ANNEX 2B

MANUFACTURE OF BIOLOGICAL MEDICINAL SUBSTANCES AND PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of biological active substances and biological medicinal products for human use ('biological active substances and medicinal products') are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of active substances and medicinal products defined as biological with the exception of Advanced Therapy Medicinal Products ("ATMPs"). The ATMPs are not covered by the present guideline. Manufacturers of ATMPs should refer to PIC/S Annnex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use.

This annex is divided into two main parts:

a) Part A contains supplementary guidance on the manufacture of biological active substances and medicinal 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 active substances and medicinal products.

This annex, along with several other annexes of the PIC/S 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.

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

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

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

Guidance for medicinal products derived from fractionated human blood or plasma is covered in Annex 14 and for non-transgenic plant products in Annex 7.

In certain cases, other legislation may be applicable to the starting materials for biologicals. For example,

(a) Tissue and cells used as starting materials for medicinal products, donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells of tissue and cells may be covered by national legislation. Such tissues and cells may provide the active substances for some biological medicinal product within the scope of this annex at which point GMP and other medicinal product legislation requirements apply.

(b) Blood or blood components used as starting materials for medicinal products, national legislation may provide the technical requirements for the selection of donors, collection, testing, processing, storage, and distribution of human blood and blood components[1].

Additionally, the manufacture and control of genetically modified organisms needs to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified micro-organism is handled[2]. 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 2B

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunosera	Collection of plant, organ, animal material or fluid[3]	Cutting, mixing, and / or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[4], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling

1 In the EEA, this is Directive 2002/98/EC and its Commission Directives.

2 In the EEA, this is Directive 2009/41/EC on contained use of genetically modified micro-organisms.

3 See section B1 for the extent to which GMP principles apply.

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

4. Animal sources: transgenic	Recombinant proteins	Master and working transgenic bank	Collection, cutting, mixing, and/or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergens	Master and working transgenic bank	Growing, harvesting[5]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid[6]	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human sources	Products from cells and tissues, not classified as ATMPs	Donation, procurement and testing of starting tissue / cells[7]	Initial processing, isolation and purification.	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling

See Glossary for explanation of acronyms.

PRINCIPLE

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

Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity

[5] In the EEA: HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005 may be applied to growing, harvesting and initial processing in open fields.

[6] For principles of GMP apply, see explanatory text in 'Scope'.

[7] In the EEA, human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.

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

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

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation 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 active substances and medicinal products.

Biological medicinal products which incorporate human tissues or cells must comply with national requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.[8] Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable national requirements[9]. Furthermore, national requirements[10] on traceability apply from the donor (while maintaining donor confidentiality) through stages applicable at the Tissue Establishment and then continued under medicines legislation through to the institution where the product is used.

Biological active substances and medicinal products must comply with the applicable national guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

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[8] In the EEA, these are Directive 2004/23/EC and Directive 2006/17/EC.

[9] In the EEA, this is the Commission Directive 2006/86/EC.

[10] In the EEA, this is Directive 2006/86/EC.

PART A: GENERAL GUIDANCE

PERSONNEL

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

2. The health status of personnel should 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 and appropriate records kept. 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. Health monitoring of staff should be commensurate with the risk, medical advice should be sought for personnel involved with hazardous organisms.

4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where exposure to live micro-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 QRM 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 active substance, intermediate or finished product and the production step, bearing in mind the potential 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, yeasts, moulds, anaerobes, etc) where indicated by the QRM process.

6. Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. 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 processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses,) control measures should be put in place, including engineering and environmental controls on the basis of

QRM principles. These QRM principles should take into account the principles and guidance from the appropriate sections of Annex 1[11] when selecting environmental classification cascades and associated controls.

7. Dedicated production areas should be used for the handling of live cells. Dedicated production area should be used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).

8. Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective 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) Where production is characterised by multiple small batches from different starting materials, factors such as the health status of donors and the risk of total loss of product should be taken into account when considering the acceptance of concurrent working during development of the control strategy.

   (c) 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.

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

   (e) Environmental monitoring, specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, 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.

   (f) 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).

   (g) Campaign based manufacturing.

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

9. For finishing (secondary) operations[12], the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological medicinal 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 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.

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

11. 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 QRM principles, should be given to the use of single pass air systems.

12. 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. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings.

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

14. Primary containment[13] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

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

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

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

18. Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks

[12] Formulation, filling and packaging

[13] See main GMP Glossary on ‘Containment’.

of these raw materials 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

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 materials derived post-mortem and from establishments such as abattoirs: examples include, 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 substanceor medicinal productin 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 pharmacopoeial 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 national requirements on the protection of animals used for scientific purposes[14]. 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 cells.

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 information[15]. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements[16] in regards to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products.

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 medicinal products from cells and tissues where

[14] In the EEA, this is Directive 2010/63/EC.

[15] In the EEA, see Article 15 of Regulation 1394/ 2007.

[16] In the EEA, these are Directives 2002/98/EC and 2005/61/EC.

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, assume greater importance particularly for products, in respect of which final sterilisation is not possible. Where a CTA or MA 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 sterilisation 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 CTA or MA.

36. The donation, procurement and testing of human tissues and cells used as starting materials for biological medicinal products should be in accordance with national law requirements. [17] Traceability for human tissues and cells used as starting materials for biological medicinal products should be maintained from the donor to the batch of a finished medicinal product. Appropriate arrangements should be made between the manufacturer and the supplier of tissues and cells regarding the transfer of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the medicinal product manufactured therefrom.

(a) Their procurement, donation and testing is regulated in some countries[18]. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting material supplier management.

(b) Where such human cells or tissues are imported, they must meet equivalent national standards of quality and safety[19]. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation[20].

(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[21].

(d) Tissue and cells are released by the Responsible Person (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 Authorised Person.

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[17] In the EEA, this is Directive 2004/23/EC or for blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing.

[18] In the EEA, this is Directive 2004/23/EC and its Commission directives.

[19] In the EEA, they must be equivalent to those laid down in Directive 2004/23/EC.

[20] In the EEA, this is Directive 2006/86/EC.

[21] In the EEA, such processing steps, are under the scope of 2004/23/EC and the Responsible Person (RP).

37. (…)[22]

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[23], including control of compliance with national requirements for human cells.

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.

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

41. As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under appropriate GMP conditions. 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 all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented. For vaccines the requirements of pharmacopoeial monographs will apply[24].

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. Ensuring compliance with measures for the storage of different seeds and/or cells in the same area or equipment should

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[22] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

[23] In the EEA, this includes compliance with Directive 2004/23 EC for human cells.

[24] In the EEA, this is Ph Eur monograph 2005;153 "Vaccines for human use".

prevent mix-up and take into account the infectious nature of the materials to prevent cross contamination.

44. (…)[25]

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

[25] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

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 potential 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 sterilisation methods of columns should be defined.

60. Where irradiated equipment and materials are used, Annex 12 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 product of the contents on the immediate and outer packaging.

In the case of autologous products, 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.

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. (…) [26]

69. For cellular products, 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 detection 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 that does not permit release when sterility testing results are provided after 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

[26] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

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 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:

(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 Responsible Person.

(b) Assessment of the final analytical tests and other information available for final certification by the Authorised 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 PRODUCTS[27]

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[28] 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 Epizooties[29]). 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 stringent standards. Account should be taken of reports from national

[27] In the EEA, see also PhEur monograph requirements, 0333

[28] See PIC/S GMP Chapter 5.

[29] http://www.oie.int/eng/en_index.htm

regulatory organisations[30] which verify compliance with the requirements of food safety and quality, veterinary and plant health legislation.

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 PIC/S 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 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.

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.

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

[30] In the EEA, this is the Food and Veterinary Office http://ec.europa.eu/food/fvo/index_en.htm.

B.3 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.

B.4 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.

B.5 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-fragment (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 CTA or MA 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] should be taken into account when drawing up such criteria.

GLOSSARY

See Annex 2A

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[31] EMA, WHO or equivalent