Environmental, Health, and Safety Guidelines for Pharmaceuticals and Biotechnology Manufacturing

Introduction

The Environmental, Health, and Safety (EHS) Guidelines are technical reference documents with general and industry-specific examples of Good International Industry Practice (GIIP)[1]. When one or more members of the World Bank Group are involved in a project, these EHS Guidelines are applied as required by their respective policies and standards. These industry sector EHS guidelines are designed to be used together with the **General EHS Guidelines** document, which provides guidance to users on common EHS issues potentially applicable to all industry sectors. For complex projects, use of multiple industry-sector guidelines may be necessary. A complete list of industry-sector guidelines can be found at: www.ifc.org/ifcext/enviro.nsf/Content/EnvironmentalGuidelines

The EHS Guidelines contain the performance levels and measures that are generally considered to be achievable in new facilities by existing technology at reasonable costs. Application of the EHS Guidelines to existing facilities may involve the establishment of site-specific targets, with an appropriate timetable for achieving them.

The applicability of the EHS Guidelines should be tailored to the hazards and risks established for each project on the basis of the results of an environmental assessment in which site-specific variables, such as host country context, assimilative capacity of the environment, and other project factors, are taken into account. The applicability of specific technical recommendations should be based on the professional opinion of qualified and experienced persons.

When host country regulations differ from the levels and measures presented in the EHS Guidelines, projects are expected to achieve whichever is more stringent. If less stringent levels or measures than those provided in these EHS Guidelines are appropriate, in view of specific project circumstances, a full and detailed justification for any proposed alternatives is needed as part of the site-specific environmental assessment. This justification should demonstrate that the choice for any alternate performance levels is protective of human health and the environment.

Applicability

The EHS Guidelines for Pharmaceuticals and Biotechnology Manufacturing include information relevant to pharmaceuticals and biotechnology manufacturing facilities. They cover the production of active pharmaceutical ingredients and secondary processing, including intermediates, formulation, blending, and packaging, and related activities research, including biotechnology research and production.

This document is organized according to the following sections:

Section 1.0 — Industry-Specific Impacts and Management
Section 2.0 — Performance Indicators and Monitoring
Section 3.0 — References
Annex A — General Description of Industry Activities

[1] Defined as the exercise of professional skill, diligence, prudence and foresight that would be reasonably expected from skilled and experienced professionals engaged in the same type of undertaking under the same or similar circumstances globally. The circumstances that skilled and experienced professionals may find when evaluating the range of pollution prevention and control techniques available to a project may include, but are not limited to, varying levels of environmental degradation and environmental assimilative capacity as well as varying levels of financial and technical feasibility.

1.0 Industry-Specific Impacts and Management

The following section provides a summary of EHS issues associated with pharmaceuticals and biotechnology manufacturing, along with recommendations for their management. Recommendations for the management of EHS issues common to most large industrial facilities during the construction and decommissioning phase(s) are provided in the **General EHS Guidelines**.

1.1 Environmental

The following environmental issues should be considered as part of a comprehensive assessment and management program that addresses project-specific risks and potential impacts. Potential environmental issues associated with pharmaceuticals and biotechnology manufacturing projects include the following:

- Air emissions
- Wastewater
- Solid and hazardous wastes
- Hazardous materials
- Threats to biodiversity
- Bioethics

Air Emissions

Volatile organic compounds, acid gases, and particulates may be emitted during pharmaceuticals and biotechnology manufacturing facilities from both point sources and fugitive emissions. Greenhouse gas emissions are also of significance.

Volatile Organic Compounds

Chemical synthesis and extraction are the manufacturing phases responsible for significant emissions of volatile organic compounds (VOCs). In primary pharmaceutical manufacturing, VOC emissions are generated from reactor vents, filtering systems in the separation process, solvent vapors from purification tanks and dryers (including loading and unloading operations), fugitive emissions from valves, tanks, pumps, and other equipment (e.g., centrifuges), solvents and other VOCs related to extraction chemicals in natural product extraction, pre-fermentation and fermentation solvents, and wastewater collection and treatment units.

VOC emissions from secondary pharmaceutical manufacturing may be generated from mixing, compounding, granulation, and formulation (e.g. use of ethanol or isopropyl alcohol), from operations involving the use of solvents (e.g. granulation) or alcoholic solutions (e.g. tablet coating), and from aerosol manufacturing processes.

Solvent and VOC emission prevention and minimization measures include the following:

- Reducing or substituting the use of solvents and other materials which have a high VOC content, and substitution with products that have lower volatilities, and switching to aqueous-based coating films and aqueous-based cleaning solutions[2];
- Implementation of VOC leak prevention and control strategies from operating equipment as described in the **General EHS Guidelines** (Air Emissions and Ambient Air Quality: Fugitive Sources);
- Implementation of VOC loss prevention and control strategies in open vats and mixing processes as described in the **General EHS Guidelines**, including installation of process condensers after the process equipment to support a vapor-to-liquid phase change and to recover solvents. Process condensers include distillation and reflux

[2] Solvent selection is a key consideration in process development. For instance, ethyl acetate, alcohols and acetone are preferable to more toxic solvents such as benzene, chloroform and trichloroethylene. An example of a solvent selection guide is provided in the EU IPPC BREF on Organic Fine Chemicals (Section 4.1.3). Solvent substitution may be the subject of strict regulatory requirements.

condensers, condensers before vacuum sources, and condensers used in stripping and flashing operations;

- Reduction of equipment operating temperatures, where possible;
- For drying operations, adoption of closed circuits under a nitrogen atmosphere;
- Use of closed-loop liquid and gas collection equipment for cleaning of reactors and other equipment.

VOCs should be collected in local exhaust ventilation hoods for subsequent control of point and fugitive emissions. VOC emissions extraction and controls, especially from fermentation processes, may also reduce nuisance odors. Recommended VOC emissions control measures include the following:

- Venting of emissions from sterilization chambers into control devices such as carbon adsorption or catalytic converters;
- Condensation and distillation of solvents emitted from reactors or distillation units. Possible installation of cryogenic condensers, reducing the gas stream temperature below dew point to achieve higher VOC recovery efficiencies;[3]
- Installation of wet scrubbers (or gas absorbers), which may remove VOCs as well as other gaseous pollutants from a gas stream,[4] and addition of hypochlorite to the scrubber in order to reduce emissions of nuisance odors;
- Installation of activated carbon adsorption or destructive control devises such as thermal oxidation / incineration, catalytic incinerators, enclosed oxidizing flares, or other methods described in further detail in the **General EHS Guidelines**.

Particulate Matter

Particulates consisting of manufactured or in-process product can be emitted from bulk (e.g. fermentation) and secondary manufacturing. The most common sources of particulates include milling, mixing, compounding, formulation, tableting, and packaging. Recommended particulate matter management strategies include:

- Collection with air filtration units and recycling of particulate matter into the formulation process (e.g. tablet dust), depending on batch record requirements and on process characteristics;
- Installation of dedicated filtration systems (sometimes double stages of filtration) in granulation equipment. An abatement room should be also provided where the particulate is removed from the air, decreasing flow speed;
- Installation of high efficiency particulate air (HEPA) filters in the heating, ventilating and air conditioning (HVAC) systems to control particulate matter emissions internally and externally as well as to prevent indoor cross-contamination. Air ducts should be segregated to prevent air cross-contamination from different processes and to ease the air stream treatment;
- Collection of particulates through air filtration units, typically baghouse / fabric filters;
- Depending on the volume of emissions and prevailing size of particulate matter, additional particulate emissions control methods should be considered, such as wet scrubbing and wet electrostatic precipitators, especially after combustion / thermal oxidation treatments.

Combustion Source Emissions

Exhaust gas emissions produced by the combustion of gas or diesel in turbines, boilers, compressors, pumps and other

[3] Cryogenic condensers allow higher removal efficiency (up to 99 percent) than traditional condensers, but they have higher energy requirements.
[4] Scrubbers may consist of packed towers, plate or tray towers, venturi scrubbers and spray towers. These options are best applied to highly water-soluble VOCs (e.g., alcohols). Water, caustic, and acidic scrubbers are widely used for organic and inorganic gas emission abatement. Acid gas emissions are controlled through water and caustic scrubbing systems (often several scrubbers in series). Scrubbers create a wastewater stream requiring further treatment.

engines for power and heat generation, are a significant source of air emissions from pharmaceuticals and biotechnology manufacturing facilities. Guidance for the management of small combustion source emissions with a capacity of up to 50 megawatt thermal (MW_{th}), including air emission standards for exhaust emissions, is provided in the **General EHS Guidelines**.

Odors

The main source of odor emissions is typically associated with fermentation activities. Recommended odor management strategies include:

- Considering the location of new facilities, taking into account proper distances to neighbors and the propagation of odors;
- Post-combustion of venting gases;
- Use of exhaust stack heights that are consistent with practices as described in the **General EHS Guidelines**;
- Use of wet scrubbers to remove odors with a high affinity to water;
- Condensation of vapors combined with scrubbers.

Wastewater

Industrial Process Wastewater

Wastewater streams in pharmaceuticals and biotechnology manufacturing depend on the specific process and may include: chemical reactions streams; product wash water; spent acid and caustic streams; condensed steam from sterilization and strippers; air pollution control scrubber blowdowns; equipment and facility wash water; and clean-in-place wastewater.

The main conventional pollutants of concern in these wastewater streams from primary manufacturing (e.g. fermentation, chemical synthesis, crystallization, purification, and biological / natural extraction) are parameters such as biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), ammonia, toxicity, biodegradability, and pH. Other chemical compounds may also be present including, but not limited to, solvents (e.g. methanol, ethanol, acetone, isopropanol, and methyl-ethyl ketone), organic acids (e.g. acetic acid, formic acid), organic halides, inorganic acids, ammonia, cyanide, toluene, and active pharmaceutical ingredients (API).

Recommended source reduction measures include:

- Material substitution, especially adoption of biodegradable water-based materials for organic solvent based materials (e.g. in tablet coating);
- Condensation and separation processes to recover used solvents and aqueous ammonia, including:
  - Low-boiling compounds from wastewater stream by fractioned distillation
  - Volatile compounds from wastewater stream by inert gas stripping and condensation
  - Solvent extraction of organic compounds (e.g. high or refractory halogenated compounds and high COD loads)
- Combination of solvent waste streams to optimize treatment.

Process Wastewater Treatment

Techniques for treating industrial process wastewater in this sector include source segregation and pretreatment of concentrated wastewater streams, especially those associated with active ingredients. Typical wastewater treatment steps include: grease traps, skimmers, dissolved air floatation or oil water separators for separation of oils and floatable solids; filtration for separation of filterable solids; flow and load equalization; sedimentation for suspended solids reduction using clarifiers; biological treatment, typically aerobic treatment, for reduction of soluble organic matter (BOD); biological nutrient removal for reduction in nitrogen and phosphorus; chlorination

of effluent when disinfection is required; dewatering and disposal of residuals in designated hazardous waste landfills. Additional engineering controls may be required for (i) containment and treatment of volatile organics stripped from various unit operations in the wastewater treatment system, (ii)advanced metals removal using membrane filtration or other physical/chemical treatment technologies, (iii) removal of recalcitrant organics and active ingredients using activated carbon or advanced chemical oxidation, (iii) residual color removal using adsorption or chemical oxidation, (iv) reduction in effluent toxicity using appropriate technology (such as reverse osmosis, ion exchange, activated carbon, etc.), (v) reduction in TDS in the effluent using reverse osmosis or evaporation, and (vi) containment and neutralization of nuisance odors.

Management of industrial wastewater and examples of treatment approaches are discussed in the **General EHS Guidelines**. Through use of these technologies and good practice techniques for wastewater management, facilities should meet the Guideline Values for wastewater discharge as indicated in the relevant table of Section 2 of this industry sector document.

Other Wastewater Streams & Water Consumption

Guidance on the management of non-contaminated wastewater from utility operations, non-contaminated stormwater, and sanitary sewage is provided in the **General EHS Guidelines**. Contaminated streams should be routed to the treatment system for industrial process wastewater. Recommendations to reduce water consumption, especially where it may be a limited natural resource, are provided in the **General EHS Guidelines**.

Solid and Hazardous Wastes

Hazardous Waste

Bulk manufacturing processes in the pharmaceutical industry are typically characterized by a low ratio of finished products to raw material resulting in significant quantities of residual waste, especially during fermentation and natural product extraction. Chemical synthesis processing generates wastes containing spent solvents, reactants, spent acids, bases, aqueous or solvent liquors, still bottoms, cyanides and metal wastes in liquid or slurry form, as well as filter cakes which may contain inorganic salts, organic by-products and metal complexes. Fermentation processes may generate spent solids, intermediates, residual products and filter cakes containing mycelia, filter media, and small amounts of nutrients. Other sources of hazardous or potentially hazardous wastes may include raw materials packaging waste, used air filter media, off-spec and expired products, laboratory wastes, sludge from the wastewater treatment process, and collected particulate from air pollution control systems.

Recommended pollution prevention and control measures include:

- Waste reduction by material substitution (e.g. use of water based solvents, etc.);
- Process modifications (e.g. continuous rather than batch operations to reduce spillage and other material losses);
- Spent solvent recycling and reuse, through distillation, evaporation, decantation, centrifugation and filtration;
- Other potential recovery options should be investigated, including inorganic salts recovery from chemical liquors produced during organic synthesis operations, high organic matter materials from biological extraction, and filter cakes from fermentation[5];
- Potentially pathogenic waste from biotechnology manufacturing should be inactivated through sterilization or chemical treatment before final disposal.

[5] Solid wastes from fermentation (e.g., mycelia) may be added to animal feeds as a nutritional supplement or as soil conditioners and fertilizers.

Hazardous and non-hazardous industrial wastes should be stored, transported, and managed as described in the relevant sections of the **General EHS Guidelines**.

Hazardous Materials Management

Pharmaceutical and biotechnology manufacturing plants should assess the risks associated with the use and handling of hazardous materials and implement practices to prevent and minimize such risks. As indicated in the **General EHS Guidelines**, the application of these management practices should be documented in a written Hazardous Materials Management Plan. The purpose of this plan is to establish and implement a systematic set of preventive actions against accidental releases of substances that can cause serious harm to the environment, and to health and safety or workers and the public from short-term exposures and to mitigate the severity of releases that do occur.

In establishing the hazardous material management plan[6], facilities should:

- Conduct a Hazard Assessment considering accident history in the last five years, worst case scenario, and alternative release analysis;
- Identify and implement management procedures including process safety, training, management of change, incident investigation, employee participation, contractor training and oversight;
- Implement prevention measures including process hazard analysis, operating procedures, mechanical integrity, pre-start review, work permit, and compliance audits;
- Develop and implement an Emergency Response Program including emergency response procedures, emergency equipment, training, review and updates.

[6] See IFC Hazardous Waste Management Manual.

Threats to Biodiversity

Bioprospecting

The process of collection of genetic resources (bioprospecting), which may be part of certain pharmaceutical or biotechnology projects, may include access to different types of habitats. In addition to the potential for negative impacts to the biodiversity of these habitats, which may also depend on the physical nature of the collection activities and the types of genetic material involved, bioprospecting may also raise issue about the rights of local communities to consent in the use or to a share in the benefits of the commercialization of their cultural heritage or the genetic resources extracted.

Recommended management practices include:

- Avoiding or minimizing harm to biodiversity in compliance with applicable legal requirements;
- Development and application of bioprospecting procedures that are consistent with internationally recognized standards and guidelines, including aspects of:[7,8]
  - Coordination with representatives from the National Focal Point[9] prior to the undertaking of bioprospecting activities to identify national and local requirements,
  - Obtaining Prior Informed Consent (PIC) from the State which is party to the Convention on Biological Diversity (CBD) in material screened for genetic use according to the basic principle of the CBD, and
  - Development and implementation of contracting agreements for the sharing of benefits arising from the

[7] Examples of internationally recognized guidelines include the Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization published by the Secretariat of the Convention on Biological Diversity (CBD, 2002) and the Akwe: Kon Guidelines applicable to the conduct of cultural, environmental, and social assessments (also published by the Secretariat of the CBD, 2004).
[8] Examples of procedures developed by the private sector include the Guidelines for BIO Members Engaging in Bioprospecting published by the Biotechnology Industry Organization (BIO), Washington DC. (2006).
[9] As per Convention on Biological Diversity.

development and commercialization of genetic resources.

Biosafety

For projects or facilities involved in research, manufacture, or trading of living modified organisms, the risks associated with their production, handling, storage, transport, and use may include threats to biological diversity due to the controlled or uncontrolled release of the organism into the environment.

Recommended biosafety management practices include:

- Development of a risk-based approach to the identification of key control points in the process cycle, including in-plant handling, off-site transport, and use of modified organisms.[10] The assessment should cover the processes used and potential releases (including living modified organisms as discussed in Annex III of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity) on the conservation and sustainable use of biological diversity, taking also into account risks to human health;[11]
- Implementation of in-plant and transport safety measures including specialized training of personnel, primary containment (e.g. containment barriers) and secondary containment (e.g. airlocks, differential pressure, exhaust air filters and treatment of contaminated material and wastes)[12], and equipment and personnel decontamination procedures;
- Preparation and implementation of Transportation Safety Plans specific to the type of organism being handled and consistent with the objectives of applicable international conventions and treaties;[13,14]
- Implementation of risk-management measures for controlled releases applicable to the specific organism including, as appropriate, training of those involved, monitoring of the activity, controlling access to the site, and application of isolation methods.[15]

Bioethics

The ethical issues faced by the pharmaceutical or biotechnology industry are potentially complex and depend significantly on the activity of the company. These issues may include the development of genetically modified foods; gene therapy experiments and stem cell research; human participant trials; animal testing; handling of genetic information; sale of genetic and biological samples; and the creation of transgenic animals, among others.[16]

Recommended bioethics management approaches include:

- Well established ethics mechanisms including management commitment; dedicated internal ethics personnel; access and use of external expertise (e.g. consultants and advisory boards); internal training and accountability mechanisms; communications programs to engage with suppliers and external stakeholders; and evaluation and reporting mechanisms;[17]

[10] Examples of risk assessment methodologies include Annex III of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity; the UNEP International Technical Guidelines for Safety in Biotechnology; and the United States Department of Agriculture, Animal and Plant Health Inspection Service (APHIS) and the related International Biosafety Protocol website, available at :http://www.aphis.usda.gov/brs/international_biosafety.html as well as the Biotechnology Regulatory Services website, available at: http://www.aphis.usda.gov/biotechnology/about.shtml and http://www.aphis.usda.gov/brs/biosafety.html

[11] The risk assessment should consider the controlled or potentially accidental nature of the environmental release of an organism.

[12] Classification and description of biosafety containment levels are provided by international organizations, such as the World Health Organization (WHO), and national institutes, such as the US Centers for Disease Control and Prevention (CDC) and US National Institutes of Health (NIH).

[13] Cartagena Protocol on Biosafety to the UN Convention on Biological Diversity.

[14] Examples of biosafety good practices can be found in the UN Recommendation on the Transport of Dangerous Goods (Orange Book).

[15] Examples of management practices applicable to controlled releases of plants, animals, and micro-organisms can be found in Annex 5 of the UNEP International Technical Guidelines for Safety in Biotechnology.

[16] Mackie, et al. (2006)

[17] Ibid.

- Adherence to internationally accepted ethical principles applicable to genetic research, clinical trials involving human participants, and any other activities with critical bioethical issues;[18]
- The use of animals for experimental and scientific purposes should be conducted according to industry good practice which includes reduction of the numbers of animals used in each study to the absolute minimum necessary to obtain valid results and refinement of the use of research animals to use less painful or the least invasive procedures whenever possible.[19,20] Animal breeding, husbandry, and care facilities of the company or its suppliers should be designed and operated according to internationally certifiable methodologies.[21]

1.2 Occupational Health and Safety

Facility-specific occupational health and safety hazards should be identified based on job safety analysis or comprehensive hazard or risk assessment using established methodologies such as a hazard identification study [HAZID], hazard and operability study [HAZOP], or a scenario-based risk assessment [QRA].

As a general approach, health and safety management planning should include the adoption of a systematic and structured system for prevention and control of physical, chemical, biological, and radiological health and safety hazards described in the **General EHS Guidelines**.

The occupational health and safety issues that may occur during the construction and decommissioning pharmaceutical and biotechnology manufacturing facilities are similar to those of other industrial facilities, and their management is discussed in the **General EHS Guidelines**. The most significant occupational health and safety hazards occur during the operational phase of pharmaceutical and biotechnology facilities and primarily include the following:

- Heat hazards
- Chemical hazards including fire and explosions
- Pathogenic and biological hazards
- Radiological hazards
- Noise
- Process safety

Heat

The use of large volumes of pressurized steam and hot water are typically associated with fermentation and with compounding operations representing potential for burns due to exposure to steam or direct contact with hot surfaces as well as heat exhaustion. Recommended management practices include:

- Steam and thermal fluid pipelines should be insulated, marked, and regularly inspected;
- Steam vents and pressure release valves should be directed away from areas where workers have access;
- High temperature areas of presses should be screened to prevent ingress of body parts.

Recommended management practices to avoid heat exhaustion are presented in the **General EHS Guidelines** (Occupational Health and Safety).

[18] Examples include the Universal Declaration on Bioethics and Human Rights and more specifically publications by specialized entities such as the International Bioethics Committee (IBC, http://portal.unesco.org); US National Bioethics Advisory Commission (http://www.bioethics.gov/); and the Biotechnology Industry Organization Statement of Ethical Principles (http://www.bio.org/).
[19] An example of this approach is the United States Department of Agriculture's Three R Concept, which includes "Reduction, Refinement, and Replacement" (National Agricultural Library (http://awic.nal.usda.gov)). It should be noted that "replacement" (consisting of the replacement of animal experiments with non-animal experiments such as mathematical models, computer simulations, and in vitro biological systems) is often considered a long term goal given the current lack of technological feasibility.
[20] See also European Union Directive 86/609/EC on protection of animals used for experimental and other scientific purposes as well as the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, 1996).
[21] Animal handling methods should be certifiable according to requirements of international accreditation bodies such as Association for Assessment and Accreditation of Laboratory Animal Care International (http://www.aaalac.org/).

Chemicals

The risk of occupational exposure to chemicals in pharmaceutical and biotechnology manufacturing activities are potentially complex. Among the most common types of chemicals and exposure routes is the inhalation of volatile organic compounds (VOCs) from recovery, isolation, and extraction activities; from handling of wet cakes in drying operations; during wet granulation, compounding, and coating operations; from uncontained filtration equipment; and from fugitive emissions for leaking pumps, valves, and manifold stations (e.g. during extraction and purification steps). Additional sources of inhalation exposures include chemical synthesis and extraction operations and sterilization activities (e.g. germicides such as formaldehyde and glutaraldehyde, and sterilization gases such as ethylene oxide) as well as exposure to synthetic hormones and other endocrine disrupters. In secondary pharmaceuticals manufacturing, workers may be exposed to airborne dusts during dispensing, drying, milling, and mixing operations.

Potential inhalation exposures to chemicals emissions during routine plant operations should be managed based on the results of a job safety analysis and industrial hygiene survey and according to the occupational health and safety guidance provided in the **General EHS Guidelines.** Protection measures include worker training, work permit systems, use of personal protective equipment (PPE), and toxic gas detection systems with alarms. Additional recommended measures include:

- Use of partitioned workplace areas with good dilution ventilation and / or differential air pressures;
- When toxic materials are handled, laminar ventilation hoods or isolation devices should be installed;
- Manufacturing areas should be equipped with suitable heating ventilation and air conditioning (HVAC)[22] systems designed according to current Good Manufacturing Practice (cGMP) protocols, including use of high efficiency particulate air (HEPA) filters in ventilation systems, particularly in sterile product manufacturing areas;
- Use of gravity charging from enclosed containers and vacuum, pressure, and pumping systems during charging and discharging operations to minimize fugitive emissions;
- Use of local exhaust ventilation (LEV) with flanged inlets to capture fugitive dusts and vapors released at open transfer points;
- Conducting liquid transfer, liquid separation, solid and liquid filtration, granulation, drying, milling, blending, and compression in work areas with good dilution and LEV;
- Enclosing of granulators, dryers, mills, and blenders, and venting to air-control devices;
- Use of dust and solvent containment systems in tablet presses, tablet-coating equipment, and capsule-filling machines. Tablet-coating equipment should be vented to VOC emission control devices;
- Whenever possible, less hazardous agents should be selected in all processes (e.g. alcohols and ammonium compounds in sterilization processes);
- Sterilization vessels should be located in separate areas with remote instrument and control systems, non-recirculated air, and LEV to extract toxic gas emissions. Gas sterilization chambers should be evacuated under vacuum and purged with air to minimize fugitive workplace emissions before sterilized goods are removed;
- Use vacuuming equipment with HEPA filters and wet mopping instead of dry sweeping and blowing of solids with compressed air.

[22] HVAC systems should be designed to meet product protection, occupational health and safety, and environmental protection needs. Air conditioning systems should be designed to include filtration of air.

Fire and Explosions

Fire and explosion hazards may arise during solvent extractions. Organic synthesis reactions may also create major process safety risks from highly hazardous materials, fire, explosion, or uncontrolled chemical reactions, which should be controlled through process safety engineering and control.

Secondary pharmaceuticals manufacturing operations (e.g. granulation, mixing, compounding and drying) also use flammable liquids, with the potential to create flammable or explosive atmospheres. In addition, some pharmaceutical dusts are highly explosive. Recommended management practices are presented in the **General EHS Guidelines**.

Pathogenic and Biological Hazards

Exposure to pathogens may occur during isolation and growth of micro-organisms in laboratory and in fermentation processes. Recommended management practices are presented in the **General EHS Guidelines**.

Radiological Hazards

Research and development operations may include the use of radiological materials which should be managed to prevent and control worker exposures according to licensing requirements. Additional guidance on the management of radiological hazards is proved in the **General EHS Guidelines**.

Noise

High noise levels may be reached in some pharmaceuticals and biotechnology manufacturing areas (e.g. chemical synthesis facilities). High sound levels may be generated by manufacturing equipment and utilities (e.g. compressed air, vacuum sources, and ventilation systems). Industry-specific hazards are related to the typical enclosed design of pharmaceutical and biotechnology workplace modules, where personnel are often operating close to equipment during manufacturing and packaging operations. Recommended management practices to prevent and control occupational exposures to noise are presented in the **General EHS Guidelines**.

Process Safety

Process safety programs should be implemented, due to industry-specific characteristics, including complex chemical reactions, use of hazardous materials (e.g., toxic and reactive materials, and flammable or explosive compounds) and multi-step reactions. Process safety management includes the following actions:

- Physical hazard testing of materials and reactions;
- Hazard analysis studies to review the process chemistry and engineering practices, including thermodynamics and kinetics;
- Examination of preventive maintenance and mechanical integrity of the process equipment and utilities;
- Worker training; and
- Development of operating instructions and emergency response procedures.

1.3 Community Health and Safety

The most significant community health and safety hazards associated with pharmaceutical and biotechnology manufacturing facilities occur during the operation phase and may include the threat from major accidents related to the aforementioned fires and explosions at the facility and potential accidental releases of finished products during their transport outside of the processing facility. Guidance for the management of these issues is presented under Major Hazards below and in the **General EHS Guidelines** including the sections on: Traffic Safety; Transport of Hazardous Materials; and Emergency Preparedness and Response.

Major Hazards

The most significant safety impacts are related to the handling and storage of solid, liquid, and gaseous substances described above. Impacts may include significant exposures to workers and, potentially, to surrounding communities, depending on the quantities and types of accidentally released chemicals and the conditions for reactive or catastrophic events, such as fire and explosion.

Major hazards should be prevented through the implementation of a Process Safety Management Program that includes all of the minimum elements outlined in the respective section of the **General EHS Guidelines** including:

- Facility-wide risk analysis, including a detailed consequence analysis for events with a likelihood above 10^{-6}/year (e.g. HAZOP, HAZID, or QRA);
- Employee training on operational hazards;
- Procedures for management of change in operations, process hazard analysis, maintenance of mechanical integrity, pre-start review, hot work permits, and other essential aspects of process safety included in the **General EHS Guidelines**;
- Safety Transportation Management System as noted in the **General EHS Guidelines,** if the project includes a transportation component for raw or processed materials;
- Procedures for handling and storage of hazardous materials;
- Emergency planning, which should include, at a minimum, the preparation and implementation of an Emergency Management Plan prepared with the participation of local authorities and potentially affected communities.

2.0 Performance Indicators and Monitoring

2.1 Environment

Emissions and Effluent Guidelines

Tables 1 and 2 present emission and effluent guidelines for this sector. Guideline values for process emissions and effluents in this sector are indicative of good international industry practice as reflected in relevant standards of countries with recognized regulatory frameworks. These guidelines are achievable under normal operating conditions in appropriately designed and operated facilities through the application of pollution prevention and control techniques discussed in the preceding sections of this document.

Emissions guidelines are applicable to process emissions. Combustion source emissions guidelines associated with steam- and power-generation activities from sources with a capacity equal to or lower than 50 Megawatt thermal (MWth) are addressed in the **General EHS Guidelines** with larger power source emissions addressed in the **EHS Guidelines for Thermal Power**. Guidance on ambient considerations based on the total load of emissions is provided in the **General EHS Guidelines**.

Effluent guidelines are applicable for direct discharges of treated effluents to surface waters for general use. Site-specific discharge levels may be established based on the availability and conditions in the use of publicly operated sewage collection and treatment systems or, if discharged directly to surface waters, on the receiving water use classification as described in the **General EHS Guidelines.** These levels should be achieved, without dilution, at least 95 percent of the time that the plant or unit is operating, to be calculated as a proportion of annual operating hours. Deviation from these levels in consideration of

Table 1. Air Emissions Levels for Pharmaceuticals and Biotechnology Manufacturing

Pollutant	Units	Guideline Value
Active Ingredient (each)	mg/Nm^3	0.15
Particulate Matter	mg/Nm^3	20
Total Organic Carbon	mg/Nm^3	50
Hazardous Air Pollutants	kg/year	900-1,800[3]
Total Class A[1]	mg/Nm^3	20[4]
Total Class B[2]	mg/Nm^3	80[5]
Benzene, Vinyl Chloride, Dichloroethane (each)	mg/Nm^3	1
VOC	mg/Nm^3	20-150[6] 50[7]
Bromides (as HBr)	mg/Sm^3	3
Chlorides (as HCl)	mg/Sm^3	30
Ammonia	mg/Sm^3	30
Arsenic	mg/Sm^3	0.05
Ethylene Oxide	mg/Sm^3	0.5
Mutagenic Substance	mg/Sm^3	0.05

Notes:

1. Class A compounds are those that may cause significant harm to human health and the environment. They include Montreal Protocol substances, as well as others identified in the EU Directive 1999/13/EC on the Limitation of Emissions of Volatile Organic Compounds due to the Use of Organic Solvents in Certain Activities and Installations. Example of Class A compounds include: acetaldehyde, acrylic acid, benzyl chloride, carbon tetrachloride, chlorofluorocarbons, ethyl acrylate, halons, maleic anhydride, 1,1,1 trichloroethane, trichloromethane, trichloroethylene, and trichlorotoluene.
2. Class B compounds are organic compounds of less environmental impact than Class A compounds. Examples include: toluene, acetone and propylene.
3. Process-based annual mass limit. 900: Actual HAP emissions from the sum of all process vents within a process; 1,800: Actual HAP emissions from the sum of all process vents within processes.
4. Applicable when total Class A compounds exceed 100 g/hr.
5. Applicable when total Class B compounds, expressed as toluene, exceed the lower of 5 t/year or 2 kg/hr.
6. EU Directive 1999/13/EC. Facilities with solvent consumption > 50 tonnes/year. Higher value (150) to be applied for waste gases from any technique which allows the reuse of the recovered solvent. Fugitive emission values (non including solvent sold as part of products and preparations in a sealed container): 5 percent of solvent input for new facilities and 15 percent for existing facilities. Total solvent emission limit values: 5 percent of solvent input for new facilities and 15 percent for existing facilities.
7. Waste gases from oxidation plants. As 15 minute mean for contained sources.

Environmental Monitoring

Environmental monitoring programs for this sector should be implemented to address all activities that have been identified to have potentially significant impacts on the environment, during normal operations and upset conditions. Environmental monitoring activities should be based on direct or indirect indicators of emissions, effluents, and resource use applicable to the particular project.

Monitoring frequency should be sufficient to provide representative data for the parameter being monitored. Monitoring should be conducted by trained individuals following monitoring and record-keeping procedures and using properly calibrated and maintained equipment. Monitoring data should be analyzed and reviewed at regular intervals and compared with the operating standards so that any necessary corrective actions can be taken. Additional guidance on applicable sampling and analytical methods for emissions and effluents is provided in the **General EHS Guidelines**.

2.2 Occupational Health and Safety

Occupational Health and Safety Guidelines

Occupational health and safety performance should be evaluated against internationally published exposure guidelines, of which examples include the Threshold Limit Value (TLV®) occupational exposure guidelines and Biological Exposure Indices (BEIs®) published by American Conference of Governmental Industrial Hygienists (ACGIH),[23] the Pocket Guide to Chemical Hazards published by the United States National Institute for Occupational Health and Safety (NIOSH),[24] Permissible Exposure Limits (PELs) published by the Occupational Safety and Health Administration of the United States (OSHA),[25] Indicative Occupational Exposure Limit Values published by European Union member states,[26] or other similar sources.

Accident and Fatality Rates

Projects should try to reduce the number of accidents among project workers (whether directly employed or subcontracted) to a rate of zero, especially accidents that could result in lost work time, different levels of disability, or even fatalities. Facility rates may be benchmarked against the performance of facilities in this sector in developed countries through consultation with published sources (e.g. US Bureau of Labor Statistics and UK Health and Safety Executive)[27].

Occupational Health and Safety Monitoring

The working environment should be monitored for occupational hazards relevant to the specific project. Monitoring should be

Table 2. Effluents Levels for Pharmaceuticals and Biotechnology Manufacturing

Pollutant		Units	Guideline Value
pH		S.U.	6-9
BOD_5		mg/L	30
COD		mg/L	150
TSS		mg/L	10
Oil and grease		mg/L	10
AOX		mg/L	1
Phenol		mg/L	0.5
Arsenic		mg/L	0.1
Cadmium		mg/L	0.1
Chromium (hexavalent)		mg/L	0.1
Mercury		mg/L	0.01
Active ingredient (each)		mg/L	0.05
Ammonia		mg/L	30
Total nitrogen		mg/L	10
Total phosphorus		mg/L	2
Ketones (each)(1)		mg/L	0.2
Acetonitrile		mg/L	10.2
Acetates (each)(2)		mg/L	0.5
Benzene		mg/L	0.02
Chlorobenzene		mg/L	0.06
Chloroform		mg/L	0.013
o-Dichlorobenzene		mg/L	0.06
1,2-Dichloroethane		mg/L	0.1
Amines (each)(3)		mg/L	102
Dimethyl sulfoxide		mg/L	37.5
Methanol / ethanol (each)		mg/L	4.1
n-Heptane		mg/L	0.02
n-Hexane		mg/L	0.02
Isobutyraldehyde		mg/L	0.5
Isopropanol		mg/L	1.6
Isopropyl ether		mg/L	2.6
Methyl cellosolve		mg/L	40.6
Methylene chloride		mg/L	0.3
Tetrahydrofuran		mg/L	2.6
Toluene		mg/L	0.02
Xylenes		mg/L	0.01
Bioassays	Toxicity to fish Toxicity to Daphnia Toxicity to algae Toxicity to bacteria	T.U.(4)	2 8 16 8

Notes:
1. Including Acetone, Methyl Isobutyl Ketone (MIBK).
2. n-Amyl Acetate, n-Butyl Acetate, Ethyl acetate, Isopropyl Acetate, Methyl Formate.
3. Including Diethylamine and Triethylamine.
4. TU = 100 / no effects dilution rate (%) of waste water. The "no effect dilution rate" should be monitored with standard toxicity tests (e.g. CEN, ISO or OECD acute toxicity testing standards.)

[23] Available at: http://www.acgih.org/TLV/ and http://www.acgih.org/store/
[24] Available at: http://www.cdc.gov/niosh/npg/
[25] Available at: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992
[26] Available at: http://europe.osha.eu.int/good_practice/risks/ds/oel/
[27] Available at: http://www.bls.gov/iif/ and http://www.hse.gov.uk/statistics/index.htm

designed and implemented by accredited professionals[28] as part of an occupational health and safety monitoring program. Facilities should also maintain a record of occupational accidents and diseases and dangerous occurrences and accidents. Additional guidance on occupational health and safety monitoring programs is provided in the **General EHS Guidelines.**

[28] Accredited professionals may include Certified Industrial Hygienists, Registered Occupational Hygienists, or Certified Safety Professionals or their equivalent.

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Annex A: General Description of Industry Activities

Pharmaceuticals and biotechnology manufacturing consists of two main production lines:

- Primary manufacturing or production of bulk substances (production of active pharmaceutical ingredients). Small molecule Active Pharmaceutical Ingredients (APIs) are organic molecules or salts of such molecules that have been synthesized or extracted from natural sources to allow production of medicinal products.
- Primary manufacture in biotechnology can involve various technologies that harness the natural machinery of certain cell lines and potentially multi-cellular organisms to produce complex biological molecules for incorporation into medicinal products.
- Secondary manufacturing (formulation, mixing, compounding, packaging), where active ingredients are treated and modified into final products. The products can be solids (e.g. tablets, coated or not and capsules), liquids (e.g. solutions, emulsions, injectables), creams and ointments, or aerosols.

Pharmaceuticals and biotechnology manufacturing should be performed, following current Good Manufacturing Practice (cGMP) procedures which allow ensuring product quality, as well as safe working environment conditions and prevention of environment impacts[29].

The cGMP procedures should determine the characteristics of production zones, relating to the presence of particulates and microbial organisms. Areas should be classified according to environmental requirements and then each operation should follow the required level of cleanness for avoiding any risk of particulate and microbial contamination of the product.

The pharmaceutical research and development include chemical synthesis and in vitro and in vivo laboratory works, which allow evaluating the pharmacodynamic of new chemical entities. Biotechnology research is mainly focused on the identification, development, and transfer of technologies for laboratory scale production of medically recombinants proteins Biosafety and chemical safety levels should be identified for each laboratory based on the hazards of the biological and chemical agents used.

Primary Pharmaceutical Manufacturing

Most of primary manufacture products are bulk materials, normally crystalline solid salts, organic acids or bases, containing an active pharmaceutical ingredient (API). The production is obtained by chemical synthesis (multistep chemical synthesis), fermentation, enzymatic reactions, extraction from natural materials, or by combination of these processes.

The chemical reaction of interest is obtained in a reactor (normally stainless steel made), blending the reagents by a mixer or / and compressed air. The reaction products can be a liquid, solid or heterogeneous phase. The active ingredient is separated from the other material by decantation, centrifugation, filtration or crystallization. In this step solvent or water are used to facilitate product separation and its purification from reaction byproducts.

The product can be further purified by dissolution, extraction, or by ultrafiltration. A new separation is then performed to obtain a wet cake that may be treated again in the same way (up to two or three times) or that is ready to be fed to a homogenizer and

[29] Facilities are generally operated according current Good Manufacturing Practice (GMP) or approval by the European Medicine Evaluation Agency (EMEA), the United States Food and Drug Administration (FDA) or other applicable medicine approval authorities. See for example European Commission Directive 2003/94/EC, of 8 October 2003

for dried (dry oven, spray drying, lyophilization). The products (are then milled and prepared for packaging. The reaction generates byproducts (solvents, trace active ingredients), which are either recycled or disposed of after treatment.

Biotechnology Manufacturing

Biotechnology can be defined as the application of biological systems to technical and industrial processes. Traditional biotechnology is the result of classic hybridization (i.e., mating or crossing of various organisms to create new organisms used in industrial application, including food industry, pharmaceutical industry, and waste water treatment). Modern biotechnology combines the principles of chemistry and biological sciences (molecular and cellular biology, genetics, and immunology) with technological disciplines to produce goods and services. It utilizes enzymes to cut and paste genetic information, DNA, from one organism to another outside living cells. The composite DNA is then reintroduced into host cells to determine whether the desired trait is expressed. The resulting cell is called an engineered clone, a recombinant or a genetically manipulated organism (GMO)[30]. In general, genetic engineering techniques are therefore used to establish cell lines, which are then used in fermentation processes to produce the biologically active molecules at industrial scale.

The biotechnology industry can be categorized in four main industry sectors:

- Biomedical pharmaceuticals, biologic and medical device products;
- Agricultural foods, transgenic animals, disease resistant and pest resistant plants;
- Genetically enhanced industrial products (e.g., detergent enzymes); and
- Wastewater treatment and decontamination of industrial wastes.

In the biomedical sector, modified cells or organisms are cultivated in monoculture bioreactors. In mammalian cell culture, the protein product is secreted from the cells into the surrounding nutrient medium, and chemical separation methods (e.g., size or affinity chromatography, electrophoresis) may be used to capture and purify the product.

Fermentation using *Escherichia coli* host organisms produces the desired product within the cell membrane. Cells are then physically ruptured in order to harvest the product. Antibiotics may be added to the production media to enhance production or maintain selective pressure on otherwise unstable genetic production elements (plasmids).

Penetrations into the bioreactor vessels are necessary for providing nutrients and oxygen, for off-gassing carbon dioxide, and for monitoring and controlling the system. Sealing and filtration (0.2 micron) is needed for each penetration to prevent contamination of the culture. Exhaust gas filtration is also necessary to protect the working environment and the outside environment from aerosols generated during the culture or fermentation. Depending on the biohazard potential of the system, biological inactivation of liquid effluents (usually by heat, steam, or chemical methods) is standard practice.

In plant biotechnology, the methods used to transfer DNA into plant cells, which have tough, cellulose cell walls, typically differ from those used for bacteria and mammalian cell lines used in the biomedical sector. Two primary methods are used for introducing engineered DNA into plant cells:

- Shooting of DNA into the cell of interest by a particle gun;

[30] International Labour Organization (ILO). Safework Bookshelf. Encyclopaedia of Occupational Health and Safety. 4th ed. Biotechnology Industry.

- Use of an engineered *Agrobacterium tumefaciens* virus, which is harmless and does not produce plant tumors, to introduce gene cassettes into the cell's genetic material.

After transformation by either method, plant cells are diluted, plated, and grown on selective tissue culture media for a relatively long (compared to bacterial growth rates) period in incubators. Plants regenerated from the treated tissue are transplanted to soil in enclosed growth chambers for further growth. They are then examined for expression of the desired traits and grown in greenhouses for several generations.

Other processes used in biotechnology manufacturing include concentration and purification (by filtration or other methods). Final production steps may include cake drying, milling of the dried product, and packaging.

Secondary Manufacturing

The purpose of secondary manufacturing is to transform prepared active products to drugs ready to be administered to the public. In this phase, the APIs are not modified, but they are joined to inert materials (excipients), which determine the final physical characteristics of the pharmaceutical products.

Active materials are diluted or incorporated with various types of excipients (e.g. lactose, starch, sugar, cellulose based products, talc, among others) and then stabilized in different pharmaceutical forms (e.g. solids, powders, liquids, creams and ointments, aerosols).

Formulation is the production step which defines the recipe for all the manufacturing components (active ingredients, non active and packaging materials).

Dispensing is performed in controlled areas under HVAC systems and with precautions to avoid cross contamination and material losses. Weighed materials are transferred to other rooms in closed containers to ensure full segregation of the products.

When solids are manufactured, **compounding** is conducted to mix active ingredients with excipients in one or two steps, depending on the presence of intermediate granulation.

Mixing is conducted using different types of machines, often involving rotating bins.

Granulation is conducted to obtain the aggregation of powdered materials (e.g. wet or dry granulation). Wet granulation requires the use of water or solvent solution. When wet granulation is used, a drying stage is needed, typically performed using hot air. Outlet air, containing traces of powders, is filtered before emission to atmosphere, and, if solvent is used, solvent recovery / absorption systems are installed before filtration.

Packaging of solid products is conducted either in mono-dose sachets or in tablets, which are produced by a pressing machine. Tablets are either packed as they are at the end of pressing, or coated.

Tablet **coating** allows for better physical - chemical and mechanical stability of the product, as well as facilitation of final packaging. Aqueous or solvent coating solution is sprayed on the product while it is slowly rotating. If solvent solution is used, an explosion proof environment is necessary. Capsule manufacturing follows the same process as tablets to obtain the final product mix, which is then inserted in hard and soft gelatin capsules.

Liquid product manufacturing may be divided in two categories: sterile products (injectables and collyria), and non sterile products (syrups and drops). Manufacturing of non sterile products consists of dissolution of ingredients and insertion into

high or small volume containers (e.g. glass, plastic, metallic, etc.).

Injectable products manufacturing requires sterile conditions. Dispensing and solution preparation are conducted in controlled areas. The active principle is normally diluted in WFI (water for injection), which has undergone several purification steps to final distillation or reverse osmosis treatment.

Packaging materials for liquid solutions are glass or plastic. In case of the use of plastic (polyethylene, polythene and polypropylene), the filling equipment is simple and compact. Plastic ampoules or bottles are preformed from granules and then welded immediately after the filling. In case of the use of glass containers (normally open ampoules or vials), they are previously washed, sterilized and depyrogenized.

Filling and welding operations are performed under laminar flow. For welding a pure fuel (natural gas or liquid propane) is used to avoid any contamination. Glass remaining from welding can be contaminated. It is typically collected, washed and filtered, and discharged as clean glass. A similar treatment is conducted if plastic materials are used.

The use of isolator technology is necessary to minimize human intervention in processing areas and to decrease the risk of microbiological contamination of aseptically manufactured products. Isolators are designed as fully sealed systems incorporating a sterilization mechanism. Air classification required for the airborne environmental parameters depends on the design of the isolator and its application. The clean room / isolator should be controlled and should meet international requirements for aseptic processing and manufacture of sterile medicinal products[31].

As an alternative to the use of primary glass containers, Blow / Fill / Seal technology may be used to package aseptic liquid products. The technology has three main steps including formation of plastic containers from a thermoplastic granulate, liquid filling, and final sealing.

Before final packaging, the product may undergo high temperature treatment (more than 121°C) by autoclave for sterilization, provided active products are not damaged by exposure to high temperatures.

Creams and ointments manufacturing: After dispensing and compounding of active principles and excipients, the manufacturing process consists of fusion of solid mass and addition of surfactant agents and water or oil. The final production stage before packaging is performed in an emulsifier.

Aerosols are obtained by mixing of a liquid product with an inert gas in pressurized metallic, plastic or glass containers.

Associated Auxiliary Facilities

Water Supply and Treatment

Water is generally needed both for the process (e.g., dilution) and for other uses including cooling water, deionized water, equipment and piping cleaning water, etc. Water for injection (WFI) is used for manufacture of injectable products and in any process where sterile conditions are needed. Water purity is obtained by deionized water distillation or by double reverse osmosis. The storage tank is blanketed with pure nitrogen or air. Piping and storage are maintained at a temperature higher than 80°C, and water is continuously recycled to avoid contamination.

[31] Airborne environmental requirements for sterile drug production and clean rooms are provided by the US Food and Drug Administration (FDA), Center for Drug and Evaluation Research; the United States Pharmacopeia Convention (USP), Chapter 1116; and by the European Commission Directive 2003/94/EC, of 8 October 2003, Annex 1.

HVAC (Heating, Ventilation, Air Conditioning) System

Pharmaceuticals and biotechnology manufacturing facilities cannot be operated without the presence of a suitable HVAC system, which should be designed according to cGMP protocols. HVAC systems should be designed to meet product protection, occupational health and safety, and environmental protection needs. Air conditioning systems should be designed to include filtration of air.

Wastewater Treatment

Pharmaceuticals and biotechnology manufacturing facilities generally include a dedicated wastewater treatment unit (WWTU) to treat liquid wastes generated from the different production processes.