

Animals

19. A wide range of animal species are used in the manufacture of a number of biological medicinal products. These can be divided into 2 broad types of sources:
- (a) Live groups, herds, flocks: examples include polio vaccine (monkeys), immunosera to snake venoms and tetanus (horses, sheep and goats), allergens (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats, cattle).
 - (b) Animal tissues and cells derived post-mortem and from establishments such as abattoirs: examples include xenogeneic cells from animal tissues and cells, feeder cells to support the growth of some ATMPs, abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).

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

20. In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.
21. Particular care should be taken to prevent and monitor infections in the source/donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimes, control of bedding and feed materials. This is of special relevance to specified pathogen free animals where PhEur monograph requirements must be met. Housing and health monitoring should be defined for other categories of animals (e.g. healthy flocks or herds).
22. For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.

23. Note should be taken of Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes as regards requirements for animal quarters, care and quarantine. Housing for animals used in production and control of biological active substances and medicinal products should be separated from production and control areas.
24. For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals.
25. Animals, biological agents, and tests carried out should be the subject of an identification system to prevent any risk of confusion and to control all identified hazards.

Documentation

26. Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.
27. Some product types may require specific definition of what materials constitutes a batch, particularly somatic cells in the context of ATMPs. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.
28. Where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health related information²¹. Traceability records²² must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of medicinal products for special use cases, such as donor-matched cells. Directives 2002/98/EC and Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events²³ apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products. For ATMPs, traceability requirement regarding human cells including haematopoietic cells must comply with the principles laid down in Directives 2004/23/EC and 2006/86/EC. The arrangements necessary to achieve the traceability and

²¹ Article 15 of Regulation 1394/ 2007

²² See ENTR/F/2/SF/dn D(2009) 35810, 'Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products' for further information on traceability of investigational ATMPs

²³ OJ L 256, 1.10.2005, p. 32.

retention period should be incorporated into technical agreements between the responsible parties.

Production

29. Given the variability inherent in many biological active substances and medicinal products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews.
30. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid in the control strategy to ensure there are robust steps that prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins. For cell based ATMPs where production batches are frequently small the risk of cross-contamination between cell preparations from different donors with various health status should be controlled under defined procedures and requirements.

Starting and raw materials

31. The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. For biological medicinal products further guidance can be found in Part I and Annex 8 and for biological active substances in Part II.
32. The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.
33. Given that the risks from the introduction of contamination and the consequences to the finished product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of Annex 1. The controls required for the quality of starting and raw materials and on the aseptic manufacturing process, particularly for cell-based products, where

final sterilisation is generally not possible and the ability to remove microbial by-products is limited, assume greater importance. Where an MA or CTA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

34. Where sterilization of starting and raw materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).
35. Reduction in bioburden associated with procurement of living tissues and cells may require the use of other measures such as antibiotics at early manufacturing stages. This should be avoided, but where it is necessary their use should be justified, they should be removed from the manufacturing process at the stage specified in the MA or CTA.
36. For human tissues and cells used as starting materials for biological medicinal products:
 - (a) Their procurement, donation and testing in the EU is regulated under Directive 2004/23/EC and its implementing Commission directives. Such EU supply sites must hold appropriate approvals from the national competent authority(ies) under this Directive which should be verified as part of starting material supplier management.
 - (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, e.g. to derive early cell lines or banks prior to establishing a Master Cell Bank (MCB). Such processing steps, 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.
37. With regard to gene therapy²⁴:
- (a) For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids to transfect the packaging cells and the MCB of the packaging cell line.
 - (b) For products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells.
 - (c) For genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations.
 - (d) The principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.
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 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. Such a system may not be applicable to all types of ATMPs.
40. The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the MA or CTA.
41. As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under circumstances which are demonstrably appropriate. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell

²⁴ Details in section 3.2 of Part IV of Annex I to Directive 2001/83/EC.

bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, documentation should be available to support traceability including issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development if applicable. For vaccines the requirements of Ph Eur monograph 2005;153 “Vaccines for human use” will apply.

42. Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.
43. Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination, (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take account the infectious nature of the materials to prevent cross contamination.
44. Cell based medicinal products are often generated from a cell stock obtained from limited number of passages. In contrast with the two tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be covered by a validation protocol.”
45. Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.
46. It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.
47. The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.

Operating principles

48. Change management should, on a periodic basis, take into account the effects, including cumulative effects of changes (e.g. to the process) on the quality, safety and efficacy of the finished product.
49. Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated, documented and be shown to be maintained within requirements.
50. A control strategy for the entry of articles and materials into production areas should be based on QRM principles. For aseptic processes, heat stable articles and materials entering a clean area or clean/contained area should preferably do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air lock with interlocked doors where they are subject to effective surface sanitisation procedures. Sterilisation of articles and materials elsewhere is acceptable provided that they are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.
51. The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents etc. to fermenters should be used where possible.
52. Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.
53. Continuous monitoring of some production processes (e.g. fermentation) may be necessary, such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.
54. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.
55. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

56. If obviously contaminated, such as by spills or aerosols, or if a potentially hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.
57. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.
58. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in the course of vaccine manufacture) the process should ensure the complete inactivation of live organism. In addition to the thorough mixing of culture and inactivant, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.
59. A wide variety of equipment is used for chromatography. QRM principles should be used to devise the control strategy on matrices, the housings and associated equipment when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilization methods of columns should be defined.
60. Where irradiated equipment and materials are used, Annex 12 to EudraLex, Volume 4, should be consulted for further guidance.
61. There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages. Filling and packaging operations need to have procedures in place to maintain the product within any specified limits, e.g. time and/or temperature.
62. Activities in handling vials containing live biological agents must be performed in such a way to prevent the contamination of other products or egress of the live agents into the work environment or the external environment. The viability of such organisms and their biological classification should take into consideration as part of the management of such risks.
63. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific products or signifying the use of genetic engineering of the contents on the immediate and outer packaging. In the case of ATMPs used for autologous use, the unique patient identifier and the statement “for autologous use only” should be indicated on

the outer packaging or, where there is no outer packaging, on the immediate packaging.²⁵

64. The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.
65. Where donor (human or animal) health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

Quality control

66. In-process controls have a greater importance in ensuring the consistency of the quality of biological active substance and medicinal products than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.
67. Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability programme.
68. Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the MA, a modified testing and sample retention strategy may be developed and documented.
69. For cell-based ATMPs, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detect fastidious organisms where appropriate.
70. For biological medicinal products with a short shelf life, which for the purposes of the annex is taken to mean a period of 14 days or less, and which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation. Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit initial batch certification should be considered (e.g. rapid microbiological methods). The

²⁵ Article 11 of Regulation (EC) No 1349/2007.
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procedure for batch certification and release may be carried out in two or more stages - :

- a) Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the Qualified Person.
- b) Assessment of the final analytical tests and other information available for final certification by the Qualified Person.

A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS²⁶

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 Ph Eur monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability²⁷ and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

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 Epizooties²⁸). 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.
2. Where abattoirs are used to source animal tissues, they should be shown to operate to standards equivalent to those used in the EU. Account should be taken of reports from organisations such as the Food and Veterinary Office²⁹ who verify compliance with the requirements of food safety and quality, veterinary and plant health legislation within the EU and in third countries exporting to the EU.
3. Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside EU GMP but should be shown to provide equivalent levels of control.
4. Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be

²⁶ See also PhEur monograph requirements, 0333

²⁷ See Chapter 5 in EudraLex, Volume 4.

²⁸ http://www.oie.int/eng/en_index.htm

²⁹ http://ec.europa.eu/food/fvo/index_en.htm

recorded within the traceability system and any breaches recorded, investigated and actions taken.

5. Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.
6. Cells, tissues and organs intended for the manufacture of xenogeneic cell-based medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and documented.
7. For xenogeneic cell therapy products appropriate guidance in relation to procurement and testing of animal cells should be followed. Reference is made to the EMA Guideline document³⁰ on xenogeneic cell-based medicinal products.

B2. ALLERGEN PRODUCTS

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

1. Source materials should be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits, method of collection. Those derived from animals should be from healthy sources. Appropriate biosecurity controls should be in place for colonies (e.g. mites, animals) used for the extraction of allergens. Allergen products should be stored under defined conditions to minimise deterioration.
2. The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated.
3. The modification processes to manufacture modified allergen extracts (e.g. allergoids, conjugates) should be described. Intermediates in the manufacturing process should be identified and controlled.

³⁰ EMEA/CHMP/CPWP/83508/2009.

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

B3. ANIMAL IMMUNOSERA PRODUCTS

1. Particular care should be exercised on the control of antigens of biological origin to assure their quality, consistency and freedom from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten carriers, adjuvants, stabilising agents), the storage of such material immediately prior to immunisation should be in accordance with documented procedures.
2. The immunisation, test bleed and harvest bleed schedules should conform to those approved in the CTA or MA.
3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or F(ab')₂) and any further modifications must be in accordance with validated and approved parameters. Where such enzymes are made up of several components, their consistency should be assured.

B4. VACCINES

1. Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) should be assured.
2. The integrity of containers used to store intermediate products and the hold times must be validated.
3. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.
4. The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with specifications.
5. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains) are to be used in manufacture or testing, appropriate containment arrangements must be in place. The approval of such arrangements should be obtained from the appropriate national authority(ies) and the approval documents be available for verification.

B5. RECOMBINANT PRODUCTS

1. Process condition during cell growth, protein expression and purification must be maintained within validated parameters to assure a consistent product with a defined range of impurities that is within the capability of the process to reduce to acceptable levels. The type of cell used in production may require increased measures to be taken to assure freedom from viruses. For production involving multiple harvest, the period of continuous cultivation should be within specified limits.
2. The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.

B6. MONOCLONAL ANTIBODY PRODUCTS

1. Monoclonal antibodies may be manufactured from murine hybridomas, human hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma / cell line should be in place to assure the safety and quality of the product. It should be verified that these are within approved limits. Freedom from viruses should be given particular emphasis. It should be noted that data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.
2. Criteria to be monitored at the end of a production cycle and for early termination of production cycles should be verified that these are within approved limits.
3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab, F(ab')₂, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) must be in accordance with validated parameters.

B7. TRANSGENIC ANIMAL PRODUCTS

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

1. A range of species may be used to produce biological medicinal products, which may be expressed into body fluids (e.g. milk) for collection and

purification. Animals should be clearly and uniquely identified and backup arrangements should be put in place in the event of loss of the primary marker.

2. The arrangements for housing and care of the animals should be defined such that they minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health-monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the animal and on previous batches of product should be determined. Care should be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.
3. The genealogy of the founder animals through to production animals must be documented. Since a transgenic line will be derived from a single genetic founder animal, materials from different transgenic lines should not be mixed.
4. The conditions under which the product is harvested should be in accordance with MA or CTA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.

B8. TRANSGENIC PLANT PRODUCTS

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

1. Additional measures, over and above those given in Part A, may be required to prevent contamination of master and working transgenic banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within defined generation numbers should be monitored.
2. Plants should be clearly and uniquely identified, the presence of key plant features, including health status, across the crop should be verified at defined intervals through the cultivation period to assure consistency of yield between crops.
3. Security arrangements for the protection of crops should be defined, wherever possible, such that they minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures should be in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring programme should be established and all results documented, any incident should be investigated

and its impact on the continuation of the crop in the production programme should be determined.

4. Conditions under which plants may be removed from production should be defined. Acceptance limits should be set for materials (e.g. host proteins) that may interfere with the purification process. It should be verified that the results are within approved limits.
5. Environmental conditions (temperature, rain), which may affect the quality attributes and yield of the recombinant protein from time of planting, through cultivation to harvest and interim storage of harvested materials should be documented. The principles in documents such as ‘Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal origin’³¹ of the Committee of Herbal Medicinal Products should be taken into account when drawing up such criteria.

B9. GENE THERAPY PRODUCTS

Point 2.1. of Part IV of the Annex to Directive 2001/83/EC contains a definition of gene therapy (GT) medicinal products.

There are several types of GT medicinal products (GT products containing recombinant nucleic acid sequence(s) or genetically modified organism(s) or virus(es) and GT medicinal products containing genetically modified cells) and all are within the scope of the guidance in this section. For cell based GT medicinal products, some aspects of guidance in section B10 of Part B may be applicable.

1. Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Particular considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials, cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant.
2. Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimise risk. This strategy should be used as a basis for the design of the process, the

³¹ Doc. Ref. EMEA/HMPC/246816/2005.
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manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

3. The manufacture and testing of GT medicinal products raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. Legislated local and, if applicable, international safety measures should be applied.
4. Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles, where possible utilising unidirectional flows. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.
5. Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated.
6. Where replication limited vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors.
7. An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.
8. Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible, sample collection additions and transfers should prevent the release of viral material.
9. Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable. Concurrent production of non-viral vectors in the same area should be controlled on the basis of QRM principles. Changeover procedures between campaigns should be demonstrated to be effective.

10. A description of the production of vectors and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non viral vector stock) to the finished product.
11. Shipment of products containing or consisting of GMO should conform to appropriate legislation.
12. The following considerations apply to the ex-vivo gene transfer to recipient cells:
 - (a) These should take place in facilities dedicated to such activities where appropriate containment arrangements exist.
 - (b) Measures (including considerations outlined under paragraph 10 in Part A) to minimise the potential for cross-contamination and mix-up between cells from different patients are required, this should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector.
 - (c) Traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s).
 - (d) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.

B10. SOMATIC AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS

Point 2.2. of Part IV of Annex I of Directive 2001/83/EC contains the definition of somatic cell therapy (SCT) medicinal products and the definition of a tissue engineered medicinal product is given in Article 2(1)(b) of Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.³² For genetically modified cell based products that are not classified as GT products, some aspects of guidance in section B9 may be applicable.

1. Where they are available, authorised sources (i.e. authorised medicinal products or CE marked medical devices) of additional substances (such as

³² OJ L 324, 10.12.2007, p. 121.

cellular products, bio-molecules, bio-materials, scaffolds, matrices) should be used in the manufacture of these products.

2. Where devices, including custom-made devices, are incorporated as part of the products:
 - (a) There should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device.
 - (b) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.
3. Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures put in place for these source materials should be ensured.
4. Manufacturing steps should be conducted aseptically where sterilisation of the finished product cannot be achieved using standard methods such as filtration.
5. Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.
6. Sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and consider the detection of fastidious organism.
7. Where relevant, a stability-monitoring programme should be in place together with reference and retain samples in sufficient quantity to permit further examination.

GLOSSARY TO ANNEX 2.

Entries are only included where the terms are used in Annex 2 and require further explanation. Definitions which already exist in legislation or other sources are cross-referenced. In addition to this glossary, the GMP-glossary in EudraLex, Volume 4³³ applies, unless indicated otherwise.

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

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

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

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

Antibody. 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:

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

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

Area. 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.

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.

³³ http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/glos4en200408_en.pdf.
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