene therapy products are obtained either  
1106 from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential  
1107 risk of contamination by adventitious agents. Special considerations must be applied  
1108 to the segregation of autologous materials obtained from infected donors. The  
1109 robustness of the control and test measures for such starting materials;  
1110 cryoprotectants, culture media, cells and vectors should be based on QRM principles  
1111 and in line with the MA or CTA. Established cell lines used for viral vector production  
1112 and their control and test measures should similarly be based on QRM principles. Virus  
1113 seed lots and cell banking systems should be used where relevant. ATMPs in which  
1114 the starting materials are obtained from animals (xenogeneic) should follow provisions  
1115 laid out in section B1.  
1116
- 1117 B2.3 Factors such as the nature of the genetic material, type of (viral or non-viral) vector  
1118 and type of cells have a bearing on the range of potential impurities, adventitious  
1119 agents and cross-contaminations that should be taken into account as part of the  
1120 development of an overall strategy to minimise risk. This strategy should be used as  
1121 a basis for the design of the process, the manufacturing and storage facilities and  
1122 equipment, cleaning and decontamination procedures, packaging, labelling and  
1123 distribution.  
1124
- 1125 B2.4 The manufacture and testing of gene therapy medicinal products raises specific issues  
1126 regarding the safety and quality of the final product and safety issues for recipients  
1127 and staff. A risk based approach for operator, environment and patient safety and the  
1128 implementation of controls based on the biological hazard class should be applied.  
1129 Legislated local and, if applicable, international safety measures should be applied.  
1130
- 1131 B2.5 Personnel (including QC and maintenance staff) and material flows, including those  
1132 for storage and testing (e.g. starting materials, in-process and final product samples  
1133 and environmental monitoring samples), should be controlled on the basis of QRM  
1134 principles, where possible utilising unidirectional flows. This should take into account  
1135 movement between areas containing different genetically modified organisms and  
1136 areas containing non-genetically-modified organisms.  
1137
- 1138 B2.6 Any special cleaning and decontamination methods required for the range of  
1139 organisms being handled should be considered in the design of facilities and  
1140 equipment. Where possible, the environmental monitoring programme should be  
1141 supplemented by the inclusion of methods to detect the presence of the specific  
1142 organisms being cultivated.  
1143
- 1144 B2.7 Where replication limited vectors are used, measures should be in place to prevent the  
1145 introduction of wild-type viruses, which may lead to the formation of replication  
1146 competent recombinant vectors.  
1147
- 1148 B2.8 An emergency plan for dealing with accidental release of viable organisms should be  
1149 in place. This should address methods and procedures for containment, protection of  
1150 operators, cleaning, decontamination and safe return to use. An assessment of impact  
1151 on the immediate products and any others in the affected area should also be made.  
1152

- 1153 B2.9 Facilities for the manufacture of viral vectors should be separated from other areas by  
1154 specific measures. The arrangements for separation should be demonstrated to be  
1155 effective. Closed systems should be used wherever possible, sample collection  
1156 additions and transfers should prevent the release of viral material.  
1157
- 1158 B2.10 A description of the production of vectors and genetically modified cells should be  
1159 available in sufficient detail to ensure the traceability of the products from the starting  
1160 material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or  
1161 non-viral vector stock) to the finished product.  
1162
- 1163 B2.11 Shipment of products containing and/or consisting of GMO should conform to  
1164 appropriate national law.  
1165
- 1166 B2.12 The following considerations apply to the ex-vivo gene transfer to recipient cells:
- 1167 (a) Measures (including considerations outlined under paragraph 3.5 in Part A) to  
1168 minimise the potential for cross-contamination and mix-up between cells from  
1169 different patients are required. This should include the use of validated cleaning  
1170 procedures. The concurrent use of different viral vectors should be subject to  
1171 controls based on QRM principles. Some viral vectors (e.g. Retro- or  
1172 Lenti-viruses) cannot be used in the manufacturing process of genetically  
1173 modified cells until they have been shown to be devoid of replication-competent  
1174 contaminating vector.
- 1175 (b) Traceability requirements must be maintained. There should be a clear definition  
1176 of a batch, from cell source to final product container(s).
- 1177 (c) For products that utilise non-biological means to deliver the gene, their physico-  
1178 chemical properties should be documented and tested.  
1179  
1180



1181 **B3 SOMATIC HUMAN AND XENOGENEIC CELL THERAPY PRODUCTS AND**  
1182 **TISSUE ENGINEERED PRODUCTS AND COMBINED ATMPs**  
1183

1184 For genetically modified cell-based products that are not classified as GT products, some  
1185 aspects of guidance in section B2 may be applicable.  
1186

1187 B3.1 Use should be made, where they are available, of authorised sources (i.e. licensed  
1188 medicinal products or medical devices which have gone through a conformity  
1189 assessment procedure) of additional substances (such as cellular products,  
1190 bio-molecules, bio-materials, scaffolds, matrices).  
1191

1192 B3.2 Where devices, including custom-made devices, are incorporated as part of the  
1193 products:

1194 (a) There should be written agreement between the manufacturer of the medicinal  
1195 product and the manufacturer of the medical device, which should provide  
1196 enough information on the medical device to avoid alteration of its properties  
1197 during manufacturing of the ATMP. This should include the requirement to  
1198 control changes proposed for the medical device.

1199 (b) The technical agreement should also require the exchange of information on  
1200 deviations in the manufacture of the medical device.

1201  
1202 B3.3 Since somatic cells are obtained either from humans (autologous or allogeneic) or  
1203 animals (xenogeneic), there is a potential risk of contamination by adventitious agents.  
1204 Special considerations must be applied to the segregation of autologous materials  
1205 obtained from infected donors or related to cell pooling. The robustness of the control  
1206 and test measures put in place for these source materials should be ensured. Animals  
1207 from which tissues and cells are collected should be reared and processed according  
1208 to the principles defined in the relevant guidelines. Somatic cell therapy medicinal  
1209 products (SCTMPs), tissue engineered products (TEPs) and combined ATMPs in  
1210 which the starting materials are obtained from animals (xenogeneic) should follow  
1211 Section B1.  
1212

1213 B3.4 Careful attentions should be paid to specific requirements at any cryopreservation  
1214 stages, e.g. the rate of temperature change during freezing or thawing. The type of  
1215 storage chamber, placement and retrieval process should minimise the risk of  
1216 cross-contamination, maintain the quality of the products and facilitate their accurate  
1217 retrieval. Documented procedures should be in place for the secure handling and  
1218 storage of products with positive serological markers.  
1219

1220 B3.5 Where relevant, a stability-monitoring programme should be in place together with  
1221 reference and retain samples in sufficient quantity to permit further examination.  
1222  
1223  
1224  
1225  
1226  
1227  
1228  
1229  
1230

1231 **COMMON GLOSSARY TO ANNEX 2A and 2B**

1232

1233 Entries are only included where the terms are used in Annex 2 and require further explanation.

1234 Definitions which already exist are cross-referenced only.

1235 **Active substance**

1236

1237 The active substance of a product is defined in the relevant CTA or MA authorisation dossier.

1238 - For cell based ATMPs are generally cells of mammalian or human origin.

1239 - For gene therapy products might be recombinant biological constructs (e.g. nucleic acid vectors, viruses).

1240

1241

1242 **Adjuvant**

1243 A chemical or biological substance that enhances the immune response against an antigen.

1244

1245 **Advance Therapeutic Medicinal Products (ATMP)**

1246 ATMP means any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products.

1248 ATMPs may incorporate, as an integral part of the product, one or more medical devices, in which case they are referred to as "Combined ATMPs"

1249

1250

1251 **Allergoids**

1252 Allergens which are chemically modified to reduce IgE reactivity.

1253

1254 **Antigens**

1255 Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.

1256

1257

1258 **Antibody**

1259 Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may be divided into 2 main types based on key differences in their method of manufacture:

1260

1261

1262 **Monoclonal antibodies (MAb)**

1263 Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

1264

1265

1266 **Area**

1267 A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air handling unit.

1268

1269

1270 **Biological Starting Material**

1271 Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (for example, cell substrates, host/vector production cells, eggs, viral strains, etc.).

1272

1273

1274

1275

1276 **Bioburden**

1277 The level and type (i.e. objectionable or not) of micro-organism present in raw materials, media, biological substances, intermediates or products. Regarded as contamination when the level and/or type exceed specifications.

1278

1279

1280

1281 **Biological medicinal product** A biological medicinal product is a product, of which the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the

1282

1283

1284 determination of its quality a combination of physico-chemical-biological testing, together with  
1285 the production process and its control.

1286

1287 **Biosafety level (BSL)**

1288 The containment conditions required to safely handle organisms of different hazards ranging  
1289 from BSL1 (lowest risk, unlikely to cause human disease) to BSL4 (highest risk, cause severe  
1290 disease, likely to spread and no effective prophylaxis or treatment available).

1291

1292 **Campaign manufacture**

1293 The manufacture of a series of batches of the same product in sequence in a given period of  
1294 time followed by strict adherence to accepted control measures before transfer to another  
1295 product. The products are not run at the same time but may be run on the same equipment.

1296

1297 **Closed system**

1298 Where an active substance or product is not exposed to the immediate room environment  
1299 during manufacture.

1300

1301 **Contained use**

1302 An operation, in which genetically modified organisms are cultured, stored, used, transported,  
1303 destroyed or disposed of and for which barriers (physical / chemical / biological) are used to  
1304 limit their contact with the general population and the environment.

1305

1306 **Critical materials**

1307 Are all materials that have a significant negative impact on product quality and patient safety  
1308 if their quality is impaired. **Starting materials, raw materials and single use equipment** or  
1309 primary packaging materials and any other material in direct contact with the product during  
1310 manufacture could fall under the definition of critical materials depending on the nature of the  
1311 individual medicinal product and the manufacturing process.

1312

1313 **Ex-vivo**

1314 Where procedures are conducted on tissues or cells outside the living body and returned to  
1315 the living body.

1316

1317 **Feeder cells**

1318 Cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell  
1319 culture, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human  
1320 embryonic fibroblasts that have been treated to prevent them from dividing.

1321

1322 **Fermenter**

1323 In case of (mammalian) cell lines the term fermenter should be understood as bioreactor.

1324

1325 **Gene**

1326 A sequence of DNA that codes for one (or more) protein(s).

1327

1328 **Gene transfer**

1329 A process to transfer a gene in cells, involving an expression system contained in a delivery  
1330 system known as a vector, which can be of viral, as well as non-viral origin. After gene transfer,  
1331 genetically modified cells are also termed *transduced cells*.

1332

1333 **Genetically modified organism (GMO)**

1334 Means an organism, with the exception of human beings, in which the genetic material has  
1335 been altered in a way that does not occur naturally by mating and/or natural recombination.

1336

1337

1338

- 1339 **Hapten**  
1340 A low molecular weight molecule that is not in itself antigenic unless conjugated to a 'carrier'  
1341 molecule.  
1342
- 1343 **Hybridoma**  
1344 An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived  
1345 by fusing B-lymphocytes with tumour cells.  
1346
- 1347 **In-vivo**  
1348 Procedures conducted in living organisms.  
1349
- 1350 **Look-back**  
1351 Documented procedure to trace ATMPs active substances or products which may be  
1352 adversely affected by the use or incorporation of animal or human materials when either such  
1353 materials fail release tests due to the presence of contaminating agent(s) or when conditions  
1354 of concern become apparent in the source animal or human.  
1355
- 1356 **Master cell bank (MCB)**  
1357 An aliquot of a single pool of cells which generally has been prepared from the selected cell  
1358 clone under defined conditions, dispensed into multiple containers and stored under defined  
1359 conditions. The MCB is used to derive all working cell banks.  
1360
- 1361 **Master virus seed (MVS)** – as above, but in relation to viruses;  
1362
- 1363 **Master transgenic bank** – as above but for transgenic plants or animals.  
1364
- 1365 **Multi-product facility**  
1366 A facility that manufactures, either concurrently or in campaign mode, a range of different  
1367 ATMPs active substances and products and within which equipment train(s) may or may not  
1368 be dedicated to specific substances or products.  
1369
- 1370 **Plasmid**  
1371 A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated  
1372 from the cell chromosome; it can be modified by molecular biology techniques, purified out of  
1373 the bacterial cell and used to transfer its DNA to another cell.  
1374
- 1375 **Primary cell lot**  
1376 A pool of primary cells minimally expanded to attain a sufficient number for a limited number  
1377 of applications.  
1378
- 1379 **Raw materials**  
1380 Are all materials that come in direct contact with the product during the manufacturing process  
1381 but are not necessarily part of the final formulation (e.g. cryoprotectants, feeder cells,  
1382 reagents, culture media, buffers, serum, enzymes, cytokines, growth factors).  
1383
- 1384 **Responsible Person (RP) for blood or tissue establishment.**  
1385 This term is equivalent to the EU term "Responsible Person".  
1386
- 1387 **Scaffold**  
1388 A support, delivery vehicle or matrix that may provide structure for or facilitate the migration,  
1389 binding or transport of cells and/or bioactive molecules.  
1390
- 1391 **Somatic cells**  
1392 Cells, other than reproductive (germ line) cells, which make up the body of a human or animal.  
1393 These cells may be autologous (from the patient), allogeneic (from another human being) or  
1394 xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo,  
1395 to be administered in humans to obtain a therapeutic, diagnostic or preventive effect.

- 1396 **Specified pathogen free (SPF)**  
1397 Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality  
1398 control of biological medicinal products derived from groups (e.g. flocks or herds) of animals  
1399 free from specified pathogens (SPF). Such flocks or herds are defined as animals sharing a  
1400 common environment and having their own caretakers who have no contact with non-SPF  
1401 groups.  
1402
- 1403 **Transgenic**  
1404 An organism that contains a foreign gene in its normal genetic component for the expression  
1405 of biological pharmaceutical materials.  
1406
- 1407 **Vector**  
1408 An agent of transmission, which transmits genetic information from one cell or organism to  
1409 another, e.g. plasmids, liposomes, viruses.  
1410
- 1411 **Viral vector**  
1412 A vector derived from a virus and modified by means of molecular biology techniques in a way  
1413 as to retain some, but not all, the parental virus genes; if the genes responsible for virus  
1414 replication capacity are deleted, the vector is made replication-incompetent.  
1415
- 1416 **Viral Vector replication limited / defective / conditional replication**  
1417 A constrained ability to replicate where the intent is for the vector may be to target a particular  
1418 tissue or target cell type with a planned integration required for clinical efficacy of the gene  
1419 therapy.  
1420
- 1421 **Viral Vector replication incompetent / devoid**  
1422 No ability of the vector to replicate.  
1423
- 1424 **Working cell bank (WCB)**  
1425 A homogeneous pool of cells, that are distributed uniformly into a number of containers derived  
1426 from a MCB that are stored in such a way to ensure stability and for use in production.  
1427
- 1428 **Working virus seed (WVS)**  
1429 As above but in relation to viruses, **working transgenic bank** – as above but for transgenic  
1430 plants or animals.  
1431
- 1432 **Zoonosis**  
1433 Animal diseases that can be transmitted to humans.