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Draft

Annex 2

Manufacture of Biological Medicinal Substances and Products for Human Use

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Annex 2 has been revised as a consequence of the restructuring of the GMP guide, the increased breadth of biological products to include several new product types such as transgenic derived products and the Advanced Therapy Medicinal Products, (ATMPs) together with associated new legislation. The GMP guidance drawn up for the latter products is to meet the requirements of Article 5 of Regulation 1394/2007 and to align with details in Directive 2009/120/EC. Significant changes have also been made as a result of the comments received from the first consultation.

For products that are either industrially prepared or manufactured by a method involving an industrial process, (such as pharmaceuticals), Directive 2004/23/EC on Human Tissue and Cells covers only the donation, procurement and testing of the tissues and cells which become the 'biological active substances' for many biological medicinal products.

MANUFACTURE OF BIOLOGICAL MEDICINAL SUBSTANCE AND PRODUCTS FOR HUMAN USE

Scope

The methods employed in the manufacture of biological medicinal substances and products are a critical factor in shaping the appropriate regulatory control. Biological medicinal substances and products can be defined therefore largely by reference to their method of manufacture.

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

- a) Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I. For some types of product (e.g. cell-based products) all manufacturing steps need to be conducted aseptically.
- b) Type of product - this annex provides guidance on the full range of medicinal substances and products defined as biological.

These two aspects are shown in Table 1, it should be noted that this table is illustrative only and not meant to describe the precise scope. It should also be understood that in line with the corresponding table in Part II of the Guide, the level of GMP increases in detail from early to later steps in the manufacture of biological substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of the annex does not imply that those steps will be routinely subject to inspection by the authorities. Although antibiotics are not included as biological products, however where biological stages of manufacture occur, guidance in this Annex may be used. Guidance for medicinal products derived from human blood or plasma is covered in Annex 14 and for non-transgenic plant products in Annex 7.

The annex is divided into two main parts:

- a) Part A contains supplementary guidance on the manufacture of biological medicinal substances and products, from control over seed lots and cell banks through to finishing activities, and testing.
- b) Part B contains further guidance on selected types of biological medicinal substances and products.

The manufacture and control of genetically modified organisms must comply with local and national requirements. According to Directive 1998/81/EC on contained use of genetically modified micro-organisms, appropriate containment should be established and maintained in facilities where any genetically modified micro-organisms are handled. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level. There should be no conflicts with GMP requirements.

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			
Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunosera, ATMPs	Collection of plant, organ, tissue or fluid ¹	Cutting, mixing, and / or initial processing	Isolation and purification	Formulation, filling
Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB ² , WCB, MSL, WSL	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
Biotechnology - fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB ² and WCB, MSL, WSL	Cell culture and / or fermentation	Isolation, purification, modification	Formulation, filling
Animal sources: transgenic	Recombinant proteins, ATMPs	Master ² and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification and modification	Formulation, filling
Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting ³	Initial extraction, isolation, purification, modification	Formulation, filling
Human sources	Urine derived enzymes, hormones	Collection of fluid ⁴	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
Human and / or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells ⁵	Manufacture vector ⁵ and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells ⁶	Establish MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells ⁵	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	formulation, combination, fill

¹ See section B1 for the extent to which elements of GMP apply.

² See section on 'Seed lot and cell bank system' for the extent to which GMP applies.

³ HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005 may be applied for growing and harvesting in open fields.

⁴ Principles of GMP apply; see explanatory text in 'Scope'.

⁵ Where these are viral vectors, the main controls are as for virus manufacture (row 2)

⁶ Human tissues and cells must comply with Directive 2004/23/EC.

Principle

The manufacture of biological medicinal 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 medicinal substances and products involves biological processes and materials, such as cultivation of cells or extraction of material 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 principles are particularly important for this class of materials and should be used to develop their 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, many products are 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, and training of the operators are key considerations to minimise such contamination events.

Specifications related to GMP (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. For active substances whose specification allows a managed level of bioburden – see guidance in Part II. For biological materials that cannot be sterilised (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. 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 crucial and in-process controls take on a particular importance in the manufacture of biological medicinal substances and products.

Biological medicinal products which incorporate human tissues or cells, such as certain Advanced Therapy Medicinal Products (ATMPs) must comply with the requirements of Directive 2004/23/EC and Directive 2006/17/EC for the donation, procurement and testing stages. In line with Commission Directive 2006/86/EC collection and testing must be done in accordance with an appropriate quality system for which standards and specifications are defined in its Annex⁷. Furthermore, the requirements of Directive 2006/86/EC on traceability and serious adverse reactions and serious adverse events notifications apply from the donor to the recipient. Tissue establishments supplying such materials are required to have a system

⁷ 'Good Practice' guidance under development.

in place to trace all substances coming into contact with the cells or tissues, while maintaining donor and patient confidentiality.

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

PART A. GENERAL GUIDANCE

Personnel

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

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

3. Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray. Medical advice should be sought for personnel involved with live and genetically modified organisms.

4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including QC, maintenance and cleaning staff) should be controlled on the basis of quality risk management principles. In general, during the course of a working day, personnel should not pass from areas where exposure to live organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, the contamination control measures should be based on quality risk management principles.

Premises and Equipment

5. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risks to the product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeast, moulds, anaerobes, etc) where indicated by risk analysis.

6. Manufacturing facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. The use of disposable technologies should also be considered. Prevention of contamination is more appropriate than detection and removal, although contamination is likely to become evident during

processes such as fermentation and cell culture. Where open processes (e.g. cell bank or seed lot establishment or expansion) or aseptic processes (e.g. additions of supplements, media, buffers, gasses, manipulations during the manufacture of ATMPs) are used, measures should be put in place, including engineering and environmental controls on the basis of quality risk management principles. These risk management principles should take into account the principles and guidance in the appropriate sections of Annex 1 when selecting environmental classification cascades and associated controls.

7. Dedicated production areas should be used for the production of BCG vaccine, for the handling of live organisms used in production of tuberculin products and for live organisms of BSL 3 or 4.

8. In general dedicated production areas should be used for the handling of live cells and organisms (e.g. for ATMP production and vaccine production) and spore forming organisms such as *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium tetani* until the inactivation process is accomplished. Similarly, for killed vaccines and toxoids, parallel processing should only be performed after inactivation of the culture or after detoxification.

9. Manufacture in a multiproduct facility may be acceptable where the following, or equivalent, considerations and measures are shown to be an effective part of the control strategy to prevent cross-contamination:

- (a) Knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility.
- (b) Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems.
- (c) Control measures to remove the organisms and spores before the subsequent manufacture of other products. Cleaning and decontamination for the organisms and spores should be validated including the HVAC system.
- (d) Environmental monitoring specific for the organism is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.
- (e) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products).
- (f) Campaign-based manufacturing.

10. For finishing operations⁸, the requirement for dedicated facilities will depend on the above considerations together with additional considerations such as the specific needs of the biological product and on the characteristics of other products, including any non-biological products, in the same facility. Other control measures for finishing operations may include

⁸ formulation, filling and packaging

the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.

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

12. Where production is characterised by multiple small batches from different starting materials (e.g. cell-based products) factors such as the health status of donors and the risk of total loss of product from and/or for specific patients should be taken into account when considering the acceptance of concurrent working during development of the control strategy.

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

14. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens) they should be surrounded by a positive pressure clean zone of appropriate grade.

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

16. Primary containment should be designed and periodically tested to demonstrate absence of leakage.

17. The use of 'clean in place' and sterilization in place (e.g. 'steam in place') systems should be used where possible. Valves on fermentation vessels should be completely steam sterilisable.

18. Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals.

19. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination and, where required by local regulation, minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

20. Due to the variability of biological products or processes, relevant/critical additives or ingredients have to be measured or weighed during the production process. In these cases, stocks of these substances may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign.

Animals

A wide range of animal species are used in the manufacture of a number of biological medicinal products or starting materials. 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).

21. 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 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 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 medicinal substance(s) or product(s) in which the 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 (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source animals must be documented and used to determine the removal of those animals from the programme for defined periods.

22. 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).

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

24. Note should be taken of Directive requirements for animal quarters, care and quarantine⁹ Housing for animals used in production and control of biological products should be separated from production and control areas.

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

⁹ Directive 86/609/EEC revision – http://ec.europa.eu/environment/chemicals/lab_animals/nextsteps_en.htm .

26. 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

27. Specifications for biological starting materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, particularly microbiological controls.

28. 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.

29. 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 information. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. Directives 2002/98/EC and 2005/61/EC apply to blood components when they are used as supportive or raw material 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.

30. For ATMPs, traceability records must be retained by the MA Holder for a minimum of 30 years after the expiry date of the product (Article 15 of Regulation 1394/ 2007). The arrangements necessary to achieve this retention period should be incorporated into technical agreements between the responsible parties.

Production

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

32. 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 advanced therapy products 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 materials

33. The source, origin and suitability of biological starting materials 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. 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 substances in Part II. 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 consider the detection of fastidious organisms.

34. The risk of contamination of starting 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 considered. Consideration should be given to reagent-derived adventitious agents.

35. Given that the risks of introducing contamination and the consequences to the product is the same irrespective of the stage of manufacture, establishment of control strategy measures to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the different sections of Annexe 1. 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. The controls required for the quality of starting materials and on the aseptic manufacturing process for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, assume greater importance.

36. Where sterilization of starting 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).

37. 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 an early stage as possible to comply with conditions in the MA or CTA.

38. 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 technical directives. Such EU supply sites must hold approvals from the national competent authority(ies) under this Directive which should be verified by the manufacturing site.
- (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. All such processing steps, are under the responsibility of the 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.

- (e) The transport of human tissues and cells to the manufacturing site is the responsibility of the manufacturing sites which 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 product, should be maintained.
- (g) A contract should be in place between the manufacturer and the tissue establishment which defines Directive responsibilities of each party, including the RP and Qualified Person.

39. For somatic cell therapy and tissue engineered products, the principles of GMP shall apply after procurement of cells and tissues.

40. With regard to gene therapy¹⁰:

- (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 master cell bank 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 master cell bank 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.

41. 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. If human cells are used they should comply with Directive 2004/23 EC including traceability and reporting of serious adverse events and reactions.

Seed lot and cell bank system

42. 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 seed lots and/or cell banks.

43. The number of generations (doublings, passages) between the seed lot or cell bank, the drug substance and finished product should be consistent with specifications in the MA or CTA.

¹⁰ Details in section 3.2 of Directive 2009/120/EC

44. 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 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 generation, where only the principles of GMP may be applied, documentation in line with ICH Q5D 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.

45. Following the establishment of master and working cell banks and 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.

46. 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.

47. 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.

48. 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.

49. 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

50. Change management should, on a periodic basis, consider the effects, including cumulative effects of changes (e.g. in the process) on the quality, safety and efficacy of the product.

51. 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.

52. Heat stable articles and materials entering a clean area or clean/contained area should 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 double wrapped and enter through an airlock with the appropriate surface sanitisation precautions.

53. 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.

54. 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.

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..

55. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.

56. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated 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.

57. 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.

58. Careful consideration should be given to the validation of any methods for sterilisation, disinfection, virus removal or inactivation undertaken (see CHMP guidance).

59. 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.

60. For products that are inactivated by the addition of a reagent, 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 the transfer to a second vessel.

61. A wide variety of equipment is used for chromatography. Quality risk management principles should be used to devise the controls on matrices, the housings and associated equipment. Consideration should be given to the need to dedicate chromatography equipment to the purification of one product in multi-product environments and the need for equipment

to be sterilized or sanitized between batches. The 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.

62. Where irradiated equipment and materials are used, Annex 12 should be consulted for further guidance.

63. 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.

64. 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. This risk assessment should take into consideration the viability of such organisms and their biological classification.

65. During finishing operations, such as formulation, filling and packaging, additional measures, dependent on the specific needs of the biological product, may be required. These may include the sequence of additions, mixing speeds, time and temperature controls, limits on exposure to light and cleaning procedures in the event of spillages.

66. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific products or signifying genetic modification of the contents on the primary container and secondary packaging. In the case of products used for autologous use, the unique patient identifier and the statement “for autologous use only” should be indicated on the immediate label.

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

68. Where donor and /or animal health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

Quality control

69. In-process controls have a greater importance in ensuring the consistency of the quality of biological 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 (e.g., virus removal, residual DNA content).

70. Where in-process hold steps exist, consideration should be given to the inclusion of final product batches made from materials held for their maximum in-process periods in the on-going stability programme.

71. 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.

72. For products with a short shelf life, 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 input materials. There should be a description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data. A continuous assessment of the effectiveness of the quality assurance system must be in place. Where end product tests are not possible due to short shelf lives, alternative methods of obtaining equivalent data to permit batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages - before and after full end process analytical test results are available:

- a) Assessment by designated person(s) of batch processing records and results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review and conditional certification by the Qualified Person.
- b) Assessment of the final analytical tests and other information available before end product dispatch for final product certification by the Qualified Person.
- c) Records should be kept in a manner which permits trend evaluation.
- d) 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 after product dispatch. Such events should be fully investigated and the relevant corrective and preventative actions taken to prevent recurrence documented.

PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on quality risk management principles need to be applied. Documentation which demonstrates the clear roles of actors 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 and control measures when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties¹¹). 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

¹¹ http://www.oie.int/eng/en_index.htm

organisations such as the Food and Veterinary Office¹² 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 at establishments such as abattoirs should include appropriate elements of 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 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 recorded within the traceability system and any breaches recorded, investigated and actions taken.

5. Written and approved technical agreements should be in place between the contract giver and contract acceptors that defines in sufficient detail the responsibilities of each party to maintain materials to a quality appropriate to their stage of manufacture.

6. Regular audits 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.

7. 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.

8. For xenogeneic cell therapy products appropriate guidance in relation to procurement and testing of animal cells should be followed. Reference is made to the Points to Consider on Xenogeneic Cell-therapy medicinal product (CPMP/1199/02), to be replaced by the Guideline on Xenogeneic Cell-based medicinal products (EMA/CHMP/CPWP/83508/2009).

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

¹² http://ec.europa.eu/food/fvo/index_en.htm

extraction of allergens. Allergen 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.

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 components and the hold times must be validated.

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

4. Once all steps designed to inactivate or remove live biological agents are complete, all subsequent processing should take place in areas dedicated to inactivated products.

5. 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.

6. 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 and in-process controls 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 may arise from products generated by the same manufacturing technology platform.

2. Criteria to be monitored at the end of a production cycle and for early termination of production cycle 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' should be taken into account when drawing up such criteria.

B9. GENE THERAPY PRODUCTS

Part IV (1) of Directive 2001/83/EC as revised in 2009 contains a definition of gene therapy (GT) medicinal products.

There are potentially 2 types of GT products (vectors and genetically modified cells) and both are within the scope of the guidance in this section. For cell based GT products, some aspects of guidance in section B10 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. Special 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 quality risk management 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 quality risk management 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 considered 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 manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

3. The manufacture and testing of gene therapy 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 quality risk management 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 quality risk management 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 and/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 quality risk management 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

Annex I, Part IV (2) of Directive 2001/83/EC as amended in 2009 contains a definition of somatic cell therapy (SCT) medicinal products and the definition of a tissue engineered medicinal product is given in Article 2 of Regulation 1394/2007/EC. For genetically modified cell based products that are not classified as GT products, some aspects of guidance in section B9 may be applicable.

1. Use should be made, where they are available, of authorised sources (i.e. licensed medicinal products or CE marked devices) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices).
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 or related to cell pooling. The robustness of the control and test measures put in place for these source materials should be ensured. Animals from which tissues and cells are collected should be reared and processed according to the principles defined in the CHMP guideline.
4. Special consideration should be given to the quality of the starting materials, cryoprotectants, feeder cells (e.g. murine or human), culture media, enzymes, cytokines, growth factors and other additional substances used in manufacture.
5. Special attention should be paid to any cryopreservation stages including any specific requirements for the rate of temperature change (during freezing or thawing). Where liquid nitrogen is used, this should be pharmaceutical grade. 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. Where relevant, a stability-monitoring programme should be in place together with reference and retain samples in sufficient quantity to permit further examination.

GLOSSARY

Entries are only included where the terms are used in Annex 2 and require further explanation. Definitions which already exist in legislation are cross-referenced only.

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.

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 substance, biological medicinal product, starting materials, raw materials

See Annex 1 to 2001/83/EC – 3.2.1.1(b)

Biological safety 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).

Closed system

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

Contained use

An operation, in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which barriers (physical / chemical / biological) are used to limit their contact with the general population and the environment (Directive 1998/81/EC).

Deliberate release

The deliberate release into the environment of genetically modified organisms (Directive 2001/18/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).

Gene transfer

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

Genetically modified organism (GMO)

An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. [2001/18/EC Article 2 (2)]

Hapten

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

Hybridoma

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

Intermediate product

See definitions in GMP Glossary and in Part II.

In-vivo

Procedures conducted in living organisms.

Look-back

A 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. [see 'trace-back' in 2005/62/EC].

Master cell bank (MCB)

A homogeneous pool of micro-organisms or cells, that are distributed uniformly into a number of containers and stored in such a way to ensure stability, normally used to manufacture working cell banks.

Master virus seed lot (MVL)

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 organism.

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.

Primary cell lot – a pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications.

Responsible Person (RP)

See 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 (SPF). 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.

Transgenic

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

Vector

An agent of transmission, which transmits genetic information from one cell or organism to another, e.g. plasmids, liposomes, viruses.

Viral vector

A vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes; if the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

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 lot (WVL)

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.