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WHO GMP for Biological Products

Proposed replacement of: TRS 822, Annex 1

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the GMP Guidelines for Biological Products to a broad audience and to improve transparency of the consultation process.

These Guidelines were developed based on the outcomes and consensus of the WHO informal consultation convened in July 2014 with participants from national regulatory authorities, national control laboratories, manufacturers and academia researchers and comments from the public consultation on WHO website in 2015.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization. Written comments proposing modifications to this text MUST be received by 14 September 2015 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Dianliang Lei at email: leid@who.int.

The outcome of the deliberations of the Expert Committee on Biological Standardization will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).

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Recommendations published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these Recommendations may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Recommendations be made only on condition that modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the recommendations set out below.

Contents

1. Introduction

The source and methods employed in the manufacture of biological products for human use represent critical factors in shaping appropriate regulatory control. Biological products can be defined, therefore, largely by reference to their method of manufacture and their source. Biological products are derived from cells, tissues or microorganisms and reflect the inherent variability characteristics of living materials. The active substances in biological products are often too complex to be fully characterized by utilizing physico-chemical testing methods and may show a marked heterogeneity from one preparation and/or batch to the next. Consequently, special considerations are needed when manufacturing biological products in order to maintain the consistency of the quality of the product.

The Good Manufacturing Practices (GMP) for biological products, as an annex to GMP for pharmaceutical products, were adopted by the Expert Committee on Biological Standardization and were first published in the WHO Technical Report Series in 1992. The GMP for biological products have been recognized and used by regulators and industry since then. This revision reflects the considerable developments since that time and current perspectives regarding GMP for the manufacture of biological products *(1–12)*.

This document is intended to serve as a basis for establishing national guidelines for GMP. The main principles and recommendations for manufacturing biological products are provided. If a national regulatory authority (NRA) so desires, these guidelines may be adopted as definitive national requirements. It is possible that modifications to this document may be justified due to the risk–benefit balance and legal considerations in each authority. In such cases, it is recommended that any modification to the principles and technical specifications of these guidelines should be made only on the condition that the modifications ensure product quality, safety and efficacy that are at least equivalent to what is recommended in these guidelines.

2. Scope

These guidelines apply to the commercial manufacture, control and testing of biological products from starting materials and preparations, including seed lots, cell banks and intermediates, through to the finished products.

Manufacturing procedures within the scope of these guidelines include:

- growth of strains of microorganisms and eukaryotic cells;

- extraction of substances from biological tissues, including human, animal and plant tissues, and fungi;
- recombinant DNA (rDNA) techniques;
- hybridoma techniques; and
- propagation of microorganisms in embryos or animals.

Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA), and diagnostic agents for in vitro use, gene therapy, cell therapy, etc. The recommendations for manufacturing blood and plasma-derived products are covered by WHO's *Guidelines on good manufacturing practices for blood establishments (11)* and *Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (13).*

Table 1 provides further guidance about the scope of application of the current guidelines *(6)*. It should be noted that this table is illustrative and is not intended to describe the precise scope.

Table 1. Guidance on the scope of the current guidelines (illustrative)

Type and source of material	**Example products**	**Application of the guideline to steps in manufacture**			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, Advanced Therapy Medicinal Products (ATMPs), immunsera	Collection of plant, organ, tissue or fluid	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 and maintenance of MCB, WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology fermentation/cell culture	Recombinant products, mAbs, allergens, vaccines, gene therapy (viral and nonviral vectors, plasmids)	Establishment and maintenance of MCB, WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources:	Recombinant proteins, ATMPs	Master and working	Collection, cutting, mixing,	Isolation, purification and	Formulation, filling

transgenic		transgenic bank	and/or initial processing	modification	
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing and/or harvesting[1]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine-derived enzymes, hormones	Collection of fluid	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue/cells[1]	Manufacture vector, and cell purification and processing	Ex vivo genetic modification of cells, establish MCB, WCB or cell stock	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue/cells[1]	Establish MCB, WCB or cell stock	Cell isolation, culture purification, combination with noncellular components	Formulation, combination, filling
	Tissue engineered Products	Donation, procurement and testing of starting tissue/cells[1]	Initial processing, isolation and purification, establish MCB, WCB, primary cell stock	Cell isolation, culture, purification, combination with noncellular components	Formulation, combination, filling

The present guidelines do not lay down detailed recommendations for specific classes of biological products (e.g. vaccines). Therefore attention is directed to other specific guidance documents issued by WHO and, in particular, to recommendations to assure the quality, safety and efficacy of the specific product.[2]

[1] GMP guidelines, as described in this document, are not applied to this step. Other national regulations, requirements, recommendations and/or guidelines may apply, as deemed necessary by the NRA.

[2] See: http://www.who.int/biologicals/en/ (accessed 3 July 2015).

3. Glossary

Besides the terms defined in WHO's *Good manufacturing practices for pharmaceutical products: main principles (1)*, the definitions given below apply to the terms as used in this document. These terms may have different meanings in other contexts.

Active substance: A defined process intermediate containing the active ingredient, which is subsequently formulated with excipients to produce the drug product. This may also be referred to as a drug substance or active ingredient in other documents**.**

Adventitious agents: Contaminating microorganisms of the cell culture or source materials, including bacteria, fungi, mycoplasmas/spiroplasmas, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents, and viruses that have been unintentionally introduced into the manufacturing process of a biological product.

> The source of these contaminants may be from the legacy of the cell line, the raw materials used in the culture medium to propagate the cells (in banking, in production, or in their legacy), the environment, personnel, equipment or elsewhere.

Allergen: An allergen is a molecule capable of inducing an Immunoglobulin E (IgE) response and/or a Type I allergic reaction.

Antibodies: Proteins produced naturally by the B-lymphocytes that bind to specific antigens. Using rDNA technology, antibodies are also produced in other (continuous) cell lines. Antibodies may be divided into two main types – monoclonal and polyclonal antibodies – on the basis of key differences in their methods of manufacture.

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

Axenic: A single organism in culture which is not contaminated with any other organism.

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

Biohazard: Biological material considered to be hazardous to personnel, visitors and/or the environment.

Biological starting materials: Starting materials derived from a biological source that mark the beginning of the manufacturing process of a drug, as described in a marketing authorization or licence application, from which the active ingredient is derived either directly (e.g. plasma derivatives, ascitic fluid, bovine lung) or indirectly (e.g. cell substrates, host/vector production cells, eggs, viral strains).

Biosafety risk group: The containment conditions required for safe handling of organisms associated with different hazards, ranging from Risk roup 1 (lowest risk, no or low individual and community risk, unlikely to cause disease) to Risk Group 4 (highest risk, high individual and community risk, cause severe disease, likely to spread and no prophylaxis or treatment available).

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

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

Cell culture: The process by which cells are grown in vitro under defined and controlled conditions where the cells are no longer organized into tissues. Cell cultures are operated and processed under axenic conditions to ensure a pure culture absent of microbial contamination.

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

Containment: The concept of using a process, equipment, personnel, utilities, system or facility for containing product, dust or contaminants in one zone, preventing them from escaping and also from entering into another zone.

Continuous culture: Process by which the growth of cells is maintained by periodically replacing a portion of the cells and the medium so that there is no lag or saturation phase.

Cross-contamination: Contamination of a starting material, intermediate product or finished product with another starting material or product during production. In multi-product facilities, cross-contamination can occur throughout the manufacturing process, from generation of the master cell bank (MCB) and working cell bank (WCB) through to finishing.

Dedicated: Facility, personnel, equipment or piece of equipment used only in the manufacture of a particular product or a closely related group of products.

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.

Finished product: A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling. This may also be referred to as a finished dosage form, drug product, or final product in other documents.

Fermentation: Maintenance or propagation of microbial cells in vitro (fermenter). Fermentation is operated and progressed under axenic conditions to ensure a pure culture absent of contaminating microorganisms.

Harvesting: Procedure by which the cells, inclusion bodies or crude supernatants containing the unpurified active ingredient are recovered.

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

Inactivation: Removal or reduction to an acceptable limit of infectivity of microorganisms or detoxification of toxins by chemical or physical modification.

Master cell bank (MCB): A quantity of well-characterized cells of animal or other origin, derived from a cell seed at a specific population doubling level (PDL) or passage level, dispensed into multiple containers and stored under defined conditions. The master cell bank is prepared from a single homogeneously mixed pool of cells. In some cases, such as genetically engineered cells, the MCB may be prepared from a selected cell clone established under defined conditions. However, the MCB may not be clonal. The MCB is used to derive a working cell bank (WCB).

Monoclonal antibodies (mAbs): Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

Pharmaceutical quality system (PQS): Management system for directing and controlling a pharmaceutical company with regard to quality.

Polyclonal antibodies: Derived from a range of lymphocyte clones and produced in humans and animals in response to the epitopes on most "non-self" molecules.

Primary containment: A system of containment that prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or biological safety cabinets along with secure operating procedures.

Quality risk management (QRM): A systematic process for the assessment, control, communication and review of risks to the quality of pharmaceutical products across the product life cycle.

Reference sample: A sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf-life of the batch concerned.

Retention sample: A sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes (e.g. presentation, packaging, labelling, patient information leaflet, batch number, expiry date) should the need arise during the shelf-life of the batch concerned.

Seed lot: A quantity of live cells (prokaryotic or eukaryotic) or viruses which has been derived from a single culture (although not necessarily clonal), has a uniform composition and is aliquoted into appropriate storage containers from which all future products will be derived, either directly or via a seed lot system.

The following derived terms are used in these guidelines:

- Master seed lot (MSL)**:** a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well-characterized collection of cells or viruses of uniform composition. Also referred to as "master virus seed" (MVS) for virus seeds, "master seed bank", "master seed antigen" or "master transgenic bank" in other documents.
- Working seed lot (WSL): a cell or viral seed lot derived by propagation from the MSL under defined conditions and used to initiate production of vaccines on a lot-by-lot basis. Also referred to as "working virus seed" (WVS) for

virus seeds, "working seed bank", "working seed antigen" or "working transgenic bank" in other documents.

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

Starting materials: Any substances of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

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

Vaccine: A preparation containing antigens capable of inducing an active immune response for the prevention, amelioration or treatment of infectious diseases.

Working cell bank (WCB): A quantity of well-characterized cells of animal or other origin, derived from an MCB at a specific PDL or passage level, dispensed into multiple containers, and stored under defined conditions. The WCB is prepared from a single homogeneously mixed pool of cells (often, this is the MCB). One or more of the WCB containers is used for each production culture.

4. Principles and general considerations

The manufacture of biological products should be undertaken in accordance with the basic principles of GMP. The points covered by these guidelines should, therefore, be considered complementary to the general recommendations set out in the current WHO *Good manufacturing practices for pharmaceutical products: main principles (1)* and in other WHO documents related specifically to the production and control of biological products established by the WHO Expert Committee on Biological Standardization.[1]

The ways in which biological products are manufactured, controlled and administered require particular necessary precautions. Control of biological products (e.g. potency testing) can rarely be expressed in units of mass, but is determined through bioassays

[1] See http://www.who.int/biologicals/en/, accessed 3 July 2015.

which are themselves highly variable in predicting the physiological or therapeutic effects on humans, when compared to physico-chemical determinations. If bioassays can be replaced with immunological assays detecting discrete antigenic sites on representative components of the product, precision may be increased.

Therefore, a robust and consistent manufacturing process with adequate in-process controls is of greater importance in the manufacture of biological products because certain deficiencies may not be revealed by testing the finished product. The combination of variability in starting materials and the potential for subtle changes during the manufacturing process of biological products also requires emphasis on production consistency which becomes a special concern because of the need to link the consistency to original clinical trials documenting the product's safety and efficacy.

It is not possible for most biological active ingredients, including live attenuated bacteria and viruses, to be terminally sterilized by heat, gas or radiation. In addition, some products, such as certain live vaccines (e.g. whole cell pertussis, cholera), must maintain the viability and purity of the organisms, and this may prevent the use of common purification techniques or sterile filtration processes. For these axenic products, aseptic processing and mild purification procedures must be used throughout the manufacturing process.

Since starting materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, extraneous microbial contaminants have the opportunity to grow. Adventitious agents arising from starting materials, from facility-derived microorganisms and from contamination of product materials by operators, constitute another critical aspect of GMP for biological products which is aimed at preventing or reducing the risk of contamination of starting materials, intermediate bulks and finished products. The design of the processes, equipment, facilities and utilities, the sampling and the training of the operators are key considerations in preventing such contamination events.

Methods for inactivating viral and bacterial agents and their associated metabolites in manufacturing areas and on surfaces coming into contact with a product must be shown to be efficacious, reliable and consistent (i.e. validated). In addition, cleaning procedures and hygiene are extremely important in contamination control.

Because of the risks inherent in producing and manipulating pathogenic and transmissible microorganisms during production and testing of biological materials, GMP must prioritize the safety of the recipient to whom the biological product is administered, the safety of the operators during operations and the protection of the

environment. As a result, quality risk management (QRM) principles are particularly important for this class of products and should be used to develop the control strategy throughout all stages of manufacture so as to achieve consistency, minimize variability and reduce the opportunity for contamination and cross-contamination.

Biosafety considerations, should follow national guidelines and (if applicable and available) international guidelines. In most countries, regulation of GMPs and biosafety are governed by different institutions. Especially in the context of manufacturing of pathogenic biological products of Biosafety risk group 3 and 4, close collaboration between those institutions is required to assure that both, product contamination and environmental contamination levels are controlled within acceptable limits. Specific recommendations regarding containment are outlined in chapter 11.

5. Pharmaceutical quality system and quality risk management

Biological products, like any pharmaceutical product, should be manufactured in accordance with the requirements of a pharmaceutical quality system (PQS) based on a life-cycle approach. This should facilitate innovation and continual improvement, and should also strengthen the link between pharmaceutical development and manufacturing activities, as defined in WHO's *Good manufacturing practices for pharmaceutical products: main principles (1)*. Thus, special attention should be paid to raw material controls, change control, trend analysis and deviation management in order to ensure production consistency.

Operations in biological production and testing require specialized knowledge in view of the risks inherent in producing and manipulating pathogenic and transmissible microorganisms. As a result, QRM principles are particularly important for this class of materials and should be used to develop the control strategy across all manufacturing and control stages – including manufacture, quality control, quality assurance, storage and distribution activities, as described in *WHO guidelines on quality risk management (14)*, and the pharmaceutical quality system as described in Q10 guideline *(15)* of the International Conference on Harmonization (ICH). QRM will also contribute to identifying the probable causes of unwanted or unanticipated factors affecting the purity, potency, safety, efficacy and stability of the product, assessing the effectiveness of measures to reduce or manage such risks, and helping to identify critical product attributes and process control parameters during development and validation phases.

Different tools may be used for QRM of the manufacture and control of biological products, including – but not limited to – Hazard Analysis and Critical Control Point (HACCP) *(16)* and Failure Mode Effects Analysis (FMEA).

6. Personnel

6.1 Personnel working in areas where biological active substances and products are manufactured and tested should receive training and periodical retraining specific to their duties and to the products being manufactured – including any specific safety measures to protect the product, personnel and the environment. The efficacy of training should be documented.

6.2 Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines such as microbiology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology, biotechnology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.

6.3 Training in cleaning and disinfection procedures, hygiene and microbiology is particularly relevant to the production of biologicals because of the risk of microbial contamination due to the handling of microorganisms, growth media and adventitious organisms.

6.4 During a working day, personnel and visitors should not pass from areas with exposure to live microorganisms, genetically modified microorganisms, animal tissue, toxins, venoms or animals to areas where other products (inactivated or sterile) or different organisms are handled. If such passage is unavoidable, the contamination control measures (e.g. clearly defined decontamination measures, including a complete change of appropriate clothing and shoes, and showering if applicable) should be followed by all staff involved in any such production unless otherwise justified on the basis of QRM.

6.5 Personnel working in animal husbandry should be dedicated to the animal facility.

6.6 Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate vaccines and should have regular health checks. Apart from the obvious risk of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid or reduce the risk of contaminating a product with these agents.

6.7 Staff assigned to production of bacille Calmette-Guerin (BCG) vaccine and tuberculin products should not work with other infectious agents. In particular, they should not work with virulent strains of *M. tuberculosis*, nor should they be exposed to a known risk of tuberculosis infection. Additionally, they should be carefully monitored, with regular health checks including validated immunological blood assays and/or radiological examination.

6.8 Health monitoring of staff should be commensurate with the risk to the product and the personnel. Medical advice should be sought for personnel involved with or exposed to hazardous organisms.

7. Starting materials

7.1 The source, origin and suitability of starting materials (e.g. cryo-protectants, feeder cells, reagents, growth media, buffers, serum, enzymes, cytokines, growth factors, amino acids) should be clearly defined. Manufacturers should retain information describing the source and quality of the biological materials used for at least two years after the expiry date of the finished products produced from them.

7.2 All starting material suppliers (i.e. manufacturers) should be initially qualified on the basis of documented criteria and with a risk-based approach, and regular assessments of their status should also be carried out. When starting materials are sourced from brokers who could increase the risk of contamination by performing repackaging operations, the brokers should be carefully qualified; an audit may be a part of such qualification, as needed.

7.3 Incoming starting materials should be sampled – on the basis of justified criteria – under appropriate conditions in order to prevent contamination. The samples should be tested using pharmacopoeial or validated approved methods and released by the Quality Unit before use. By no means should the sampling process adversely affect the quality of the product, and particularly its sterility when applicable. The level of testing should be commensurate with the qualification level of the supplier and its continuous performance. However, at least an identity test, or equivalent, is required on each container unless justified on the basis of QRM principles and in agreement with all applicable guidelines.

7.4 Where the necessary tests for approving starting materials take a significantly long time, it may be permissible to process starting materials before the test

results are available. The risk of using not-yet-approved material on the quality of the product should be clearly justified in a documented manner, understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. It must be ensured that this is not common practice and occurs only exceptionally. The identification of all starting materials should be in compliance with the requirements appropriate to the stage of manufacture.

7.5 Where required, sterilization of starting materials should be carried out by heat where possible. Where necessary, other appropriate validated methods may also be used for this purpose (e.g. irradiation and filtration).

7.6 The risk of contamination of starting materials during their passage along the supply chain must be assessed, with particular emphasis on transmissible spongiform encephalopathy (TSE) *(17)*. Other materials that come into direct contact with manufacturing equipment and/or with potential product contact surfaces (such as filter media, growth media during aseptic process simulations, and lubricants) should also be controlled. A quality risk assessment should be performed to evaluate the potential for adventitious agents in biological starting materials.

7.7 The controls required for the quality of starting materials and on the aseptic manufacturing process (particularly for cell-based products, where final sterilization is generally not possible and the ability to remove microbial by-products is limited) assume greater importance and should be based on the principles and guidance contained in the current *WHO good manufacturing practices for sterile pharmaceutical products (2)* and on the section "Clean rooms" of the present document, as applicable.

7.8 The transport of critical materials, reference materials, drug substances, human tissues and cells to the manufacturing site must be controlled by a written quality agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions, including cold chain requirements. The continuation of traceability requirements – starting at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues – should be maintained.

8. Seed lots and cell banks

Recommendations set out in WHO's *Good manufacturing practices for active pharmaceutical ingredients*, Section 18 on Specific guidance for APIs manufactured by cell culture/fermentation *(3)* should be followed.

8.1 Where human or animal cells are used as feeder cells in the manufacturing process, appropriate controls over the sourcing, testing, transport and storage should be in place.

8.2 In order to prevent the unwanted drift of genetic properties which might result from repeated subcultures or multiple generations, the production of biological 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, which is the beginning of the manufacturing process of certain biological products (e.g. vaccines).

8.3 The number of generations (e.g. passages) between the seed lot or cell bank and the finished product, defined as maximum, should be consistent with the marketing auhorization dossier and should be followed.

8.4 Cell-based medicinal products are often generated from a cell stock obtained from a limited number of passages. In contrast with the two-tier system of MCBs and WCBs, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be covered by a validation protocol and communicated to the NRA, as applicable.

8.5 Establishment and handling of the MCBs and WCBs should be performed under conditions which are demonstrably appropriate. These should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling them. To establish the minimum requirements for clean room grade and environmental monitoring, see WHO's *Environmental monitoring of clean rooms in vaccine manufacturing facilities: points to consider for manufacturers of human vaccines, 2012 (18).* During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or microbial strains) should be handled simultaneously in the same area or by the same persons, as defined in WHO's *Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (19).*

8.6 Quarantine and release procedures for master and working cell banks/seed lots should be followed, including adequate characterization and testing for contaminants. Initially, full characterization testing of the MCB should be done, including genetic identification. A new MCB (from a previous initial clone, MCB or WCB) should be subjected to the same established testing as the original MCB, unless justified. Thereafter, the identity, viability and purity of seed lots and cell banks should be checked regularly according to justified criteria. In the case of anti-sera production, the potency of venoms is usually included as part of the testing. Evidence of the stability and recovery of the seed lots and banks should be documented and records should be kept in a manner that permits trend evaluation.

8.7 Each storage container should be adequately 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 should be monitored. Any deviation from the set limits, and any corrective and preventive action taken, should be recorded. Temperature deviations should be detected as early as possible (e.g. with the use of an alarm system for temperature and nitrogen levels).

8.8 Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination or alteration (e.g. stored in qualified ultra-low temperature freezers or liquid nitrogen storage containers). Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and should take into account the infectious nature of the materials in order to prevent cross-contamination.

8.9 MSLs, MCBs, and preferably also WSLs and WCBs, should be stored in two or more controlled separate sites in order to minimize the risks of total loss due to natural disaster, equipment malfunction or human error. A contingency plan should be in place.

8.10 The storage and handling conditions for the cell or seed banks should be defined. Access should be restricted to authorized personnel and controlled; appropriate records must be maintained. Records of location, identity and inventory of individual containers should be kept. Once containers are removed from the seed lot/cell bank management system, they should not be returned to stock.

9. Premises and equipment

9.1 In general, preparations containing live microorganisms should not be manufactured, and containers should not be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms, the use of multi-product facilities may be justifiable. When multi-product facilities involve live microorganisms, the manufacturer should demonstrate and validate effective decontamination of the previously-used live microorganisms. In addition, measures such as campaign production, closed systems and/or disposable systems should be considered and should be based on QRM (see sections on "Containment" and "Campaign production").

9.2 Documented QRM should be carried out for every additional product in a biological manufacturing multi-product facility, which may include a potency and toxicological evaluation based on cross-contamination risks. Other factors to be taken into account include facility/equipment design and use, personnel and material flows, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products. The outcome of the QRM process should be the basis for determining the necessity for premises and equipment to be dedicated to a particular product or product family and extent to which this should be the case. This may include dedicating specific product contact parts. The NRA should approve the use of a manufacturing facility for production of multiple products on case-to-case basis.

9.3 Killed vaccines, antisera and other biological products – including those made by rDNA techniques, toxoids and bacterial extracts – may, after inactivation, be manufactured on the same premises provided that adequate decontamination and cleaning measures are implemented on the basis of QRM.

9.4 Cleaning and sanitization require special attention since production of biological products usually involves the handling of growth media and other growth-promoting agents. Validation studies should be carried out for effective cleaning, sanitization and disinfection, including elimination of residues of used agents. Environmental and personnel safety precautions should be taken during the cleaning and sanitization processes. Use of cleaning and sanitizing agents should not pose any major risk to the performance of equipment; therefore reasonable, but not excessive, use of cleaning, sanitization and disinfection agents would be recommended.

Where open systems are utilized during processing (e.g. during addition of growth supplements, media, buffers, gasses, sampling and aseptic manipulations during the handling of live cells such as in cell therapy products), control measures should be put in place to prevent contamination, mix-up and cross-contamination. Logical and unidirectional flows of personnel, materials and processes, use of clean-in-place (CIP) and sterilize-in-place (SIP) systems should be considered wherever possible. Modern technologies such as the use of sterile single-use disposable systems, connectors or components are encouraged.

9.5 Because of the variability of biological products and the corresponding manufacturing processes, approved starting materials that have to be measured or weighed for the production process (e.g. growth media, solutions and buffers) may be kept in small stocks in the production area for a specified period of time according to defined criteria – such as for the duration of manufacture of the batch or of the campaign. Appropriate storage conditions and controls should be maintained during such temporary storage. These materials should not be returned to the general stock. Materials used to formulate buffers, growth media, etc. should be weighed and made into a solution in a contained area using local protection (e.g. classified weighing booth) outside the aseptic processing areas in order to minimize particulate contamination of the latter areas.

9.6 In manufacturing facilities, logically designed change rooms should be used to enter and exit clean areas where live organisms are handled. The mix-up of entry and exit of personnel should be avoided (e.g. by separate entry/exit change rooms).

10. Containment

10.1 Airborne dissemination of live microorganisms and viruses used for the production process, including those from personnel, should be avoided.

10.2 Adequate precautions should be taken to avoid contamination of the drainage system with dangerous effluents. Drainage systems should be designed in such a way that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination. Local regulations must be complied with in order to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

Specific decontamination systems should be considered for effluents when infectious and/or potentially infectious materials are used for production.

19.3 Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment, for pathogenic organisms of Biosafety Risk Group 3 or 4, and/or for spore-forming organisms until the inactivation process is accomplished and verified. For *Bacillus anthracis*, *Clostridium tetani* and *Clostridium botulinum*, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at any one time.

Use of any pathogenic organism above Biosafety Risk Group 3 may be permitted by the NRA according to the biohazard classification of the organism, the risk–benefit analysis of the biological product and its emergency demand.

10.4 Production of BCG vaccine should take place in a completely separated area and by means of dedicated equipment and utilities (e.g. ventilation systems) in order to eliminate the hazard of cross-contamination to other production/ manufacturing areas.

10.5 Specific containment requirements may apply for certain products (e.g. polio vaccine) where containment requirements are defined in accordance with the *WHO global action plan to minimize poliovirus facility-associated risk (20)* and WHO's *Guidelines for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses (21).* The measures and procedures necessary for containment (i.e. for the environment and safety of the operator) should not conflict with those for product quality.

10.6 Air-handling systems should be designed, constructed and maintained to minimize the risk of cross-contamination between different manufacturing areas, as required. The need for dedicated air-handling units or single-pass systems should be based on QRM principles, taking into account the relevant organisms' biohazard classification, containment requirements, process and equipment risk. In the case of Biosafety Risk Group 3 organisms, air should not be recirculated to any other area in the facility and should be exhausted through high-efficiency particulate air (HEPA) filters that are regularly checked for performance. A dedicated non-recirculating ventilation system and HEPA-filtered exhaust air should be provided for handling Biosafety Risk Group 4 organisms.

10.7 Primary containment equipment should be designed and initially qualified for integrity in order to ensure that the escape of biological agents and/or material into the immediate working area and outside environment is prevented. Thereafter, in line with relevant guidelines and QRM principles, periodical tests should be performed to ensure that the equipment is in proper working condition.

10.8 Activities associated with the handling of live biological agents (e.g. centrifugation and blending of products which can lead to aerosol formation) should be contained in such a way as to prevent contamination of other products or egress of live agents into the working and/or outside environment. The viability of such organisms and their biohazard classification should be taken into consideration as part of the management of such risks.

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 the strains vary significantly in their resistance to the agent(s) involved

10.9 Areas where Biosafety Risk Group 3 or 4 organisms are handled should always have a negative air pressure relative to the environment. This will ensure the containment of the organism in unlikely events such as failure of the door interlock. Air-lock doors should be interlocked to avoid their being opened simultaneously. Differential pressure alarms should be present wherever required, and should be validated and monitored.

10.10 Equipment air-vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at well-justified appropriate intervals.

10.11 Where filtration of exhaust air is necessary, safe changing of filters or bag-in-bag-out housings should be employed. Once removed, these filters should be decontaminated and properly destroyed. Other inactivation technologies such as heat inactivation and steam scavenging may be considered for exhaust air, in addition to HEPA filtration, for effective inactivation of pathogenic organisms of Biosafety Risk Groups 3 and/or 4.

11. Clean rooms

11.1 The *WHO good manufacturing practices for sterile pharmaceutical products (2)* defines and establishes the required class/grade of clean areas for the manufacture of sterile products according to the operations performed, including final aseptic fill. Additionally, in order to address the specific manufacturing processes involved in the production of biological products, and particularly vaccines, the WHO guidance document *Environmental monitoring of clean rooms in vaccine manufacturing facilities: points to consider for manufacturers of human vaccines (18)* gives additional recommendations for consideration when defining the environmental classification needed for typical biological manufacturing processes.

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 intermediate or finished product and also to the production step, taking into account the potential level of contamination of the starting materials and the risks to the biological product.

11.2 The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms used for production (e.g. recombinant yeast and toxin and polysaccharide producing bacterium). The environmental monitoring programme may also include detection of produced organisms (e.g. viruses or virus-like particles) and adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.

12. Production

12.1 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 to the control strategy for ensuring that there are effective steps for preventing or minimizing the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin, and associated metabolites.

12.2 The QRM process should be the basis for implementing the technical and organizational measures required to control risks of cross-contamination. These could include, though are not limited to, the following:

- carrying out processing and filling in segregated areas;
- containing material transfer by means of airlocks, clothing change and effective washing and decontamination of equipment;
- avoiding recirculation of untreated air;
- acquiring knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility;
- when considering the acceptability of concurrent work in cases where production is characterized by multiple small batches from different starting materials (e.g. cell-based products), taking into account factors such as the health status of donors and the risk of total loss of a product from or for specific patients during development of the cross-contamination control strategy;
- preventing live organisms and spores from entering non-related areas or equipment by addressing all potential routes of cross-contamination (e.g. through the heating, ventilation and air conditioning (HVAC) system, the use of single-use components and closed systems);
- conducting environmental monitoring specific to the microorganism being manufactured in adjacent areas while paying attention to cross-contamination risks arising from the use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore-forming organisms; and
- using campaign-based production (see section on "Campaign production").

12.3 When applicable, the inoculum preparation area should be designed such as to control the risk of contamination effectively and should be equipped with a biosafety hood for local containment.

12.4 If possible, growth media should be sterilized in situ by heat or in-line sterilizing filters. Additionally, retentive in-line filters should be used for routine addition of gases, media, acids or alkalis, etc., to fermenters or bioreactors.

12.5 Data from continuous monitoring of certain production processes (e.g. fermentation) should form part of the batch record. Where continuous culture is used, special consideration should be given to parameters such as temperature, pH, pO_2, CO_2 and the rate of feed or carbon source with respect to growth of cells.

12.6 In cases where a viral inactivation or removal process is performed, measures (e.g. related to facility layout, unidirectional flow and equipment) should be

taken to avoid the risk of recontamination of treated products by non-treated products.

12.7 For products that are inactivated by the addition of a reagent, the process should ensure the complete inactivation of the live organism (e.g. during vaccine manufacture). In addition to the adequate mixing of culture and inactivant, consideration should be given to assuring complete contact of all product contact surfaces exposed to live culture and, where required, the transfer to a second vessel.

12.8 A wide variety of equipment and components (e.g. resins, matrices and cassettes) are used for purification purposes. QRM principles should be applied to devise the control strategy regarding these pieces of equipment and associated components when used in campaign manufacture and in multi-product facilities. While the reuse of components at different stages of processing of one product is discouraged, the reuse of components for different products is not acceptable. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilization methods of reused components should be defined and validated.

12.9 Where donor (human or animal) health information becomes available after procurement and/or processing, and this information relates to product quality, appropriate measures should be taken – including product recall, if applicable.

12.10 Antibiotics may be used during the early stages of production to help prevent inadvertent microbial contamination or to reduce the bioburden of living tissues and cells. In this case, the use of antibiotics should be well justified and they should be removed from the manufacturing process at the stage specified in the marketing authorization. Acceptable residual levels should be defined and validated. Beta-lactam antibiotics should not be used at any stage of the process.

13. Campaign production

13.1 The decision to use a facility or filling line for campaign manufacture should be justified in a documented manner and should be based on a systematic risk approach for each product (or strain), taking into account the containment requirements and the risk of cross-contamination to the next product. Campaign changeover procedures, including sensitive techniques used for the determination of residues, should be validated and proper acceptance criteria should be defined on the basis of toxicity residues of product from the last

campaign, as applicable. Where equipment is assigned to continued production or campaign production of successive batches of the same intermediate product, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. product degradants or objectionable levels of microorganisms).

13.2 For downstream operations of certain products, campaign production may be acceptable if well justified (e.g. pertussis, diphtheria). For finishing operations (i.e. formulation and filling), the need for dedicated facilities or the use of campaigns in the same facility will depend on the specific needs of the biological product, on the characteristics of the other products (including any nonbiological products), on the filling technologies used (e.g. single-use closed systems), and on local NRA regulations. Labelling and packaging operations can be done in a multi-product facility.

13.3 Campaign changeover involves intensive cleaning and decontamination of the equipment and manufacturing area. The decontamination and cleaning should include all equipment and accessories used during production, as well as the facility itself. The following recommendations should be considered:

- Waste should be removed from the manufacturing area or sent to the bio-waste system in a safe manner.
- Materials should be transferred by a validated procedure.
- The Quality Unit should confirm area clearance by inspection, along with a review of the campaign changeover data (including monitoring results), prior to releasing the area for the next product.

13.4 When required, the corresponding diluent for the product can be filled in the same facility in line with the defined campaign production strategy.

13.5 When campaign-based manufacturing is considered, the facility layout and the design of the premises and equipment should permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.

14. Labelling

14.1 The information provided on the inner label (on the container) and on the outer label (on the package) should be readable, legible and approved by the NRA.

14.2 Minimal key information should be printed on the inner label (also called the container label), and additional information should be provided on the outer label (e.g. carton) and/or product leaflet.

Special consideration should be given to the following information on labels of vaccines, if applicable:

- the nature and amount of any preservative present in the vaccine;
- the nature and amount of the adsorbing agent;
- a warning that the vaccine should not be frozen, cold chain requirements and Vaccine Vial Monitor (VVM) labelling; and
- a warning that the vaccine should be shaken before use.

14.3 Care should be taken and utmost security ensured in the preparation, printing, storage and application of labels – including any specific text for patient-specific products, indicating the use of genetically-engineered contents on outer packaging. In the case of a cell therapy product used for autologous use, the unique patient identifier and the statement "For autologous use only" should be indicated on the outer packaging or, where there is no outer packaging, on the immediate packaging.

14.4 The compatibility of labels for ultra-low storage temperatures, where such temperatures are used, should be verified. The label should remain properly attached to the container under different storage conditions and should have no adverse effect on the quality of the product by leaching, migration and/or other means.

15. Validation

Biological processes, handling of live materials and usual campaign-based production, if applicable, are the major aspects of biological products which require process and cleaning validation. The validation of such processes – in view of the typical existing variability of biological products, possible use of harmful and toxic materials and inactivation processes – plays an important role in demonstrating production consistency and in proving that the critical process parameters and product attributes are controlled. A QRM approach should be used to determine the scope and extent of validation.

15.1 All critical biological processes (e.g. inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation, aseptic filling, etc.), as applicable, are

subject to process validation. Manufacturing control parameters to be validated may include specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure, containment and cleaning procedures.

15.2 After initial process validation studies have been finalized and routine production has begun, a "continued process verification" *(22)* approach should be defined, taking into consideration the inherent variability of biological products. A system or systems for detecting unplanned departures from the process as designed should be in place to ensure that the process remains in a state of control. Collection and evaluation of information and data on the performance of the process will allow for detection of undesired process variability and will determine whether action should be taken to prevent, anticipate and/or correct problems so that the process remains in control.

15.3 Cleaning validation should be performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances, growth media, process reagents, etc. Careful consideration should be given to cleaning validation when campaign-based production is practised.

15.4 Critical processes for inactivation or elimination of potentially harmful microorganisms of Biosafety Risk Group 2 or above, including genetically modified ones, are subject to validation.

15.5 Where they exist, WHO guidance documents should be consulted on the validation of specific manufacturing methods (e.g. virus removal or inactivation).

15.6 Process revalidation may be triggered immediately by a process change, as part of the change control system. In addition, because of the variability of processes, products and methods, process revalidation may be conducted at predetermined regular intervals according to risk considerations. A detailed review of all changes, trends and deviations occurring within a defined time period (e.g. 1 year, based on the regular Product Quality Review) may require process revalidation.

15.7 The integrity and specified hold times of containers used to store intermediate products should be validated unless such intermediate products are freshly prepared and used immediately, as appropriate.

16. Quality control

16.1 As part of quality control sampling and testing procedures for biological materials and products, special consideration should be given to the nature of the materials being sampled in order to ensure that the testing carried out is representative.

16.2 Samples may fall into two categories – reference samples and retention samples – for the purposes of analytical testing and identification, respectively. For finished products, in many instances the reference and retention samples will be presented identically – i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

16.3 Reference samples of biological starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Reference samples of other starting materials (other than solvents, gases and water), as well as intermediates of which critical parameters cannot be tested in the final product, should be retained for at least two years after the release of the product if their stability allows this storage period. Certain starting materials such as components of growth media need not necessarily be retained. When a change of vendor is needed, as appropriate, an impurity profile comparison should be done as part of the relevant risk analysis.

16.4 Retention samples of a finished product should be stored in the final packaging under the recommended storage conditions for at least one year after the expiry date.

16.5 For cell-based products, microbiological tests (e.g. sterility test or purity check) should be conducted on cultures of cells or cell banks free of antibiotics and other inhibitory substances in order to provide evidence for absence of bacterial and fungal contamination and to be able to detect fastidious organisms where appropriate. Where antibiotics are used, they should be neutralized or removed by filtration at the time of testing.

16.6 The traceability, proper use and storage of reference standards should be ensured, defined and recorded. The stability of reference standards should be monitored, and their performance trended. WHO's Recommendations for the preparation, characterization and establishment of international and other biological reference standards (23) should be followed.

16.7 All stability studies – including real-time/real-condition stability, accelerated stability and stress-testing – should be carried out according to relevant guidelines (e.g. WHO's Guidelines on stability evaluation of vaccines (24), or other recognized documents). Trend analysis of test results of the stability monitoring programme should assure early detection of any process or assay drift, and this information should be part of the product quality review (PQR) of biological products.

16.8 For products where ongoing stability monitoring would normally require testing using animals, and no appropriate alternative or validated techniques are available, the frequency of testing may take into account a risk–benefit approach. The principle of bracketing and matrix designs may be applied if scientifically justified in the stability protocol.

16.9 Methods suitable for the quality control of biological starting materials, critical intermediates and finished products should be used. In particular, for biological products manufactured in multi-product facilities, methods should be in place to address cross-contamination risks, if any.

16.10 All analytical methods used in the quality control of biological products should be well characterized, fully validated and documented to a satisfactory standard in order to yield reliable results. The fundamental parameters of this validation include accuracy, precision, selectivity, sensitivity and reproducibility (25–29).

16.11 In general, animal tests performed for quality control release are well described in the relevant pharmacopoeias and in WHO guidance documents (25–29). Animal potency tests are designed with multiple or single dilutions and replicates to address variability and linearity. These tests are performed in comparison with international/national reference standards and with appropriate assay controls. For test methods described in relevant monographs, only a qualification of the laboratory test equipment and personnel has to be performed. In addition to this, repeat precision and comparability precision have to be shown in the case of animal tests. Repeatability and reproducibility can also be demonstrated by reviewing retrospective test data.

In addition to the common parameters typically used for validating assays (e.g. accuracy, precision, etc.), additional measurements should be considered during the validation of bioassays based on the biological nature of the assay and reagents used.

17. Documentation (batch processing records)

17.1 In general, the processing records of regular production batches must provide a complete account of the manufacturing activities of each batch of biological products, showing that it has been produced, tested and dispensed into containers in accordance with the approved procedures.

In the case of vaccines, a batch processing record and a summary protocol should be prepared for each batch for the purpose of lot release by the NRA. The information included in the summary protocol should follow WHO's *Guidelines for independent lot release of vaccines by regulatory authorities (30)*. The summary protocol and all associated records should be of a type approved by the NRA.

Records should be retained for at least two years after the expiry date of the batch of the biological product and should be available at all times for inspection by the NRA.

17.2 Starting materials and raw materials may require additional documentation on source, origin, distribution chain, method of manufacture and controls applied in order to ensure an appropriate level of control, including microbiological quality, if applicable.

17.3 Some product types may require specific definition of what materials constitute a batch – particularly somatic cells in the context of Advanced Therapy Medicinal Products (ATMPs). For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

18. Use of animals

A wide range of animals may be used for the manufacture or quality control of biological products. Special considerations are required when animal facilities are present at a manufacturing site. Areas used for processing animal tissue materials and for performing tests involving animals or microorganisms, including breeding, must be completely separated from premises used for manufacturing products and should have completely separate ventilation systems and separate staff. No animals should be used in the production area. Separation of different animal species before (quarantine/test) and under test

should be considered, as should the necessary animal acclimatization process as part of the test requirements.

18.1 Animals may be used for different purposes. They may be categorized as:

- animals used for organ extraction (e.g. kidney);
- animals used for body fluids extraction (e.g. serum);
- animals for breeding; and
- animals for testing.

18.2 In addition to monitoring of compliance with TSE regulations *(17)*, other adventitious agents that are of concern (e.g. zoonotic diseases, diseases of source animals) should also be monitored and recorded in line with specialist advice on 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 (e.g. in manufacture, as sources of starting and raw materials, in quality control and safety testing). Decisions should be documented.

18.3 A look-back procedure should be in place related to the decision-making process on the continued suitability of the biological active substance or medicinal product in which animal-sourced starting or raw materials have been used or incorporated. This decision-making process may include the retesting of retention 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 should be utilized in determining the removal of those animals from the programme for defined periods.

18.4 Particular care should be taken to prevent and monitor infections in source/donor animals. Measures should include, and be related to, the sourcing, facilities, husbandry, biosafety procedures, testing regimes, control of bedding and feed materials, 100% fresh air supply, appropriate temperature and humidity conditions considering the species being handled, and water supply. This is of special relevance to specific pathogen free (SPF) animals where pharmacopoeial monograph requirements must be met. Housing and health monitoring should also be defined for other categories of animals (e.g. healthy flocks or herds).

18.5 For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals. Note should be taken of national requirements for animal quarters, care and quarantine.

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

18.7 Animals, biological agents and tests carried out should be appropriately identified to prevent any risk of mix-up and to control all identified hazards.

18.8 The facility layout should ensure a unidirectional and segregated flow of healthy animals, inoculated animals and waste decontamination areas. Personnel and visitors should also follow a defined flow in order to avoid cross-contamination.

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Authors and acknowledgements

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