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EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Annex 2
Manufacture of Biological active substances and Medicinal Products for Human Use

1 **Legal basis for publishing the detailed guidelines**: Article 47 of Directive 2001/83/EC on
2 the Community code relating to medicinal products for human use and Article 51 of Directive
3 2001/82/EC on the Community code relating to veterinary medicinal products. This document
4 provides guidance for the interpretation of the principles and guidelines of good
5 manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC
6 for medicinal products for human use and Directive 91/412/EEC for veterinary use.

7 **Status of the document**: revision 2
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9 **Reasons for changes:** Annex 2 of the GMP Guide has been revised as a consequence of the
10 adoption of the Guidelines on Good Manufacturing Practice specific to Advanced Therapy
11 Medicinal Products pursuant to Article 5 of Regulation (EC) 1394/2007 of the European
12 Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products
13 and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.[1]

14 **Deadline for coming into operation**: 26 June 2018

15

16 **Scope**
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18 The methods employed in the manufacture of biological active substances and biological
19 medicinal products for human use ('biological active substances and medicinal products') are
20 a critical factor in shaping the appropriate regulatory control. Biological active substances
21 and medicinal products can be defined therefore largely by reference to their method of
22 manufacture. This annex provides guidance on the full range of active substances and
23 medicinal products defined as biological, with the exception of Advanced Therapy Medicinal
24 Products ("ATMPs"), as defined in Article 1(1) of Regulation (EC) No 1394/2007[1]. The
25 ATMPs are not covered by the present guideline. Manufacturers of ATMPs should refer to
26 the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal
27 Products referred to in Article 5 of the above quoted Regulation.

28 This annex is divided into two main parts:

29 a) Part A contains supplementary guidance on the manufacture of biological active
30 substances and medicinal products, from control over seed lots and cell banks through
31 to finishing activities, and testing.

32 b) Part B contains further guidance on selected types of biological active substances and
33 medicinal products.

34 This annex, along with several other annexes of the Guide to GMP in EudraLex Volume 4,
35 provides guidance which supplements that in Part I and in Part II of that Guide. There are two
36 aspects to the scope of this annex:

37 a) Stage of manufacture - for biological active substances to the point immediately prior
38 to their being rendered sterile, the primary guidance source is Part II. Guidance for
39 the subsequent manufacturing steps of biological products are covered in Part I.

40 b) Type of product - this annex provides guidance on the full range of medicinal products
41 defined as biological, with the exception of ATMPs.

42 These two aspects are shown in Table 1, it should be noted that this table is illustrative only
43 and is not meant to describe the precise scope. It should also be understood that in line with
44 the corresponding table in Part II of EudraLex, Volume 4, the level of GMP increases in detail
45 from early to later steps in the manufacture of biological active substances but GMP
46 principles should always be adhered to. The inclusion of some early steps of manufacture
47 within the scope of this Annex does not imply that those steps will be routinely subject to
48 inspection by the authorities.

49 Antibiotics are not defined as biological medicinal products, however where biological stages
50 of manufacture occur, guidance in this Annex may be used.

[1] Regulation (EC) No 1394 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p.121

51 Guidance for medicinal products derived from fractionated human blood or plasma is covered
52 in Annex 14 of EudraLex, Volume 4, and for non-transgenic plant products in Annex 7.

53 In certain cases, other legislation is applicable to the starting materials. For example,

54 (a) Tissue and cells used as starting materials for medicinal products: Directive 2004/23/EC
55 of the European Parliament and of the Council of 31 March 2004 on setting standards of
56 quality and safety for the donation, procurement, testing, processing, preservation, storage and
57 distribution of human tissues and cells,[2] and Commission Directive 2006/17/EC of 8 February
58 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as
59 regards certain technical requirements for the donation, procurement and testing of human
60 tissues and cells[3] cover only their donation, procurement and testing. Such tissues and cells
61 may provide the active substances for some biological medicinal product within the scope of
62 this annex at which point GMP and other medicinal product legislation requirements apply.

63 (b) Blood or blood components used as starting materials for medicinal products: Directive
64 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting
65 standards of quality and safety for the collection, testing, processing, storage and distribution
66 of human blood and blood components and amending Directive 2001/83/EC[4] and its
67 Commission Directives provides the technical requirements[5] for the selection of donors and
68 the collection and testing of blood and blood components.

69 Additionally, the manufacture and control of genetically modified organisms needs to comply
70 with local and national requirements. In accordance with Directive 2009/41/EC of the
71 European Parliament and of the Council of 6 May 2009 on the contained use of genetically
72 modified micro-organisms,[6] appropriate containment and other protective measures shall be
73 established and maintained in facilities where any genetically modified micro-organism are
74 handled. Advice should be obtained according to national legislation in order to establish and
75 maintain the appropriate Biological Safety Level. There should be no conflicts with GMP
76 requirements.

77 Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2.

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources:	Heparins, insulin,	Collection of plant, organ,	Cutting, mixing, and /or initial	Isolation and purification	Formulation, filling

[4] OJ 10.136.120.18

[5] Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components and Good Practice Guidelines for blood establishments as referenced in Directive 2016/1214, amending Directive 2005/62/EC.
[6] OJ L 125,21.5.2009, p. 75.

non-transgenic	enzymes, proteins, allergen extract, immunosera,	animal material or fluid[7]	processing		
2. Virus or bacteria/ fermentation/ cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[8], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotech-nology - fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins,	Master and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting[9]	Initial extraction, isolation, purification, modification	Formulation, filling
6.Human sources	Urine derived enzymes, hormones	Collection of fluid[10]	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human sources	Products from cells tissues	Donation, procurement and testing of starting tissue / cells[11]	Initial processing, isolation and purification.	Cell isolation, culture, purification, combination with non-cellular components.	Formulation, combination, filling

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81 See Glossary for explanation of acronyms.

[7] See section B1 for the extent to which GMP principles apply.
[8] See section on 'Seed lot and cell bank system' for the extent to which GMP applies.

[9] HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005.
[10] Principles of GMP apply, see explanatory text in 'Scope'.

[11] Human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.

Principle

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

Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.

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

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

Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore

120 crucial and in-process controls take on a particular importance in the manufacture of
121 biological active substances and medicinal products.

122 Biological medicinal products which incorporate human tissues or cells must take into
123 account the requirements of Directive 2004/23/EC and Commission Directive 2006/17/EC. In
124 line with Commission Directive 2006/86/EC of 24 October 2006 implementing Directive
125 2004/23/EC of the European Parliament and of the Council as regards traceability
126 requirements, notification of serious adverse reactions and events and certain technical
127 requirements for the coding, processing, preservation, storage and distribution of human
128 tissues and cells,[12] collection and testing must be done in accordance with an appropriate
129 quality system for which standards and specifications are defined in its Annex..

130 Biological active substances and medicinal products must comply with the latest version of
131 the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform
132 Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products.

133 **PART A. GENERAL GUIDANCE**

134 **Personnel**

135 1. Personnel (including those concerned with cleaning, maintenance or quality control)
136 employed in areas where biological active substances and products are manufactured
137 and tested should receive training, and periodic retraining, specific to the products
138 manufactured to their work, including any specific security measures to protect
139 product, personnel and the environment.

140 2. The health status of personnel should be taken into consideration for product safety.
141 Where necessary, personnel engaged in production, maintenance, testing and animal
142 care (and inspections) should be vaccinated with appropriate specific vaccines and
143 have regular health checks.

144 3. Any changes in the health status of personnel, which could adversely affect the quality
145 of the product, should preclude work in the production area and appropriate records
146 kept. Production of BCG vaccine and tuberculin products should be restricted to staff
147 who are carefully monitored by regular checks of immunological status or chest X-
148 ray. Health monitoring of staff should be commensurate with the risk, medical advice
149 should be sought for personnel involved with hazardous organisms.

150 4. Where required to minimise the opportunity for cross-contamination, restrictions on
151 the movement of all personnel (including quality control (QC), maintenance and
152 cleaning staff) should be controlled on the basis of QRM principles. In general,
153 personnel should not pass from areas where exposure to live micro-organisms,
154 genetically modified organisms, toxins or animals to areas where other products,
155 inactivated products or different organisms are handled. If such passage is
156 unavoidable, the contamination control measures should be based on QRM principles.

[12] OJ L 294, 25.10.2006, p. 32.

157 **Premises and Equipment**

158 5. As part of the control strategy, the degree of environmental control of particulate and
159 microbial contamination of the production premises should be adapted to the active
160 substance, intermediate or finished product and the production step, bearing in mind
161 the potential level of contamination of the starting materials and the risks to the
162 product. The environmental monitoring programme should be supplemented by the
163 inclusion of methods to detect the presence of specific microorganisms (i.e. host
164 organism, yeast, moulds, anaerobes, etc) where indicated by the QRM process.

165 6. Manufacturing and storage facilities, processes and environmental classifications
166 should be designed to prevent the extraneous contamination of products. Prevention of
167 contamination is more appropriate than detection and removal, although
168 contamination is likely to become evident during processes such as fermentation and
169 cell culture. Where processes are not closed and there is therefore exposure of the
170 product to the immediate room environment (e.g. during additions of supplements,
171 media, buffers, gasses) control measures should be put in place, including engineering
172 and environmental controls on the basis of QRM principles. These QRM principles
173 should take into account the principles and guidance from the appropriate sections of
174 Annex 1[13] to EudraLex, Volume 4, when selecting environmental classification
175 cascades and associated controls.

176 7. Dedicated production areas should be used for the handling of live cells capable of
177 persistence in the manufacturing environment. Dedicated production area should be
178 used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).

179 8. Manufacture in a multi-product facility may be acceptable where the following, or
180 equivalent (as appropriate to the product types involved) considerations and measures
181 are part of an effective control strategy to prevent cross-contamination:

182 (a) Knowledge of key characteristics of all cells, organisms and any adventitious
183 agents (e.g. pathogenicity, detectability, persistence, susceptibility to
184 inactivation) within the same facility.

185 (b) Where production is characterised by multiple small batches from different
186 starting materials factors such as the health status of donors and the risk of total
187 loss of product should be taken into account when considering the acceptance of
188 concurrent working during development of the control strategy.

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[13] Although the title of Annex 1 refers to the manufacture of sterile medicinal products it is not the intention to force the manufacture of sterile product at a stage when a low bioburden is appropriate and authorised. Its use is because it is the only EU GMP source of guidance on all of the classified manufacturing areas including the lower grades D and C.

189 (c) Live organisms and spores are prevented from entering non-related areas or
190 equipment by addressing all potential routes of cross-contamination and utilizing
191 single use components and engineering measures such as closed systems.

192 (d) Control measures to remove the organisms and spores before the subsequent
193 manufacture of other products, these control measures should also take the
194 heating, ventilation and air conditioning (HVAC) system into account. Cleaning
195 and decontamination for the organisms and spores should be validated.

196 (e) Environmental monitoring specific for the micro-organism being manufactured,
197 where the micro-organisms are capable of persistence in the manufacturing
198 environment and where methods are available, is conducted in adjacent areas
199 during manufacture and after completion of cleaning and decontamination.
200 Attention should also be given to risks arising with use of certain monitoring
201 equipment (e.g. airborne particle monitoring) in areas handling live and/or spore
202 forming organisms.

203 (f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and
204 disposable items are only moved within and removed from such areas in a
205 manner that prevents contamination of other areas, other products and different
206 product stages (e.g. prevent contamination of inactivated or toxoided products
207 with non-inactivated products).

208 (g) Campaign-based manufacturing.

209 9. For finishing (secondary) operations[14], the need for dedicated facilities will depend on
210 consideration of the above together with additional considerations such as the specific
211 needs of the biological medicinal product and on the characteristics of other products,
212 including any non-biological products, in the same facility. Other control measures for
213 finishing operations may include the need for specific addition sequences, mixing
214 speeds, time and temperature controls, limits on exposure to light and containment and
215 cleaning procedures in the event of spillages.

216 10. The measures and procedures necessary for containment (i.e. for environment and
217 operator safety) should not conflict with those for product quality.

218 11. Air handling units should be designed, constructed and maintained to minimise the
219 risk of cross-contamination between different manufacturing areas and may need to be
220 specific for an area. Consideration, based on QRM principles, should be given to the
221 use of single pass air systems.

222 12. Positive pressure areas should be used to process sterile products but negative pressure
223 in specific areas at the point of exposure of pathogens is acceptable for containment
224 reasons. Where negative pressure areas or safety cabinets are used for aseptic
225 processing of materials with particular risks (e.g. pathogens) they should be

[14] Formulation, filling and packaging

226 surrounded by a positive pressure clean zone of appropriate grade. These pressure
227 cascades should be clearly defined and continuously monitored with appropriate alarm
228 settings.

229 13. Equipment used during handling of live organisms and cells, including those for
230 sampling, should be designed to prevent any contamination during processing.

231 14. Primary containment[15] should be designed and periodically tested to ensure the
232 prevention of escape of biological agents into the immediate working environment.

233 15. The use of 'clean in place' and ‘steam in place’ (‘sterilisation in place’) systems should
234 be used where possible. Valves on fermentation vessels should be completely steam
235 sterilisable.

236 16. Air vent filters should be hydrophobic and validated for their scheduled life span with
237 integrity testing at appropriate intervals based on appropriate QRM principles.

238 17. Drainage systems must be designed so that effluents can be effectively neutralised or
239 decontaminated to minimise the risk of cross-contamination. Local regulation must be
240 complied with to minimise the risk of contamination of the external environment
241 according to the risk associated with the biohazardous nature of waste materials.

242 18. Due to the variability of biological products or manufacturing processes,
243 relevant/critical raw materials (such as culture media and buffers) have to be measured
244 or weighed during the production process. In these cases, small stocks of these raw
245 materials may be kept in the production area for a specified duration based on defined
246 criteria such as for the duration of manufacture of the batch or of the campaign.

247 **Animals**

248 19. A wide range of animal species are used in the manufacture of a number of biological
249 medicinal products. These can be divided into 2 broad types of sources:

250 (a) Live groups, herds, flocks: examples include polio vaccine (monkeys),
251 immunosera to snake venoms and tetanus (horses, sheep and goats), allergens
252 (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats,
253 cattle).

254 (b) Animal materials derived post-mortem and from establishments such as abattoirs:
255 examples include abattoir sources for enzymes, anticoagulants and hormones
256 (sheep and pigs).

257 In addition, animals may also be used in quality control either in generic assays, e.g.
258 pyrogenicity, or specific potency assays, e.g. pertussis vaccine (mice), pyrogenicity (rabbits),
259 BCG vaccine (guinea-pigs).

[15] See main GMP Glossary on ‘Containment’

260 20. In addition to compliance with TSE regulations, other adventitious agents that are of
261 concern (zoonotic diseases, diseases of source animals) should be monitored by an
262 ongoing health programme and recorded. Specialist advice should be obtained in
263 establishing such programmes. Instances of ill-health occurring in the source/donor
264 animals should be investigated with respect to their suitability and the suitability of in-
265 contact animals for continued use (in manufacture, as sources of starting and raw
266 materials, in quality control and safety testing), the decisions must be documented. A
267 look-back procedure should be in place which informs the decision-making process on
268 the continued suitability of the biological active substance or medicinal product in
269 which the animal sourced starting or raw materials have been used or incorporated.
270 This decision-making process may include the re-testing of retained samples from
271 previous collections from the same donor animal (where applicable) to establish the
272 last negative donation. The withdrawal period of therapeutic agents used to treat
273 source/donor animals must be documented and used to determine the removal of those
274 animals from the programme for defined periods.

275 21. Particular care should be taken to prevent and monitor infections in the source/donor
276 animals. Measures should include the sourcing, facilities, husbandry, biosecurity
277 procedures, testing regimes, control of bedding and feed materials. This is of special
278 relevance to specified pathogen free animals where PhEur monograph requirements
279 must be met. Housing and health monitoring should be defined for other categories of
280 animals (e.g. healthy flocks or herds).

281 22. For products manufactured from transgenic animals, traceability should be maintained
282 in the creation of such animals from the source animals.

283 23. Note should be taken of Directive 2010/63/EU on the protection of animals used for
284 scientific purposes[16]. Housing for animals used in production and control of biological
285 active substances and medicinal products should be separated from production and
286 control areas.

287 24. For different animal species, key criteria should be defined, monitored, and recorded.
288 These may include age, weight and health status of the animals.

289 25. Animals, biological agents, and tests carried out should be the subject of an
290 identification system to prevent any risk of confusion and to control all identified
291 hazards.

292 **Documentation**

293 26. Starting and raw materials may need additional documentation on the source, origin,
294 distribution chain, method of manufacture, and controls applied, to assure an
295 appropriate level of control including their microbiological quality.

[16] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 10.10.2010, p.33

296 27. Some product types may require specific definition of what materials constitutes a
297 batch, particularly cells. For autologous and donor-matched situations, the
298 manufactured product should be viewed as a batch.

299 28. Where human cell or tissue donors are used full traceability is required from starting
300 and raw materials, including all substances coming into contact with the cells or
301 tissues through to confirmation of the receipt of the products at the point of use whilst
302 maintaining the privacy of individuals and confidentiality of health related
303 information. Traceability records must be retained for 30 years after the expiry date of
304 the medicinal product. Particular care should be taken to maintain the traceability of
305 medicinal products for special use cases, such as donor-matched cells. Directives
306 2002/98/EC and Commission Directive 2005/61/EC of 30 September 2005
307 implementing Directive 2002/98/EC of the European Parliament and of the Council as
308 regards traceability requirements and notification of serious adverse reactions and
309 events[17] apply to blood components when they are used as starting or raw materials in
310 the manufacturing process of medicinal products.

311 **Production**

312 29. Given the variability inherent in many biological active substances and medicinal
313 products, steps to increase process robustness thereby reducing process variability and
314 enhancing reproducibility at the different stages of the product lifecycle such as
315 process design should be reassessed during Product Quality Reviews.

316 30. Since cultivation conditions, media and reagents are designed to promote the growth
317 of cells or microbial organisms, typically in an axenic state, particular attention should
318 be paid in the control strategy to ensure there are robust steps that prevent or minimise
319 the occurrence of unwanted bioburden and associated metabolites and endotoxins. For
320 medicinal products from cells and tissues where production batches are frequently
321 small the risk of cross-contamination between cell preparations from different donors
322 with various health status should be controlled under defined procedures and
323 requirements.

324 **Starting and raw materials**

325 31. The source, origin and suitability of biological starting and raw materials (e.g.
326 cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes,
327 cytokines, growth factors) should be clearly defined. Where the necessary tests take a
328 long time, it may be permissible to process starting materials before the results of the
329 tests are available, the risk of using a potentially failed material and its potential
330 impact on other batches should be clearly understood and assessed under the
331 principles of QRM. In such cases, release of a finished product is conditional on
332 satisfactory results of these tests. The identification of all starting materials should be
333 in compliance with the requirements appropriate to its stage of manufacture. For

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

334 biological medicinal products further guidance can be found in Part I and Annex 8 and
335 for biological active substances in Part II.

336 32. The risk of contamination of starting and raw materials during their passage along the
337 supply chain must be assessed, with particular emphasis on TSE. Materials that come
338 into direct contact with manufacturing equipment or the product (such as media used
339 in media fill experiments and lubricants that may contact the product) must also be
340 taken into account.

341 33. Given that the risks from the introduction of contamination and the consequences to
342 the finished product is the same irrespective of the stage of manufacture,
343 establishment of a control strategy to protect the product and the preparation of
344 solutions, buffers and other additions should be based on the principles and guidance
345 contained in the appropriate sections of Annex 1. The controls required for the quality
346 of starting and raw materials and on the aseptic manufacturing process assume greater
347 importance, particularly for products in respect of which final sterilisation is not
348 possible. Where an MA or CTA provides for an allowable type and level of bioburden,
349 for example at active substance stage, the control strategy should address the means by
350 which this is maintained within the specified limits.

351 34. Where sterilization of starting and raw materials is required, it should be carried out
352 where possible by heat. Where necessary, other appropriate methods may also be used
353 for inactivation of biological materials (e.g. irradiation and filtration).

354 35. Reduction in bioburden associated with procurement of living tissues and cells may
355 require the use of other measures such as antibiotics at early manufacturing stages.
356 This should be avoided, but where it is necessary their use should be justified, they
357 should be removed from the manufacturing process at the stage specified in the MA or
358 CTA.

359 36. The donation, procurement and testing of human tissues and cells used as starting or
360 raw materials should be in accordance with Directive 2004/23/EC.[18] Traceability for
361 human tissues and cells used as starting materials for biological medicinal products
362 should be maintained from the donor to the batch of a finished medicinal product.
363 Appropriate arrangements should be made between the manufacturer and the supplier
364 of tissues and cells regarding the transfer of health donor information that may
365 become available after the supply of the starting material and which may have an
366 impact on the quality or safety of the medicinal product manufactured therefrom.

367 (a) Their procurement, donation and testing in the EU is regulated under Directive
368 2004/23/EC and its implementing Commission directives. Such EU supply sites
369 must hold appropriate approvals from the national competent authority(ies) under
370 this Directive which should be verified as part of starting material supplier
371 management.

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

(b) Where such human cells or tissues are imported from third countries they must meet equivalent Community standards of quality and safety equivalent to those laid down in Directive 2004/23/EC. The traceability and serious adverse reaction and serious adverse event notification requirements are set out in Directive 2006/86/EC.

(c) There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments. Such processing steps, e.g. freezing, are under the scope of Directive 2004/23/EC, which provides for the need of a Responsible Person (RP).

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

(e) The transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

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

(g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MA Holder) which defines the tasks of each party, including the RP and Qualified Person.

38. Where human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over the sourcing, testing, transport and storage should be in place, including control of compliance with donation, procurement and testing standards equivalent to ones set in the Directive 2004/23.

Seed lot and cell bank system

39. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal substances and products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working virus seed lots and/or cell banks.

411 40. The number of generations (doublings, passages) between the seed lot or cell bank, the
412 active biological substance and the finished product should be consistent with
413 specifications in the MA or CTA.

414 41. As part of product lifecycle management, establishment of seed lots and cell banks,
415 including master and working generations, should be performed under circumstances
416 which are demonstrably appropriate. This should include an appropriately controlled
417 environment to protect the seed lot and the cell bank and the personnel handling it.
418 During the establishment of the seed lot and cell bank, no other living or infectious
419 material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the
420 same area or by the same persons. For stages prior to the master seed or cell bank
421 generation, where only the principles of GMP may be applied, documentation should
422 be available to support traceability including issues related to components used during
423 development with potential impact on product safety (e.g. reagents of biological
424 origin) from initial sourcing and genetic development if applicable. For vaccines the
425 requirements of Ph Eur monograph 2005;153 "Vaccines for human use" will apply.

426 42. Following the establishment of master and working cell banks and master and working
427 seed lots, quarantine and release procedures should be followed. This should include
428 adequate characterization and testing for contaminants. Their on-going suitability for
429 use should be further demonstrated by the consistency of the characteristics and
430 quality of the successive batches of product. Evidence of the stability and recovery of
431 the seeds and banks should be documented and records should be kept in a manner
432 permitting trend evaluation.

433 43. Seed lots and cell banks should be stored and used in such a way as to minimize the
434 risks of contamination, (e.g. stored in the vapour phase of liquid nitrogen in sealed
435 containers) or alteration. Control measures for the storage of different seeds and/or
436 cells in the same area or equipment should prevent mix-up and take account the
437 infectious nature of the materials to prevent cross contamination.

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

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

445 47. The storage and handling conditions for stocks should be managed according to the
446 same procedures and parameters. Once containers are removed from the seed lot / cell
447 bank management system, the containers should not be returned to stock.

448 **Operating principles**

449 48. Change management should, on a periodic basis, take into account the effects,
450 including cumulative effects of changes (e.g. to the process) on the quality, safety and
451 efficacy of the finished product.

452 49. Critical operational (process) parameters, or other input parameters which affect
453 product quality, need to be identified, validated, documented and be shown to be
454 maintained within requirements.

455 50. A control strategy for the entry of articles and materials into production areas should
456 be based on QRM principles. For aseptic processes, heat stable articles and materials
457 entering a clean area or clean/contained area should preferably do so through a double-
458 ended autoclave or oven. Heat labile articles and materials should enter through an air
459 lock with interlocked doors where they are subject to effective surface sanitisation
460 procedures. Sterilisation of articles and materials elsewhere is acceptable provided that
461 they are multiple wrappings, as appropriate to the number of stages of entry to the
462 clean area, and enter through an airlock with the appropriate surface sanitisation
463 precautions.

464 51. The growth promoting properties of culture media should be demonstrated to be
465 suitable for its intended use. If possible, media should be sterilized in situ. In-line
466 sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming
467 agents etc. to fermenters should be used where possible.

468 52. Addition of materials or cultures to fermenters and other vessels and sampling should
469 be carried out under carefully controlled conditions to prevent contamination. Care
470 should be taken to ensure that vessels are correctly connected when addition or
471 sampling takes place.

472 53. Continuous monitoring of some production processes (e.g. fermentation) may be
473 necessary, such data should form part of the batch record. Where continuous culture is
474 used, special consideration should be given to the quality control requirements arising
475 from this type of production method.

476 54. Centrifugation and blending of products can lead to aerosol formation and
477 containment of such activities to minimise cross-contamination is necessary.

478 55. Accidental spillages, especially of live organisms, must be dealt with quickly and
479 safely. Qualified decontamination measures should be available for each organism or
480 groups of related organisms. Where different strains of single bacteria species or very
481 similar viruses are involved, the decontamination process may be validated with one
482 representative strain, unless there is reason to believe that they may vary significantly
483 in their resistance to the agent(s) involved.

484 56. If obviously contaminated, such as by spills or aerosols, or if a potential hazardous
485 organism is involved, production and control materials, including paperwork, must be
486 adequately disinfected, or the information transferred out by other means.

487 57. In cases where a virus inactivation or removal process is performed during
488 manufacture, measures should be taken to avoid the risk of recontamination of treated
489 products by non-treated products.

490 58. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in
491 the course of vaccine manufacture) the process should ensure the complete
492 inactivation of live organism. In addition to the thorough mixing of culture and
493 inactivant, consideration should be given to contact of all product-contact surfaces
494 exposed to live culture and, where required, the transfer to a second vessel.

495 59. A wide variety of equipment is used for chromatography. QRM principles should be
496 used to devise the control strategy on matrices, the housings and associated equipment
497 when used in campaign manufacture and in multi-product environments. The re-use of
498 the same matrix at different stages of processing is discouraged. Acceptance criteria,
499 operating conditions, regeneration methods, life span and sanitization or sterilization
500 methods of columns should be defined.

501 60. Where irradiated equipment and materials are used, Annex 12 to EudraLex, Volume 4,
502 should be consulted for further guidance.

503 61. There should be a system to assure the integrity and closure of containers after filling
504 where the final products or intermediates represent a special risk and procedures to
505 deal with any leaks or spillages. Filling and packaging operations need to have
506 procedures in place to maintain the product within any specified limits, e.g. time
507 and/or temperature.

508 62. Activities in handling vials containing live biological agents must be performed in
509 such a way to prevent the contamination of other products or egress of the live agents
510 into the work environment or the external environment. The viability of such
511 organisms and their biological classification should take into consideration as part of
512 the management of such risks.

513 63. Care should be taken in the preparation, printing, storage and application of labels,
514 including any specific text for patient-specific product of the contents on the
515 immediate and outer packaging.

516 In the case of autologous products, the unique patient identifier and the statement "for
517 autologous use only" should be indicated on the outer packaging or, where there is no
518 outer packaging, on the immediate packaging.

519 64. The compatibility of labels with ultra-low storage temperatures, where such
520 temperatures are used, should be verified.

521 65. Where donor (human or animal) health information becomes available after
522 procurement, which affects product quality, it should be taken into account in recall
523 procedures.

524 **Quality control**

525 66. In-process controls have a greater importance in ensuring the consistency of the
526 quality of biological active substance and medicinal products than for conventional
527 products. In-process control testing should be performed at appropriate stages of
528 production to control those conditions that are important for the quality of the finished
529 product.

530 67. Where intermediates can be stored for extended periods of time (days, weeks or
531 longer), consideration should be given to the inclusion of finished product batches
532 made from materials held for their maximum in-process periods in the on-going
533 stability programme.

534 68. Certain types of cells (e.g. autologous cells) may be available in limited quantities and,
535 where allowed in the MA, a modified testing and sample retention strategy may be
536 developed and documented.

537 69. For cellular products, sterility tests should be conducted on antibiotic-free cultures of
538 cells or cell banks to provide evidence for absence of bacterial and fungal
539 contamination and to be able to detection fastidious organisms where appropriate.

540 70. For biological medicinal products with a short shelf life, which for the purposes of the
541 annex is taken to mean a period of 14 days or less, and which need batch certification
542 before completion of all end product quality control tests (e.g. sterility tests) a suitable
543 control strategy must be in place. Such controls need to be built on enhanced
544 understanding of product and process performance and take into account the controls
545 and attributes of starting and raw materials. The exact and detailed description of the
546 entire release procedure, including the responsibilities of the different personnel
547 involved in assessment of production and analytical data is essential. A continuous
548 assessment of the effectiveness of the quality assurance system must be in place
549 including records kept in a manner which permit trend evaluation.

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

554 a) Assessment by designated person(s) of batch processing records, results from
555 environmental monitoring (where available) which should cover production
556 conditions, all deviations from normal procedures and the available analytical
557 results for review in preparation for the initial certification by the Qualified
558 Person.

559 b) Assessment of the final analytical tests and other information available for final
560 certification by the Qualified Person. A procedure should be in place to describe
561 the measures to be taken (including liaison with clinical staff) where out of
562 specification test results are obtained. Such events should be fully investigated

563 and the relevant corrective and preventive actions taken to prevent recurrence
564 documented.

565
566

567 **PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES**
568
569 **B1. ANIMAL SOURCED PRODUCTS**[19]
570
571 This guidance applies to animal materials which includes materials from establishments such
572 as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM
573 principles need to be applied, see also requirements of Ph Eur monographs, including the need
574 for specific tests at defined stages. Documentation to demonstrate the supply chain
575 traceability[20] and clear roles of participants in the supply chain, typically including a
576 sufficiently detailed and current process map, should be in place.

577 1. Monitoring programmes should be in place for animal disease that are of concern to
578 human health. Organisations should take into account reports from trustworthy
579 sources on national disease prevalence when compiling their assessment of risk and
580 mitigation factors. Such organisations include the World Organisation for Animal
581 Health (OIE, Office International des Epizooties[21]). This should be supplemented by
582 information on health monitoring and control programme(s) at national and local
583 levels, the latter to include the sources (e.g. farm or feedlot) from which the animals
584 are drawn and the control measures in place during transport to the abattoirs.

585 2. Where abattoirs are used to source animal tissues, they should be shown to operate to
586 standards equivalent to those used in the EU. Account should be taken of reports from
587 organisations such as the Food and Veterinary Office[22] who verify compliance with
588 the requirements of food safety and quality, veterinary and plant health legislation
589 within the EU and in third countries exporting to the EU.

590 3. Control measures for starting or raw materials at establishments such as abattoirs
591 should include appropriate elements of a Quality Management System to assure a
592 satisfactory level of operator training, materials traceability, control and consistency.
593 These measures may be drawn from sources outside EU GMP but should be shown to
594 provide equivalent levels of control.

595 4. Control measures for starting or raw materials should be in place which prevent
596 interventions which may affect the quality of materials, or which at least provides
597 evidence of such activities, during their progression through the manufacturing and
598 supply chain. This includes the movement of material between sites of initial
599 collection, partial and final purification(s), storage sites, hubs, consolidators and
600 brokers. Details of such arrangements should be recorded within the traceability
601 system and any breaches recorded, investigated and actions taken.

602 5. Regular audits of the starting or raw material supplier should be undertaken which
603 verify compliance with controls for materials at the different stages of manufacture.

[19] See also PhEur monograph requirements, 0333
[20] See Chapter 5 in EudraLex, Volume 4.
[21] http://www.oie.int/eng/en_index.htm
[22] http://ec.europa.eu/food/fvo/index_en.htm

604 Issues must be investigated to a depth appropriate to their significance, for which full
605 documentation should be available. Systems should also be in place to ensure that
606 effective corrective and preventive actions are taken.

607 **B2. ALLERGEN PRODUCTS**

608 Materials may be manufactured by extraction from natural sources or manufactured by
609 recombinant DNA technology.

610 1. Source materials should be described in sufficient detail to ensure consistency in their
611 supply, e.g. common and scientific name, origin, nature, contaminant limits, method
612 of collection. Those derived from animals should be from healthy sources.
613 Appropriate biosecurity controls should be in place for colonies (e.g. mites, animals)
614 used for the extraction of allergens. Allergen products should be stored under defined
615 conditions to minimise deterioration.

616 2. The production process steps including pre-treatment, extraction, filtration, dialysis,
617 concentration or freeze-drying steps should be described in detail and validated.

618 3. The modification processes to manufacture modified allergen extracts (e.g. allergoids,
619 conjugates) should be described. Intermediates in the manufacturing process should be
620 identified and controlled.

621 4. Allergen extract mixtures should be prepared from individual extracts from single
622 source materials. Each individual extract should be considered as one active
623 substance.

624 **B3. ANIMAL IMMUNOSERA PRODUCTS**

625 1. Particular care should be exercised on the control of antigens of biological origin to
626 assure their quality, consistency and freedom from adventitious agents. The
627 preparation of materials used to immunise the source animals (e.g. antigens, hapten
628 carriers, adjuvants, stabilising agents), the storage of such material immediately prior
629 to immunisation should be in accordance with documented procedures.

630 2. The immunisation, test bleed and harvest bleed schedules should conform to those
631 approved in the CTA or MA.

632 3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab
633 or F(ab')2) and any further modifications must be in accordance with validated and
634 approved parameters. Where such enzymes are made up of several components, their
635 consistency should be assured.

636 **B4. VACCINES**

637 1. Where eggs are used, the health status of all source flocks used in the production of
638 eggs (whether specified pathogen free or healthy flocks) should be assured.

639 2. The integrity of containers used to store intermediate products and the hold times must
640 be validated.

641 3. Vessels containing inactivated products should not be opened or sampled in areas
642 containing live biological agents.

643 4. The sequence of addition of active ingredients, adjuvants and excipients during the
644 formulation of an intermediate or final product must be in compliance with
645 specifications.

646 5. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains)
647 are to be used in manufacture or testing, appropriate containment arrangements must
648 be in place. The approval of such arrangements should be obtained from the
649 appropriate national authority(ies) and the approval documents be available for
650 verification.

651 **B5. RECOMBINANT PRODUCTS**

652 1. Process condition during cell growth, protein expression and purification must be
653 maintained within validated parameters to assure a consistent product with a defined
654 range of impurities that is within the capability of the process to reduce to acceptable
655 levels. The type of cell used in production may require increased measures to be taken
656 to assure freedom from viruses. For production involving multiple harvest, the period
657 of continuous cultivation should be within specified limits.

658 2. The purification processes to remove unwanted host cell proteins, nucleic acids,
659 carbohydrates, viruses and other impurities should be within defined validated limits.

660 **B6. MONOCLONAL ANTIBODY PRODUCTS**

661 1. Monoclonal antibodies may be manufactured from murine hybridomas, human
662 hybridomas or by recombinant DNA technology. Control measures appropriate to the
663 different source cells (including feeder cells if used) and materials used to establish
664 the hybridoma / cell line should be in place to assure the safety and quality of the
665 product. It should be verified that these are within approved limits. Freedom from
666 viruses should be given particular emphasis. It should be noted that data originating
667 from products generated by the same manufacturing technology platform may be
668 acceptable to demonstrate suitability.

669 2. Criteria to be monitored at the end of a production cycle and for early termination of
670 production cycles should be verified that these are within approved limits.

671 3. The manufacturing conditions for the preparation of antibody sub-fragment (e.g. Fab,
672 F(ab')2, scFv) and any further modifications (e.g. radio labelling, conjugation,
673 chemical linking) must be in accordance with validated parameters.

674 **B7. TRANSGENIC ANIMAL PRODUCTS**

675 Consistency of starting material from a transgenic source is likely to be more problematic
676 than is normally the case for non-transgenic biotechnology sources. Consequently, there is an
677 increased requirement to demonstrate batch-to-batch consistency of product in all respects.

678 1. A range of species may be used to produce biological medicinal products, which may
679 be expressed into body fluids (e.g. milk) for collection and purification. Animals
680 should be clearly and uniquely identified and backup arrangements should be put in
681 place in the event of loss of the primary marker.

682 2. The arrangements for housing and care of the animals should be defined such that they
683 minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate
684 measures to protect the external environment should be established. A health-
685 monitoring programme should be established and all results documented, any incident
686 should be investigated and its impact on the continuation of the animal and on
687 previous batches of product should be determined. Care should be taken to ensure that
688 any therapeutic products used to treat the animals do not contaminate the product.

689 3. The genealogy of the founder animals through to production animals must be
690 documented. Since a transgenic line will be derived from a single genetic founder
691 animal, materials from different transgenic lines should not be mixed.

692 4. The conditions under which the product is harvested should be in accordance with MA
693 or CTA conditions. The harvest schedule and conditions under which animals may be
694 removed from production should be performed according to approved procedures and
695 acceptance limits.

696 **B8. TRANSGENIC PLANT PRODUCTS**

697 Consistency of starting material from a transgenic source is likely to be more problematic
698 than is normally the case for non-transgenic biotechnology sources. Consequently, there is an
699 increased requirement to demonstrate batch-to-batch consistency of product in all respects.

700 1. Additional measures, over and above those given in Part A, may be required to
701 prevent contamination of master and working transgenic banks by extraneous plant
702 materials and relevant adventitious agents. The stability of the gene within defined
703 generation numbers should be monitored.

704 2. Plants should be clearly and uniquely identified, the presence of key plant features,
705 including health status, across the crop should be verified at defined intervals through
706 the cultivation period to assure consistency of yield between crops.

707 3. Security arrangements for the protection of crops should be defined, wherever
708 possible, such that they minimise the exposure to contamination by microbiological
709 agents and cross-contamination with non-related plants. Measures should be in place
710 to prevent materials such as pesticides and fertilisers from contaminating the product.
711 A monitoring programme should be established and all results documented, any

712 incident should be investigated and its impact on the continuation of the crop in the
713 production programme should be determined.

714 4. Conditions under which plants may be removed from production should be defined.
715 Acceptance limits should be set for materials (e.g. host proteins) that may interfere
716 with the purification process. It should be verified that the results are within approved
717 limits.

718 5. Environmental conditions (temperature, rain), which may affect the quality attributes
719 and yield of the recombinant protein from time of planting, through cultivation to
720 harvest and interim storage of harvested materials should be documented. The
721 principles in documents such as 'Guideline on Good Agricultural and Collection
722 Practice for Starting Materials of Herbal origin'[23] of the Committee of Herbal
723 Medicinal Products should be taken into account when drawing up such criteria.

724 **GLOSSARY TO ANNEX 2.**

725 Entries are only included where the terms are used in Annex 2 and require further
726 explanation. Definitions which already exist in legislation or other sources are cross
727 referenced. In addition to this glossary, the GMP-glossary in EudraLex, Volume 4[24] applies,
728 unless indicated otherwise.

729 **Active substance.** See Article 1(3a) of Directive 2001/83/EC.

730 **Adjuvant.** A chemical or biological substance that enhances the immune response against an
731 antigen.

732 **Allergoids.** Allergens which are chemically modified to reduce IgE reactivity.

733 **Antigens.** Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing
734 specific immune responses.

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

737 **Monoclonal antibodies** (MAb) – homogenous antibody population obtained from a single
738 clone of lymphocytes or by recombinant technology and which bind to a single epitope.

739 **Polyclonal antibodies** – derived from a range of lymphocyte clones, produced in human and
740 animals in response to the epitopes on most 'non-self' molecules.

741 **Area.** A specific set of rooms within a building associated with the manufacturing of any one

742 product or multiple products that has a common air handling unit.

[23] Doc. Ref. EMEA/HMPC/246816/2005.
[24] http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/glos4en200408_en.pdf.

Bioburden. 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.

Biological medicinal product. See 3rd paragraph of point 3.2.1.1.b. of Part I of Annex I to Directive 2001/83/EC.

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

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

Cell bank - a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell stock - primary cells expanded to a given number of cells to be aliquoted and used as starting material for production of a limited number of lots of a cell based medicinal product.

Closed system. Where a drug substance or product is not exposed to the immediate room environment during manufacture.

Contained use: See Article 2(c) of Directive 2009/41/EC for all genetically modified organisms.

Deliberate release. See Article 2(3) of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.34

Excipient. See Article 1(3b) of Directive 2001/83/EC.

Ex-vivo. Where procedures are conducted on tissues or cells outside the living body and returned to the living body.

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

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

Genetically modified organism (GMO). See Article 2(2) of Directive 2001/18/EC.

Hapten. A low molecular weight molecule that is not in itself antigenic unless conjugated to a ‘carrier’ molecule.

Hybridoma. An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumour cells.

Intermediate product - see definitions in GMP Glossary and in Part II.

In-vivo. Procedures conducted in living organisms.

Look-back: documented procedure to trace biological medicinal substances or products which may be adversely affected by the use or incorporation of animal or human materials when either such materials fail release tests due to the presence of contaminating agent(s) or when conditions of concern become apparent in the source animal or human.

Master cell bank (MCB) –An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks. **Master virus seed** (MVS) – as above, but in relation to viruses; **master transgenic bank** – as above but for transgenic plants or animals.

Monosepsis (axenic). A single organism in culture which is not contaminated with any other

Multi-product facility. A facility that manufactures, either concurrently or in campaign mode, a range of different biological medicinal substances and products and within which equipment train(s) may or may not be dedicated to specific substances or products.

Plasmid. A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome; it can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

Raw materials. See 4th paragraph of point 3.2.1.1.b. of Part I of Annex I to Directive 2001/83/EC.

Responsible Person (RP). The person designated in accordance with Article 17 of Directive 2004/23/EC.

Scaffold – a support, delivery vehicle or matrix that may provide structure for or facilitate the migration, binding or transport of cells and/or bioactive molecules.

Somatic cells. Cells, other than reproductive (germ line) cells, which make up the body of a human or animal. These cells may be autologous (from the patient), allogeneic (from another human being) or xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo, to be administered in humans to obtain a therapeutic, diagnostic or preventive effects.

Specified pathogen free (SPF)- Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from groups (e.g. flocks or herds) of animals free from specified pathogens. Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

Starting materials. See the 1st and 2nd paragraph of point 3.2.1.1.b of Part I of Annex I to Directive 2001/83/EC.

Transgenic: an organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

Working cell bank (WCB) – a homogeneous pool of micro-organisms or cells, that are distributed uniformly into a number of containers derived from a MCB that are stored in such a way to ensure stability and for use in production. **Working virus seed** (WVS) – as above but in relation to viruses, **working transgenic bank** – as above but for transgenic plants or animals.

Zoonosis: Animal diseases that can be transmitted to humans