

**Our Mandate:**

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

# Health Products and Food Branch Inspectorate

## Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)

### GUI-0027

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***Disclaimer***

*This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.*

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## 1.0 Introduction

Biological drugs are listed in Schedule D to the *Food and Drugs Act* (<http://laws-lois.justice.gc.ca/eng/F-27/index.html>) and are regulated under the *Food and Drug Regulations*. (<http://laws-lois.justice.gc.ca/eng/C.R.C.-c.870/index.html>) The *Regulations* which pertain to biological drugs are, for the most part, found within Divisions 1, 1A, 2, 4 and 8. The requirements of Division 1A and Division 2 apply to biological drugs, both as bulk process intermediates and in dosage form. Section 12 of the *Food and Drugs Act* prohibits the sale of Schedule D drugs unless the premises in which the drug was manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

The approach to the regulatory control of biological drugs is largely determined by the source of biological starting materials and the method of manufacture. Since the biological processes employed are inherently variable, there is a consequential effect on the end products and by-products. These processes also have great potential for the inadvertent introduction and/or proliferation of microbial contaminants.

The guidance included in this Annex when placed in context with the “Good Manufacturing Practices (GMP) Guidelines (GUI-0001)” (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>), should facilitate compliance with Division 2 of the *Food and Drug Regulations*. In order to avoid repetition, only those interpretations that are additional to those included in the “GMP Guidelines (GUI-0001)” are contained in this Annex. **Therefore, unless otherwise stated in this Annex, all interpretations included in the “GMP Guidelines (GUI-0001)” are applicable to Schedule D (Biological) drugs and their bulk process intermediates.**

The guidance given in this document has been written with a view to harmonize with GMP standards from other countries and with those of the World Health Organization (WHO), the Pharmaceutical Inspection Cooperation/Scheme (PIC/S) and the International Conference on Harmonisation (ICH).

The present edition of this document reflects updates to terminology, clarification of existing requirements, and additional requirements such as annual product quality review. Other regulations including the *Transportation of Dangerous Goods Act and Regulations* (<http://laws-lois.justice.gc.ca/eng/T-19.01/index.html>), and the *Human Pathogen Importation Regulations* (<http://laws-lois.justice.gc.ca/eng/SOR-94-558/index.html>) should be consulted for references to specific controls required for microorganisms. The *Health Canada Laboratory Biosafety Guidelines* (<http://www.phac-aspc.gc.ca/ols-bsl/lbg-ldmbl/>) should also be consulted for classification of facilities involved in the large-scale production of microorganisms.

## 2.0 Purpose

To provide additional interpretive guidance for Part C, Division 2, of the *Food and Drug Regulations* for Schedule D (biological) drugs. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

## 3.0 Scope

The guidance provided in this Annex is applicable to the manufacture and control of bulk intermediates and finished Schedule D (biological) drugs including: vaccines; fractionated plasma products (human, animal); antigens; allergens; hormones; cytokines; enzymes and products of prokaryotic and eukaryotic cell cultures (including monoclonal antibodies and products derived from rDNA technology). Interpretation of GMP

requirements for the collection and processing of human blood and blood components is not within the scope of this guidance.

#### **4.0 Interpretation of Regulations**

##### **Premises**

###### **C.02.004**

1. Air handling units are dedicated to specific processing areas and air from areas handling pathogens is not recirculated but exhausted through high-efficiency particulate air (HEPA) filters which have regular, documented performance checks. Air from live areas may not be recirculated into non-live areas or into other live areas with different organisms.
  - 1.1 Air handling units that supply, but are not dedicated to, specific areas handling risk group 1 or 2 pathogens may not be recirculated but must be exhausted whereby the use of HEPA filters for exhaust air is optional.
  - 1.2 Air handling units are dedicated to specific processing areas and air from areas handling risk group 3 or 4 pathogens is not recirculated but exhausted through HEPA filters. In all instances where HEPA filters are used, they must have regular, documented performance checks.
2. Positive pressure areas are used to process sterile products but negative pressure may be used in specific areas at point of exposure of pathogens as necessary for containment purposes.
3. Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, the areas are surrounded by a positive pressure zone.
  - 3.1 Where negative pressure areas are used for the aseptic processing of risk group 1 or 2 pathogens, the adjoining rooms surrounding the negative pressure area must be at a higher (less negative or positive) differential pressure. Where negative pressure areas are used for the aseptic processing of risk group 3 pathogens, the adjoining rooms, ceiling space, service spaces, and floor space (if not continuous and impervious or the negative pressure area is not on the lowest level of a multi-level building), surrounding the negative pressure area must be at a higher controlled (less negative or positive) differential pressure.
  - 3.2 Where negative pressure areas are used for the aseptic processing of risk group 4 pathogens, the negative pressure area must be completely surrounded by a controlled positive pressure zone on all faces, including adjoining rooms, service spaces, the ceiling space, and floor space (if not continuous and impervious).
4. Product contact pipework systems, including valves, pumps, vent filters and housings, must be designed to facilitate cleaning and sterilization. Cleaning procedures must be validated and where possible, “clean-in-place” (CIP) and “sterilize-in-place” (SIP) systems are used.
5. Layout and design of production areas permits effective cleaning and decontamination.

6. Facilities are designed to prevent cross-contamination during movement of personnel and materials between different areas.
  - 6.1 Where required, facilities are designed to permit effective segregation between processes, materials and personnel involved at different stages of production (for example, pre- and post-viral inactivation/reduction, and detoxification).
  - 6.2 If different biological products are fabricated, packaged and tested, or diagnostic work is done in the same premises, precautions are taken to prevent the risk of cross-contamination (for example, location of inlet/exhaust, separation of air supply). The extent of the precautions necessary is dictated by the nature of the products and equipment used. Concurrent production in the same area using closed systems may be acceptable for products which pose lower safety risks.
7. All steps of manufacture involving open handling of raw materials, intermediates or products are performed in clean areas or under appropriate local protection (for example, use of a unidirectional air flow cabinet).
8. Spore-forming microorganisms such as *Bacillus anthracis*, *Clostridium botulinum*, *Clostridium tetani*, as well as BCG vaccine (attenuated *Mycobacterium tuberculosis*, *Bacillus Calmette-Guerin* strain) and live organisms used in the production of tuberculin products are handled in dedicated facilities with dedicated equipment.
9. Once inactivated, certain spore forming microorganisms such as *Clostridium tetani* may be handled in non-dedicated facilities.
10. Separate, specially designed rooms with appropriate environmental and physical containment controls are provided for preparing, handling and storing microorganisms. Reference should be made to the Health Canada Laboratory Biosafety Guidelines, in designing facilities involved in the large-scale production of microorganisms.
11. Animal facilities: Animals may be used for the manufacture or quality control of biological drugs. Special considerations are required when animal facilities are present at a fabrication site.
  - 11.1 Procedures for animal quarantine and husbandry are required and must conform to Good Laboratory Practices (GLP) principles (Organisation for Economic Co-Operation and Development) and/or the Canadian Committee on Animal Care Guidelines or other relevant international guidelines (for example, EC Directive 86/609/EEC and Recommendation 2007/526/EC).
  - 11.2 Quarters for animals used in production and control of biological products are separate from all other manufacturing areas. The health status of animals from which some biological starting materials are derived and of those used for quality control and safety testing are monitored, recorded and reported as appropriate (for example, certification of origin and certification of fitness for use).

- 11.3 Separate staff is on site for animal care. Staff employed for work in animal facilities is provided with special clothing and separate changing facilities within the animal facility.
- 11.4 Where non-human primates are used for the production or quality control, special consideration is required. International guidance documents should be consulted (for example, current World Health Organisation requirements and EC Recommendation 2007/526/EC).

## **Equipment**

### **C.02.005**

- 1. Equipment is designed to be effectively cleaned and decontaminated.
- 2. Where possible, closed systems are used. When open equipment is used, or equipment is opened during manufacturing, appropriate precautions are in place to minimize the risk of contamination.
- 3. Where appropriate, product contact equipment is dedicated to specific manufacturing steps and/or products (for example, ultrafiltration cassettes, and chromatography media).
- 4. Equipment used for handling microbial, viral, and/or cell cultures is designed, operated and maintained in a state to ensure that these cultures are not contaminated during processing and storage operations. Valves on fermentation vessels are of sanitary design and steam sterilizable.
- 5. Air vent filters have hydrophobic media, are tested for integrity prior to use and have a scheduled life span based on scientific evidence.
- 6. Equipment and utensils are cleaned, stored, and where appropriate, sanitized or sterilized to prevent contamination or carry-over of material.

## **Personnel**

### **C.02.006**

- 1. All personnel engaged in the fabrication of biologicals receive training, specific to their duties and to the products being manufactured. Training in hygiene and microbiology is particularly relevant to biological production, because of the risk of microbial contamination.
- 2. Persons responsible for fabrication and quality control have an adequate background in relevant scientific disciplines such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.
- 3. For fabrication involving pathogenic microorganisms, viruses or biohazardous raw materials, it may be appropriate to have a designated Biosafety Officer who is experienced and knowledgeable in the handling of the relevant pathogens, with expertise in large scale manufacturing.
- 4. Adequate numbers of qualified/trained personnel are available to preclude having the same personnel working in different areas on the same day. Where this is unavoidable, clearly defined

decontamination measures, including change of clothing and shoes and, where necessary, showering are followed by staff prior to entering the new area.

## **Sanitation**

C.02.007 and C.02.008

1. Approved procedures are in place describing the appropriate handling and disposition of biological materials used in or derived from the fabrication of biologics. These procedures are designed to mitigate the risks to products and personnel.
2. Effluent which may contain pathogenic microorganisms is effectively decontaminated according to approved procedures.
3. Appropriate decontamination procedures must be used when handling animal tissue or microbial, viral, and/or cell cultures, particularly when these pose a potential risk for cross-contamination.
4. Equipment cleaning processes are designed to remove endotoxins, bacteria, toxic elements and residual contaminating proteins, and/or other potential contaminants.
5. Validated cleaning procedures are critical to mitigate the risk of cross-contamination in multi-product facilities involved in the production of biological drugs. Further guidance is available in the Health Canada document entitled “Cleaning Validation Guidelines (GUI-0028)” ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui\\_0028\\_tc-tm-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_0028_tc-tm-eng.php)). Validated effective cleaning procedures are in place for reusable product-contact equipment and the use of disposable equipment is encouraged as appropriate.
6. Appropriate control measures are in place to limit the risk of contamination of manufacturing equipment. Hold times for both dirty and clean equipment are validated. Equipment is sanitized and sterilized as appropriate for the intended use.
7. Validated product-specific effective facility and equipment cleaning and decontamination procedures are in place when inactivated or detoxified killed vaccines, toxoids, and bacterial extracts are filled in the same premises as other sterile products.
8. A shelf-life is established for each agent used for decontamination, disinfection and cleaning. There is evidence of effectiveness for each of these agents throughout the established shelf-life.
9. Manufacturing processes that require manipulation of in-process material, bulk intermediates, excipients, and drug product by personnel in an open system pose a significant risk of contamination. These processes must be designed to mitigate the risk of contamination from personnel and the environment.
10. Material and reagents used in the manufacture of biologics as well as the products themselves may present health hazards for employees. Consideration of these hazards should be reflected in the environmental and personal protective procedures and controls.
11. The health status of personnel should be considered for their own as well as for product safety. All



personnel engaged in fabrication, maintenance, testing and/or animal care (including any outside persons entering the areas) are vaccinated with appropriate specific vaccines and have regular health checks. Adverse health conditions of staff may present hazards to products. Persons whose presence could adversely affect the safety and quality of the product (such as a person with known infectious diseases, serious infections or exposed skin lesions) are excluded from the fabrication area.

### **Raw Material Testing**

C.02.009 and C.02.010

1. Specifications for biological materials (for example, starting material, auxiliary material or excipient) include details of their source, origin, method of fabrication, and the (biological and microbiological) controls applied to ensure their suitability for use. These specifications are in line with the marketing authorization. All bovine materials are sourced from a country that is considered at low risk of bovine spongiform encephalomyelitis (BSE). Human derived products such as albumin are sourced from donors known to be free of adventitious agents as outlined in accepted criteria for blood donors and are approvable when used as an excipient.
2. The complete testing of some biological starting materials or intermediates may take a considerable length of time (for example, adventitious virus testing of fermentation bulk harvest). In these instances, the biological starting material or intermediate may be used before the results of these tests are available. The release of a finished product remains conditional upon satisfactory results being obtained for all tests. Appropriate inventory control should be in place to ensure that this is not a common practice for starting materials.
3. Provisions for reduced testing in the “GMP Guidelines (GUI-0001)” may not be applicable to some biological products because of the inherent variability in range and nature of biological starting materials.
4. Biological starting materials, where full traceability is required (for example, plasma for fractionation), may have reduced raw material testing requirements.
5. There is evidence to support the suitability of environmental conditions (for example, temperature) during transportation and storage of raw materials and intermediates.
6. There is evidence to support the suitability for use, storage conditions and expiry dating of all reagents used in the manufacture of bulk intermediates and final drug products.
7. Seed lot and Cell Bank System: In addition to the principles stated in other guidances such as ICH Q5A: *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*, ICH Q5B: *Quality of Biotechnology Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Proteins*, and ICH Q5D: *Derivation and Characterization of Cell Substrates Used for Production of Biotechnology/Biological Products*, the following should be noted:
  - 7.1 The fabrication of biological drugs by means of viral culture, microbial culture, cell culture or propagation in embryos and animals is based on a system of master and working seed lots and cell banks to ensure a characterized common starting material for each production lot.

- 7.2 Seed lots and cell banks are established in a suitably controlled environment to protect the seed lot or the cell bank and the personnel. No other living or infectious material (for example, viral cultures, cell lines or microbial strains) is handled simultaneously in the same area or by the same persons.
- 7.3 Seed lots and cell banks are characterized according to ICH Q5D and maintained in such a way as to minimize the risks of contamination or alteration.
- 7.4 The stability of seed lots and cell banks is documented, including the efficiency of recovery. Storage containers are appropriate to their function, clearly labeled, and kept at a suitable temperature. Storage temperatures are properly monitored. Deviations from set limits and any corrective actions are evaluated and documented.
- 7.5 Only authorized personnel under the supervision of a responsible person, may handle seed lots and cell banks. An inventory is meticulously kept. A system is in place to ensure security and retrievability of seed lot or cell bank vials, without confusion or cross-contamination. A system is in place to mitigate the risk to the entire seed lot or cell bank with respect to catastrophic events.
- 7.6 All vials of master or working cell banks and seed lots are treated identically during storage. Once removed from storage, the vials are not returned.

### **Manufacturing Control**

C.02.011 and C.02.012

- 1. Campaign operations for different products require validated changeover procedures which include appropriate and effective cleaning procedures for shared product-contact equipment.
- 2. Concurrent production of different products requires validated closed systems with effective barriers which preclude cross-contamination from other processes (for example, adventitious agents from different host/vector production cells).
- 3. The processing and storage of inactivated and non-inactivated products is performed in segregated areas, to avoid the potential for cross-contamination.
- 4. Adequate measures are in place (for example, segregated areas, separate air handling systems, dedicated personnel) to avoid contamination of products that have undergone viral inactivation.
- 5. In the course of a working day, personnel working with live organisms (for example, viruses, cell cultures, microorganisms, or animals) do not pass from one area to another area where different products or different organisms are handled without appropriate sanitary measures.
- 6. Pure cultures are handled using appropriate controls to prevent adventitious contamination during production.
- 7. Sampling from or the addition of media, buffers, materials or cultures to fermenters and other vessels

- is carried out using validated procedures to prevent contamination and/or cross-contamination. Adequate measures are in place to prevent incorrect connections during the addition of materials or sampling.
8. Measures are taken to avoid aerosol formation. Containment of activities which result in aerosol formation such as centrifugation and blending of products is required to avoid cross-contamination of product and to protect personnel.
  9. Suitable, in-line, sterilizing filters are used for the routine addition of gases, media, buffering agents or defoaming agents to fermenters, or these materials are pre-sterilized and introduced aseptically.
  10. Additives or ingredients that must be measured or weighed during the production process (for example, buffers) may be stored in small quantities in the production area.
  11. Virus removal and/or viral inactivation methods are validated using specific viruses or appropriate model viruses, and do not adversely affect the product.
  12. Chromatography resins and diafiltration/molecular sieving membranes are dedicated to the purification of a single product and use of the same equipment at different processing steps is not recommended.
    - 12.1 The resins and membranes are sanitized and/or sterilized between uses, as appropriate.
    - 12.2 The life span of resins and membranes and the acceptance criteria for continued use are defined.
    - 12.3 Non-dedicated column housings or diafiltration units must be adequately cleaned and sanitized prior to changeover.
  13. Batch records must document all biological starting materials and in-process materials used, in addition to all relevant test results.
  14. Expected yields with appropriate ranges are established for critical production steps of bulk intermediates based on product development and manufacturing experience. The actual yield is compared to the expected yields and any deviations is investigated to determine their potential impact on the quality of the affected batches.
  15. Each batch of bulk intermediate incorporated into a blend must be manufactured according to an established process, individually tested and meet appropriate specifications prior to blending. Batches that are out-of-specification must not be blended.
  16. Blending of bulk intermediates follows first-in-first-out (FIFO). Blending of a large number of small quantities is discouraged. Plasma derivatives are blended to control donor exposure according to the marketing authorization.
  17. Procedures are in place to maintain an appropriate environment during all phases of manufacturing and storage of intermediates and final product including visual inspection and packaging.

18. Processing times for major processing steps are defined in batch documentation and supported by validation data. In-process hold times are established for non-continuous processes (where intermediates are held before forward processing) and based on appropriate data.
19. Maximum storage time and conditions are established for bulk intermediates.
20. If filling and sealing is not carried out immediately following final formulation of the drug, a validated holding and/or shipping period in accordance with the marketing authorization may be allowed.
21. Special, appropriately documented precautions must be exercised in the storage and handling of microorganisms, in particular spore forming organisms. Procedures for control of access of personnel into restricted storage and handling areas are strictly enforced.
22. The handling and destruction of rejected biological materials takes into consideration designation of the material (for example, infectious, bio-hazard), and environmental protection requirements for their disposal.
23. The Annual Product Quality Review requirements outlined in the “GMP Guidelines (GUI-0001)” apply to bulk process intermediates as well as finished drug product in the case of biological drugs.

### **Quality Control Department**

C.02.013 to C.02.015

1. Biological analytical techniques are essential for control of most biological drugs.
2. The inherent variability of biological processes and the inability to fully characterize most biological drugs requires a greatly enhanced emphasis on the importance of in-process controls during fabrication, packaging and labeling to ensure consistency in quality, safety and efficacy of the end product.
3. Controls which are crucial for product quality (for example, adventitious agent testing) but which cannot be carried out on the finished product, are performed at an appropriate stage of production.
4. Out-of-specification and out-of-trend results are investigated according to written procedures. The investigation includes an assessment of root cause, description of corrective actions and preventive actions carried out and conclusions.
5. Invalidation of test results as well as any retesting or resampling follows written procedures.
6. Storage, handling and transportation procedures (including distribution) may have major impacts on bulk intermediates and biological drugs. In some cases, transit time, transit method, temperature, humidity, light and/or vibration may be critical factors that may adversely affect the quality and effectiveness of the product. Bulk intermediates and biological drugs are stored, transported and handled in strict compliance with the marketing authorization and Health Canada’s document entitled “Guidance for Temperature Control of Drug Products During Storage and Transportation (GUI-0069)” ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069\\_tc-tm-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069_tc-tm-eng.php)).

7. Primary reference standards are obtained as appropriate for the testing of bulk intermediates and finished product. The source of each primary reference standard is documented. Where a primary reference material is not available from an officially recognized source, an “in-house” reference is established. Testing, to fully characterize the identity and purity of the “in-house” reference standard, is documented.
8. Secondary reference standards are manufactured, tested and approved in a manner appropriate to their intended use. The suitability of each batch of secondary reference standard is determined by comparison to the primary reference standard and periodically requalified according to written procedure.
9. There is evidence to support the suitability for use, storage conditions, and expiry/retest dating for all reagents used in the testing of in-process samples, bulk intermediates, and final drug products.
10. Production methods utilizing continuous culture have specific requirements for in-process quality control. For example, continuous monitoring of critical parameters is required during fermentation. Such data should form part of the batch record.
11. The health status of animals used in quality control or safety testing is monitored, documented and reported, as appropriate (for example, certificate of origin and certification of fitness for use).
12. For imported biological drugs that have been subjected to reprocessing, the quality control department of the importer is responsible for ensuring that the (documented) reprocessing carried out by the fabricator complies with the marketing authorization.
13. Reworking of an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch/lot is an unexpected occurrence and as such, the release of the final product is subjected to approval of both the procedure and the results by the Biologics and Genetic Therapies Directorate.

### **Packaging Material Testing**

C.02.016 and C.02.017

1. Many biological drugs and bulk intermediates are extremely susceptible to the environment in which they are stored. The container/closure system is designed to protect the contents from the impact of environmental factors while minimizing deleterious effects of the packaging itself. Therefore, it is imperative to maintain strict control of the identity and quality of primary packaging in accordance with approved specifications.
2. For imported biological drugs, the quality control department of the importer is responsible for ensuring that the (documented) packaging materials used, comply with approved specifications.

### **Finished Product Testing**

C.02.018 and C.02.019

1. The variable nature of the systems used in the manufacture of biological drugs requires consistent

manufacturing practices in addition to finished product testing to adequately ensure the quality of the product. The release of some biological drugs should also take into consideration:

- 1.1 compliance with specifications for raw materials, processing aids and intermediates.
- 1.2 review of critical process parameters and results of in-process controls.
2. For imported biological drugs, the quality control department is responsible for ensuring that finished product specifications and the testing done, comply with the marketing authorization.

### **Records**

C.02.020 to C.02.024

1. For imported biological drugs, detailed summaries (for example, Certified Product Information Document) of the current fabrication, packaging, labeling and testing procedures are maintained by the legal agent in Canada and master production documents are available on site at the fabricator.
2. Records are retained indefinitely on site at the fabricator, for biological drugs containing human blood-derived excipients (for example, human albumin).

### **Samples**

C.02.025 and C.02.026

1. See the “GMP Guidelines (GUI-0001)”.

### **Stability**

C.02.027 and C.02.028

1. For biological drugs, stability assessment is linked to retaining biologic activity within the label claim and is subjected to premarket authorization.
2. The stability assessment includes analysis of both the lyophilized and reconstituted single and multi-dose dosage forms of the drug product.

### **Sterile Products**

C.02.029

1. Due to their labile nature, most sterile biological drugs are produced by sterile filtration/aseptic compounding, followed by aseptic filling rather than by terminal sterilization. Direct-contact packaging materials (for example, vials, syringes, stoppers, etc.) are subjected to processing which ensures and maintains sterility prior to filling.

## Appendix A

### Glossary of Terms

The following definitions supplement the definitions provided under the Glossary of Terms in the “GMP Guidelines (GUI-0001)”.

**Adventitious Virus** - Unintentionally introduced contaminant virus.

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

**Biological Auxiliary Material** - Raw material from a biological source which is intended to be used as a processing aid in the fabrication of the drug. It may be absent from the drug or may remain as an impurity in the drug at the end of the manufacturing process (for example, biological additives used to supplement cell culture medium in production fermenter; human antithrombin III used to complex and remove human thrombin).

**Biological Starting Material** - Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (for example, cell substrates, host/vector production cells, eggs, viral strains, etc.).

**By-Product** - A product arising incidentally in the fabrication of a specific biological drug.

**Cell Bank** - 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 cells *in vitro*. Cell culture is performed according to good aseptic/sterile techniques to ensure the absence of microbial contamination.

**Cleaning Procedures Validation** - Testing of methods used to clean equipment/surfaces in a processing suite/facility with assays to validate the effectiveness of the cleaning. The use of worst-case cleaning challenges and the addition of a safety factor in the standard operating procedure, can provide further assurance of acceptability. Such challenge might be created by artificially soiling a piece of equipment or by using reduced cleaning parameters (rinse time or volume).

**Closed System** - Process equipment (fermenter, transfer lines, harvest apparatus, etc.) or process step in which the product is not exposed to the external environment. A closed system requires that the quality of materials entering or leaving the system and the manner in which these materials are added/removed from the system is carefully controlled.

**Concurrent Production** - Simultaneous processing of more than one product in the same room/suite of a multi-product facility, or simultaneous processing of more than one lot of a product in a dedicated facility.

**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 MCB and WCB through finishing.

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

**Detoxification** - Conversion of bacterial toxins to toxoids (non-toxic but immunogenic derivatives of toxins) by chemical treatment.

**Drug Product** - (dosage form, finished product, final container 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** - A process in which cells or microorganisms are cultured in a container (bioreactor or fermenter), in liquid or solid medium, for experimental or commercial processes.

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

**Inactivation** - Removal of infectivity of microorganisms 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 all 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.

**Multi-Product Facility** - Facility where more than one product of the same type or products from different classes are fabricated (for example, pharmaceutical and biological drugs).

**Product-Specific Cleaning** - Cleaning procedure performed to ensure removal of product residuals from non-dedicated product-contact equipment/containers which includes appropriate assays to validate the effectiveness of the cleaning.

**Production Cells** - Cell substrate used to fabricate the product.

**Pure Culture** - A culture broth/medium containing a single type of microorganism.

**Seed Lot** - Collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. In contrast to cell bank, seed lot may describe collections of plasmids, viruses etc. For master and working seed lots, refer to definitions provided for MCB and WCB.



**Suite** - Functional manufacturing area consisting of one or more rooms with shared air handling and personnel access and which is segregated from the rest of the facility. It contains a separate air supply and exhaust, separate personnel access/egress and separate process equipment. It does not necessarily include a separate supply of water, compressed air/gas or steam, provided that suitable engineering controls are in place to prevent product contamination of these systems. A suite is referred to as a facility within a facility.

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