WHO GMP for Biological Products

Proposed replacement of: TRS 822, Annex 1
(3rd Draft Version 2, 18FEB2015)

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, vaccine manufacturers and academia researchers.

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 31 March 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 the 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.
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Introduction

The source and methods employed in the manufacture of biological products for human use represent critical factors in shaping the appropriate regulatory control. Biological products can be defined therefore, largely by reference to their method of manufacture and source. Biological products are derived from cells, tissues, or microorganisms and reflect the inherent variability characteristic of living materials. The drug 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 to the next. Therefore, special considerations should be taken in manufacturing biological products to maintain the consistency of the quality of product.

The Good Manufacturing Practices (GMP) for biological products as an annex to GMP for pharmaceutical products was adopted by the Expert Committee on Biological Standardization (ECBS) and published in the WHO Technical Report Series (TRS) in 1992. It has been recognized and used by regulators and industry. This revision reflects the considerable developments and current perspectives of GMP for the manufacture of biological products (1-12).

This document is intended to serve as a guide for establishing national guidelines for GMP. The main principles and requirements for manufacturing biological products are provided. If an 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 risk-benefit and legal considerations to each national regulatory authority (NRA). In such case, it is recommended that modification to the principles and technical specification of these guidelines be made only on the condition that the modifications ensure product quality, safety and efficacy at least equivalent to that in these guidelines.

Scope

This guidance document applies to the commercial manufacture and testing of biological products from quality of starting materials and preparations, including control over seed lots, cell banks and intermediates, through finished product and testing.

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, plant tissues and fungi (allergens);
- recombinant DNA (rDNA) techniques;
- hybridoma techniques;
- 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\(^{(\ast)}\), 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 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 the recommendations to assure the quality, safety and efficacy of the specific product (http://www.who.int/biologicals/en/).

**Glossary**

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

**Adjuvant**: Substances or combinations of substances that are used in conjunction with a vaccine antigen to enhance (e.g., increase, accelerate, prolong and/or possibly target) or modulate a specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine.

**Adventitious virus**: Unintentionally introduced contaminant virus.

**Allergen**: An allergen is a molecule capable of inducing an IgE response and/or a Type I allergic reaction, meaning, mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated).

**Antibody**: Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may be divided into two main types, monoclonal and polyclonal antibodies, based on key differences in their method of manufacture.

**Antigens**: The active ingredient in a vaccine against which the immune response is induced. Antigens may be live attenuated or inactivated preparations of bacteria, viruses or parasites; crude cellular fractions or purified antigens, including recombinant proteins (i.e. those derived from recombinant DNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; venoms;

synthetic antigens; polynucleotides (such as plasmid DNA vaccines); or living vectored cells expressing specific heterologous antigens.

**Bioburden:** The level and type (i.e. objectionable or not) of micro-organisms present in raw materials, media, biological substances, intermediates or finished products.

**Bio-Hazard:** Biological material considered to be hazardous to personnel, visitors and/or the environment.

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

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

**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, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

**Cell Culture:** Maintenance or propagation of mammalian, human, or insect cells *in vitro* (bioreactor). Cell cultures are operated and processed under axenic conditions to ensure a pure culture absent of microbial contamination.

**Cell stock:** 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.

**Clean area:** An area maintained and controlled to prevent contamination of pharmaceutical products with microorganisms or foreign substances, in compliance with defined particle and microbiological cleanliness standards.

**Cleaning Procedures Validation:** A challenge study designed to prove that the cleaning methods of product contact equipment/surfaces are effective based on
determining the most difficult to clean equipment/product (“worst case”), a certain allowable level of a selected residue and the analytical methodology.

**Containment:** A process, equipment, system or facility to contain product, dust or contaminants in one zone, preventing it from escaping but also entering to another zone.

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

**Cross-Contamination:** Contamination of a drug or biological starting material or in-process intermediate with another drug or biological starting material or in-process intermediate. 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 finishing.

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

**Drug Product** (dosage form, finished product, or final product): A pharmaceutical product type that contains a biological drug substance, generally in association with excipients. It corresponds to the dosage form in the immediate packaging intended for marketing.

**Drug Substance:** A defined process intermediate containing the active ingredient, which is subsequently formulated with excipients to produce the drug product.

**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 tumour 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):** An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive a
Working Cell Bank (WCB). The testing performed on a new MCB (from a previous initial clone, MCB or WCB) should be the same as for the MCB unless justified.

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

**Pharmaceutical Quality System:** Management system to direct and control a pharmaceutical company with regard to quality.

**Polyclonal antibodies:** Derived from a range of lymphocyte clones, produced in human 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 safety biological cabinets along with secure operating procedures.

**Quality Risk Management:** Quality risk management is a systematic process for the identification, assessment and control of risks to the quality of pharmaceutical products across the product lifecycle.

**Raw materials:** A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates, Bulk Drug Substance, APIs or final products.

**Risk Group:** The containment conditions required to safely handle organisms of different hazards ranging from Risk Group 1 (lowest risk, no or low individual and community risk) to Risk Group 4 (highest risk, high individual and community risk).

**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.

**Starting materials:** Materials that mark the beginning of the manufacturing process, as described in a market authorization or product license. Generally, starting material refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element(s) to the active substance (examples for vaccines: synthetic peptides, synthetic glycans and starting materials for adjuvants). The starting material for an antigen (drug substance) obtained from a biological source is considered to consist of: 1) cells; 2) microorganisms; 3) plants, plant parts, macroscopic fungi or algae; or 4) animal tissues, organs or body fluid from which the antigen (drug substance) is derived.
Vaccine: Preparation containing antigens capable of inducing an active immune response for the prevention, amelioration or treatment of infectious diseases.

Working Cell Bank (WCB): Cell bank prepared from aliquots of a homogenous suspension of cells obtained from culturing the fully characterized Master Cell Bank under defined culture conditions.

Principles and general consideration

The manufacturing 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 GMP 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 (ECBS) (http://www.who.int/biologicals/en/).

The ways in which biological products are manufactured, controlled and administered require particular precautions necessary. Potency of biological products can rarely be expressed in units of mass, but determined through bioassays which are themselves highly variable and often not predictive of the physiological or therapeutic effects on humans. When bioassays can be replaced with immunological assays detecting very discrete antigenic sites on representative components of the product, precision may be increased.

Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinations. 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 calls for emphasis on production consistency which becomes a special concern with the need to link the consistency to original clinical trials documenting the product's safety and efficacy.

It is not possible for some biological active ingredients including live attenuated bacteria and viruses, to be terminally sterilized by heat, gas, or radiation. In addition, the efficiency of standard purification techniques or even sterile filtration may not be possible due to the size and complexity of certain biological active ingredients (e.g., whole cell pertussis, cholera), thus requiring a aseptic processing and mild purification procedures 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, constitutes another critical aspect of GMP for biological products aimed at preventing or reducing the risk of contamination of starting materials, intermediate bulks, and finished products. The design of the processes, equipment, facilities, utilities, sampling and training of the operators are key considerations to prevent such contamination events.

Methods for inactivating viral and bacterial agents and their associated metabolites from manufacturing areas and surfaces coming into contact with a product must be shown to be efficacious, reliable, and consistent (i.e., validated). In addition, there is a significant importance of cleaning procedures and hygiene as part of contamination control.

Due to 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 administered with the biological product, 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 across all stages of manufacture so as to achieve consistency, to minimize variability and to reduce the opportunity for contamination and cross-contamination. Risk assessment 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.

Personnel

1. Personnel working in areas where biological active substances and products are manufactured and tested should receive training and periodic retraining specific to their duties and to the products being manufactured, including any specific security measures to protect the product, personnel and the environment.

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

4. During a working day, personnel and visitors should not pass from areas with exposure to live micro-organisms, 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.

5. Personnel working in animal husbandry should be dedicated.

6. 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. 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 contamination of a product with these agents.

7. Production of bacille Calmette-Guerin (BCG) vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular health checks to include immunological status or chest X-ray.

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

**Starting and Raw Materials**

1. The source, origin and suitability of starting and raw materials (e.g., cryo-protectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors and 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 products produced from them.

2. All starting and raw material suppliers should be initially qualified based on a documented criteria and based on a risk based approach, including regular assessments of their status. When materials are sourced from third parties (e.g., brokers, who could increase the risk of contamination, especially if repackaging is performed), both brokers and material manufacturers should be qualified and audited as needed.
3. Incoming starting and raw materials should be sampled under appropriate conditions (e.g., Class A air supply) and based on justified criteria, tested using Pharmacopoeial or validated approved methods and released by the Quality Unit before use. The level of testing should be commensurate to the qualification level of the supplier and its continuous performance, however, at least an identity test is required on each container. Certificate of analysis could be used to replace some testing, if appropriately justified. However, reduced testing may not be applicable to some biological materials because of the inherent variability in range and nature of biological starting materials.

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 non approved material on the quality of the product should be clearly justified in a documented manner, understood and assessed under the principles of Quality Risk Management (QRM). In such cases, release of a finished product is conditional on satisfactory results of these tests. It must be assured that this is not a common practice and only occurs exceptionally. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture.

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

6. The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on Transmissible Spongiform Encephalopathy (TSE) (13). Other materials that come into direct contact with manufacturing equipment or the product (such as growth media during aseptic process simulations, and lubricants) must also be controlled.

7. The controls required for the quality of starting and raw 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 this guideline, as applicable.

8. 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.

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 including cold chain requirements and traceability.

10. Preparations extracted or purified from animal blood, bone, or tissues, such as peptides and proteins, lipids, nucleic acids, enzyme preparations, virus or bacteria should be purified in such a way as to prevent contamination; the removal process should be demonstrated through validation studies. A risk assessment should be determined to evaluate the potential for adventitious agents in biological starting and raw materials. Labile biological starting and raw materials should be free of adventitious agents (e.g., bacterial and fungal agents, cultivatable and non-cultivatable mycoplasmas, mycobacteria and viruses) of the species from which they are derived. WHO 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 should be considered for these products (14).

Seed Lots and Cell Banks

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

1. In order to prevent the unwanted drift of genetic properties which might ensue 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 actually the beginning of the manufacturing process of certain biological products (e.g., vaccines).

2. The number of generations (e.g., passages) between the seed lot or cell bank and the finished product should be consistent with the MA dossier and followed.

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

4. Establishment of seed lots and cell banks, including master and working generations, should be performed under conditions which are demonstrably appropriate. This 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 air grade and environmental monitoring see WHO Environmental Monitoring of Clean Rooms in Vaccine Manufacturing Facilities - Points to consider for manufacturers of human vaccines, 2012 (15). 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 Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (16).

5. 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 shall be done including genetic identification. Thereafter, the identity, viability and purity of seed lots and cell banks should be regularly checked 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 permitting trend evaluation.

6. 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 using calibrated instruments and where used, the liquid nitrogen level should be monitored. Any deviation from 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 level).

7. 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 take into account the infectious nature of the materials to prevent cross contamination.

8. Both master and working seed lots and cell banks should be stored in two or more controlled separate locations within the facility or at a separate site in order to minimize the risks of total loss due to natural disaster, equipment malfunction or human error.

9. 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. Record 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.

Premises and Equipment

1. Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may, after inactivation, be manufactured on the same premises as other sterile products provided that adequate decontamination and cleaning measures are implemented based on quality risk management.

2. Cleaning and sanitization requires special attention to the fact that production of biological products usually involves the handling of culture media and other growth promoting agents. Consideration may be given to decontamination of manufacturing areas with gaseous sterilants such as chlorine dioxide or hydrogen peroxide.

3. Where processes are not closed (e.g., during additions of supplements, media, buffers, gases and manipulations during the manufacture of cell therapy products) control measures should be put in place, including engineering and environmental controls on the basis of QRM principles.

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

5. Wherever possible, the use of 'clean in place' and 'sterilization in place' systems, steam sterilizable valves on fermentation vessels and sterile single use disposable connectors should be used for aseptic connections to avoid exposure to the environment and to human intervention, thus reducing the contamination risk.

6. Due to the variability of biological products and corresponding manufacturing processes, approved starting materials that have to be measured or weighed for the production process (e.g., culture media and buffers) may be kept in small stocks in the production area for a specified period of time based on defined criteria such as for the duration of manufacture of the lot or of the campaign, provided that they are not returned to the general stock assuring proper inventory traceability and control. Otherwise, materials used to formulate buffers, culture media, etc., should be weighed and put into a solution in a contained area outside the purification and aseptic areas in order to minimize particulate contamination of the product.

7. In manufacturing facilities, separate changing rooms for entering and leaving clean areas where live organisms are handled should be used.
**Containment**

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

2. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Drainage systems must be designed so that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination. Local regulations must be complied with 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 potentially infectious materials are used for production.

3. Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment and for pathogenic organisms (i.e. Risk group 3 and 4 or 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.

4. Production of BCG vaccine shall take place in a completely separated area and by means of dedicated equipment and utilities. The hazard of cross-contamination to other production/manufacturing areas should be reduced to a minimum by use of a proper dedicated ventilation system.

5. Specific containment requirements may apply (e.g., Polio vaccine containment requirements as per WHO global action plan to minimize poliovirus facility-associated risk (GAP III) (17)) and WHO Guidelines for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses (18). 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.

6. Air handling units should be designed, constructed and maintained to minimize the risk of cross-contamination between different manufacturing areas as required and may need to be dedicated for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems. In the case of organisms in a group above Biosafety Risk Group 2, air should not be recirculated and it shall be exhausted through HEPA filters that are regularly checked for performance.

7. Primary containment equipment should be designed and initially qualified and validated for integrity to ensure the prevention of the escape of biological agents
into the immediate working environment. Thereafter, based on relevant guidance and QRM, periodic tests should be performed on the primary containment equipment to ensure proper working conditions.

8. Activities in handling live biological agents must be performed in such a way to prevent contamination of other products or egress of live agents into the work environment or the outside environment. The viability of such organisms and their biological classification should be taken into consideration as part of the management of such risks.

9. Areas above Biosafety Risk Group 2 should always have a negative differential pressure versus any adjacent non-biocontained areas. This will ensure that in the unlikely event that both air lock doors are opened simultaneously, air will flow from the non-biocontained area to the biocontained area. Differential pressure alarms should be present.

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

11. HEPA filters from air handling units should have a containment system to safely remove the filter and thus, avoid exposure to operator and the environment in non-controlled areas (i.e., a bag in bag out system). Once removed, these filters should be decontaminated and properly destroyed.

**Clean Rooms**

1. The WHO *GMP for Sterile Pharmaceutical Products* (2) defines and establishes the required level of air grade classification according to the operations performed for injectable products including final aseptic fill. Additionally, in order to address the specific manufacturing processes involved in the production of biological products, the WHO guidance document, *Environmental Monitoring of Clean Rooms in Vaccine Manufacturing Facilities - Points to consider for manufacturers of human vaccines* (15), gives additional recommendations to be considered when defining the environmental classification needed for typical biological manufacturing processes.

2. With the exception of aseptic preparation, all processing of biological products prior to the final fill of a drug product should be, at minimum, maintained in a low bioburden environment. Additional controls should be taken as appropriate, when open manipulation of the product is performed.
3. 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 the production step, considering the potential level of contamination of the starting materials and the risks to the biological product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific host microorganisms (i.e., yeast, moulds, anaerobes, etc.) where indicated by the QRM principles.

Production

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 to ensure there are effective steps to prevent or minimize the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin and associated metabolites.

2. The principle of campaign manufacturing in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. Detailed recommendations on campaign production are given in the section Campaign Production of this document.

3. The inoculum preparation area shall be designed such as to effectively control the risk of contamination and should be equipped with a biosafety hood for local containment.

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

5. Data from continuous monitoring of some production processes (e.g., fermentation) should form part of the lot record. Where continuous culture is used, special consideration to parameters such as temperature pH, pO₂, CO₂, and the rate of feed or carbon source with respect to growth of cells should be given for this type of production method.

6. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimize cross-contamination is necessary. 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 they vary significantly in their resistance to the agent(s) involved.
7. Cross-contamination should be prevented by adoption of some or all of the following measures:

- processing and filling in segregated areas;
- containing material transfer by means of airlocks, clothing change and effective washing and decontamination of equipment;
- avoid recirculation of untreated air, or re-entry of extracted air;
- prevent aerosol formation (especially by centrifugation and blending);
- acquire knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g., pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility;
- where production is characterized by multiple small lots from different starting materials (e.g., cell-based products), factors such as the health status of donors and the risk of total loss of a product from or for specific patients should be taken into account when considering the acceptance of concurrent work during development of the control strategy;
- prevent live organisms and spores from entering non-related areas or equipment by addressing all potential routes of cross-contamination, the HVAC system, the use of single use components and closed systems;
- conduct environmental monitoring specific for the micro-organism being manufactured in adjacent areas. Attention should also be given 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;
- use of campaign based production (see section on Campaign production section).

8. To avoid contamination by spills or aerosols of potentially hazardous organisms, production and control materials (including paper based documents) must be adequately decontaminated.

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

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

11. A wide variety of equipment is used for chromatography. QRM principles should
be used to devise the control strategy on chromatographic columns, ultrafiltration
or diafiltration cassettes, housings and associated equipment when used in
campaign manufacture and in multi-product environments. The re-use of the same
column at different stages of processing of one product is discouraged and the
re-use of the same column for different products is not acceptable. Acceptance
criteria, operating conditions, regeneration methods, life span and sanitization or
sterilization methods of columns should be defined and validated.

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

13. Reduction in bioburden associated with the procurement of living tissues and
cells may require the use of other measures such as antibiotics at early
manufacturing stages. In this case, their use should be justified and they should
be removed from the manufacturing process at the stage specified in the MA.
Acceptable residual levels should be defined and validated. Betalactam based
antibiotics should not be used during any stage of the process.

Campaign Production

1. For finishing (i.e., formulation, filling) operations, the need for dedicated
facilities or the use of campaigns in the same facility will depend on consideration
of the specific needs of the biological product; on the characteristics of other
products including any non-biological products; on fill technologies used; single
use-closed systems and on local NRA regulations. Packaging operations can be
done in a multiproduct facility.

2. The decision to use a facility or filling line on a campaign basis should be
justified in a documented manner and based on a systematic risk approach for
each product (or strain) considering the containment requirements and the
contamination risk and carry over to the next product. Campaign change
procedures, including sensitive techniques used for the determination of residues
shall be validated and proper acceptance criteria based on toxicity shall be
defined. Where equipment is assigned to continuous production or campaign
production of successive lots of the same intermediate, equipment should be
cleaned at appropriate intervals to prevent build-up and carry-over of
contaminants (e.g., degradants or objectionable levels of microorganisms).
3. Campaign changeover involves intensive cleaning and decontamination of the manufacturing area. The decontamination and cleaning should include all equipment and accessories used during production and the facility. It should consider the following recommendations:

- all waste is removed from the manufacturing area or sent to the bio-waste system in a safe manner;
- equipment is decontaminated and cleaned;
- the area and processing equipment is effectively decontaminated, cleaned, and sterilized (if applicable);
- as required, product and materials should be transferred by a validated transfer procedure;
- a Quality Control and Quality Assurance unit shall review the campaign changeover data (including monitoring results) and an area inspection is executed prior to releasing the area for the next product.

4. When required, the corresponding diluent for the product can be filled in the same facility based on the defined campaign production strategy.

5. To avoid cross-contamination and mix up, sufficient evidence should be provided for bracketing different products in a multiproduct facility based on a documented risk assessment.

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

**Labelling**

1. The information given on the inner label (on the container) and the outer label (on the package) shall be approved by the NRA.

2. Special consideration should be taken on the following information for labels of vaccines:

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

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

**Validation**

The nature of biological processes, handling of live materials and usual campaign based production are the major aspects of biological products which require process and cleaning validation. The validation of such processes considering the typical existing variations of biological products, possible use of harmful and toxic materials and inactivation processes, play an important role in demonstrating the production consistency and in proving that the critical process parameters and product attributes are controlled. A risk assessment approach should be used to determine the scope and extent of validation.

1. All critical biological processes (i.e., inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives etc.) 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.

2. After initial process validation studies have been finalized and routine production begins, a Continued Process Verification (19) 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 assure that the process remains in a state of control. Collection and evaluation of information and data on the performance of the process will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action should be taken to correct, anticipate and prevent problems so that the process remains in control.

3. Cleaning validation should be performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances and culture media. Careful consideration should be given to the cleaning validation when campaign base production is practiced.
4. Critical processes for inactivation or elimination of potentially harmful microorganisms, including genetically modified microorganism with a biosafety Risk group of 2 or above, are subject to validation.

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

6. Due to the variability of processes, products and methods, process revalidation should be triggered based on a detailed review of all changes, trends and deviations occurred in a period of time (e.g., 1 year).

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

Quality Control

1. Control of starting materials and intermediate, bulk and finished products

1.1. As part of Quality Control (QC) testing, sampling and sample handling procedures for biological materials must take special consideration on the nature of the materials being sampled to ensure testing carried out is representative of the process.

1.2. Reference samples of each lot of a finished product should be stored in its final packaging under the recommended conditions for at least one year after the expiry date. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Samples of other starting materials as well as intermediate 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, e.g., components of culture media, need not necessarily be retained. When a change of the vendor is needed and as appropriate, an impurity profile comparison should be done as part of the risk analysis.

2. Test requirements

2.1. For cell-based products, microbiological tests (e.g., sterility test or purity check) should be conducted on antibiotic free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detect fastidious organisms where appropriate. Where antibiotics are used, these need to be neutralized at the time of testing.

2.2 The traceability of reference standards should be ensured. The use and storage of
reference standards for testing should be defined and recorded. The stability of
reference standards should be monitored and the performance of reference
standards should be trended and WHO Recommendations for the preparation,
characterization and establishment of international and other biological
reference standards (20) should be followed.

3. Stability Programme

3.1. All stability studies including real-time/real-condition stability, accelerated
stability and stress-testing, should be carried out according to the Guidelines on
stability evaluation of vaccines (21) and other relevant requirements.
Trend analysis should assure early detection of any process drift or assay drift,
and this information be part of the Product Quality Review of biological
products.

3.2. For products where on-going 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 protocol.

4. Analytical Method Validation

All the 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 for this validation include
accuracy, precision, selectivity, sensitivity, reproducibility and stability, etc. (22-26).

In general, animal tests performed for quality control release are well described in the
relevant Pharmacopoeias and WHO guidance documents (22-26). Animal potency
tests are designed with multiple or single dilutions and replicates to take care of
variability and linearity and they are performed in comparison with
international/national reference standards and with appropriate assay controls.
Moreover, the respective tests are international standard methods. In the case of test
methods described in the relevant monographs, only a qualification of the laboratory,
laboratory 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.
However, repeatability and reproducibility can be demonstrated by reviewing
retrospective data over the years of the tests performed. In addition to the common
parameters typically used for validating assays (e.g., accuracy, precision, etc.) and
additional measurements should be considered during the validation of bioassays
based on the biological nature of the assay and reagents used.
Documentation (Lot processing records)

1. A separate vaccine lot processing record, summary protocol, should be prepared for each lot, for the purpose of lot release by the NRA and the information included should follow the *WHO Guidelines for independent lot release of vaccines by regulatory authorities* (27). The summary protocol and all associated records shall be of a type approved by the NRA and records shall be retained for at least two years after the expiry date of the lot of the vaccine and be available at all times for inspection by the NRA.

2. 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.

3. Some product types may require specific definition of which materials constitute a lot, particularly somatic cells treatment. For autologous and donor-matched situations, the manufactured product should be viewed as a lot.

4. 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 the confirmation of the receipt of the products at the point of use, whilst maintaining the privacy of individuals and confidentiality of health related information.

Use of Animals

Animals may be used for the manufacture or quality control of biological products. Special considerations are required when animal facilities are present at a fabrication 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 biological products and should have completely separate ventilation systems and separate staff. No animals shall be used in the production area. Separation of different animals before (quarantine/test) and under test should be considered, as well as the necessary animal acclimatization process as part of the testing requirements.

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

1. A wide range of animal species are used in the manufacture of a number of biological medicinal products. The use of animals may also be divided into:

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

2. In addition to compliance with TSE regulations (13), other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded and 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.

3. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

4. Particular care should be taken to prevent and monitor infections in the source/donor animals. Measures should include 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 SpecificPathogenFree (SPF) 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).

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. Housing for animals used in the production and control of biological products should be separated from production and control areas.

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

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

**Pharmaceutical Quality System (PQS) and Quality Risk Management**

Biological products, as any pharmaceutical product, should be manufactured considering the requirements of a Pharmaceutical Quality System (PQS) based on a life-cycle approach, which should facilitate innovation and continual improvement, and also strengthen the link between pharmaceutical development and manufacturing activities, as defined in *WHO Good manufacturing practices for pharmaceutical products: Main Principles* (1). Therefore, special attention should be paid to raw material controls, change control, trend analysis and deviation management in order to assure production consistency.

Operations in biological production and testing require specialized knowledge considering the risks inherent in producing and manipulating pathogenic and transmissible microorganisms. 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 among the supply chain, as described in *WHO Guidelines on quality risk management* (28) and the Pharmaceutical Quality System as described in ICH Q10 (29).

The QRM tools which may be used include Hazard Analysis and Critical Control Point (HACCP) and Failure Mode Effect and Criticality Analysis (FMECA) for preventive evaluation of the risks associated to a process in order to reduce the level of uncertainty as required by WHO in Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals (30).

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