PHARMACEUTICAL OPERATIONS

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1.0 SCOPE

This data sheet contains loss prevention recommendations covering various operations and equipment related to the making of pharmaceutical products. This includes the manufacture of prescription (ethical and generic) and over-the-counter medications; biotechnology manufacturing; pharmaceutical laboratories; vivariums; chemical/molecule libraries, and the manufacturing of implanted medical devices (e.g., artificial joints). For the manufacturing of primary active pharmaceutical ingredients (APIs), the guidance presented here applies in addition to the applicable chemical data sheets.

This data sheet does not provide guidance on basic construction, occupancy, basic design of programs for process safety, burglary and theft, operator training, or asset integrity or common protection features, necessary for property loss prevention; see the applicable data sheets for those types of recommendations.

In addition to the recommendations in this data sheet, refer to specific guidance in following data sheets:

- For the design of water mist systems, see Data Sheets 3-26, *Fire Protection for Non-Storage Occupancies*, and 4-2, *Water Mist Systems*.
- For exhaust systems, see Data Sheet 7-78, *Industrial Exhaust Systems*.
- For the protection of ignitable liquids, see Data Sheets 7-14, *Fire Protection for Chemical Plants*; 7-29, *Ignitable Liquid Storage in Portable Containers*; 7-32, *Ignitable Liquids Operations*; 7-98 *Hydraulic Fluids*; and 7-88, *Outdoor Ignitable Liquid Storage Tanks*.
- For the storage and use of radioactive materials, see Data Sheet 7-61, *Facilities Processing Radioactive Materials*.
- For control and safety systems, and mitigation of cyber hazards, see Data Sheets 7-45, *Safety, Controls, Alarms and Interlocks*, and 7-110, *Industrial Control Systems*.
- For combustible dusts, see Data Sheet 7-76, *Combustible Dusts*.
- For heat transfer systems used in lyophilizers, see Data Sheet 7-99, *Heat Transfer Fluid Systems*.
- For refrigeration, coolers, and freezers, see Data Sheets 7-13, *Mechanical Refrigeration*, and 2-0, *Installation Guidelines for Automatic Sprinklers*.
- For the storage and use of compressed gases, see Data Sheet 7-50, *Compressed Gases in Portable Cylinders and Bulk Storage*.
- For the design and protection of HVAC systems, see Data Sheet 1-45, *Air Conditioning and Ventilating Systems*.
- For the protection of dryers, see Data Sheets 6-9, *Industrial Ovens and Dryers*, and 7-59, *Inerting and Purging Vessels and Equipment*.
- For backup power, see Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*.
- For the design and protection of chemical and pharmaceutical reactors, see Data Sheet 7-46, *Chemical Reactors and Reactions*.

1.1 Hazard

Pharmaceutical manufacturing, research, and development often work with small volumes of very high-value product, with associated exposures potentially coming from very small incidents.

Large amounts of ignitable liquids are present in primary and secondary pharmaceutical plants. Spills involving heated or unheated ignitable liquids, or vapor releases from heated processes conducted at reflux (i.e., at the boiling point of the liquid) can lead to large loss events.

Most pharmaceutical products are also susceptible to any type of contamination, such as nonthermal damage or a small leak of liquid.

Finally, the nature of the product determines the need for compliance with numerous government regulations. This can increase the time required for recovery from an incident.

Other hazards present at pharmaceutical operations are addressed by data sheets for fire, natural hazards, and equipment loss prevention.

1.2 Changes

July 2021. Interim revision. Relocated inspection guidance for sealed concealed sprinklers to Data Sheet 2-81, *Fire Protection Systems Inspection, Testing and Maintenance.*

2.0 LOSS PREVENTION RECOMMENDATIONS

2.1 Introduction

Unless otherwise stated in this data sheet, use FM Approved equipment and materials whenever they are applicable. For a list of products that are FM Approved, see the *Approval Guide*, an online resource of FM Approvals.

2.1.1 Apply principles of inherent safety wherever possible when designing or improving processes. Inherent safety includes the following general principles:

A. Intensification: Using smaller amounts of hazardous substances.

B. Substitution: Replacing a hazardous chemical with a non-hazardous or less-hazardous one.

C. Attenuation: Using less-hazardous process conditions or a less-hazardous form of a material.

D. Limitation of effects: Designing a facility to minimize the impact of a release of hazardous material or energy (e.g., by sufficient spacing or more-resistant construction).

E. Simplification/error tolerance: Designing a facility so operating errors are less likely, or the process is more forgiving if errors are made.

2.1.2 Implement programs to manage process safety per Data Sheet 7-43, *Process Safety*. Pay particular attention to the process hazard analysis/review (PHA) of routine and non-routine operations, including the following:

- Startup
- Shutdown (normal and emergency)
- Sampling
- Cleaning
- Maintenance operations

2.2 Construction and location

2.2.1 Use noncombustible construction materials.

2.2.1.1 Where noncombustible construction materials are not available, use FM Approved materials.

2.2.1.2 For walls and ceilings, use FM Approved 4882 materials.

2.2.2 Do not route liquid pipes above areas containing sterile processing or high-value equipment.

2.2.2.1 Wherever liquid piping exists above these areas, seal (make liquid-tight) the floor of the room of origin or the ceiling of the room below and provide spill containment.

2.2.2.2 Provide leak detection wherever liquid leakage potentials exist.

2.3 Occupancy

2.3.1 Consider separation of inventory (raw materials, intermediates, and finished products) so they are not subject to a common event. For additional guidance, see Section 2.10.

2.3.2 Arrange processes or logistics to minimize the combustible loading in cleanrooms and adjacent preparation areas.

2.4 Protection

2.4.1 Provide automatic sprinklers wherever combustible construction or occupancy is present, per the applicable data sheets.

2.4.2 Protect pharmaceutical cleanrooms with FM Approved non-storage sprinklers, preferably quick response, pendant-type.

Water mist systems are acceptable provided they meet the guidance in FM Data Sheets 3-26 *Fire Protection for Non-Storage Occupancies* and 4-2 *Water Mist Systems*.

2.4.2.1 If sealed concealed sprinklers are required by others, use an FM Approved model.

2.4.2.2 For inspection, testing and maintenance guidance of sealed concealed sprinklers, see Data Sheet 2-81, *Fire Protection System Inspection, Testing and Maintenance*.

2.4.3 Protect ductwork in accordance with Data Sheet 7-78, *Industrial Exhaust Systems*.

2.4.4 Protect ignitable liquids in accordance with this data sheet and other applicable data sheets. These include:

- Data Sheet 7-14, *Fire Protection for Chemical Plants*
- Data Sheet 7-29, *Ignitable Liquid Storage in Portable Containers*
- Data Sheet 7-32, *Ignitable Liquids Operations*
- Data Sheet 7-88, *Outdoor Ignitable Liquid Storage Tanks*

2.4.5 Protect processes in which radioactive materials are used in accordance with Data Sheet 7-61, *Facilities Processing Radioactive Materials*.

2.4.6 Provide an FM Approved smoke detection system in pharmaceutical processing/manufacturing areas that are:

A. not constantly attended **AND**

B. not covered by the HVAC detection systems.

2.5 Equipment and Processes

2.5.1 General

The following guidance applies also to prefabricated and modular construction that may be assembled off-site and delivered for final installation.

2.5.1.1 Use noncombustible materials where possible for the construction of all equipment.

2.5.1.1.1 Where these is not available, equipment constructed from materials that have passed the FM Approvals Cleanroom Materials Flammability Test Protocol (FM 4910 materials), can be used where practical to reduce the combustible loading in the area.

2.5.1.2 Perform a full cyber risk security assessment of equipment and controls in accordance with Data Sheet 7-110, *Industrial Control Systems*.

2.5.1.3 Where ignitable liquids are used, implement safeguards for fire and explosion per Data Sheets 7-14, *Fire Protection for Chemical Plants*, and/or 7-32, *Ignitable Liquid Operations*.

2.5.1.3.1 In cleanrooms or biopharma environments, open drains may not be acceptable due to quality requirements. Where closed drains are present or required in areas with ignitable liquid operations, apply the following guidance in order of preference:

A. Minimize the quantities of ignitable liquids present.

B. Provide automatic shutoffs for any ignitable liquid feeds.

C. Provide sealed cleanroom drainage that can be opened automatically.

Where installed, shutoffs and remote opening drains are to be automatically interlocked with FM Approved Leak Detection systems and/or upon operation of automatic sprinkler systems within the area.

2.5.1.3.2 Provide manual activation (e.g., switches, levers, buttons) for ignitable liquid shutoffs and remote opening drains at accessible locations (e.g., near the exit of the room or in the control room). Manual activation systems are secondary systems. They are to be installed in addition to the primary fully automatic systems and in accordance with Data Sheet 7-32, *Ignitable Liquid Operations*.

2.5.1.4 Where combustible dusts are used, implement safeguards for fire and explosion per Data Sheet 7-76, *Combustible Dusts*.

2.5.1.5 Where heat transfer systems are used, follow the guidance in Data Sheet 7-99, *Heat Transfer Fluid Systems*.

2.5.1.5.1 Where heat transfer systems are associated with lyophilizers, follow the guidance in this data sheet.

2.5.1.6 Arrange refrigeration systems in accordance with Data Sheet 7-13, *Mechanical Refrigeration*.

2.5.1.7 Where compressed gases are used in laboratories (e.g., gas chromatographs) follow the guidance in Data Sheet 7-50, *Compressed Gases in Portable Cylinders and Bulk Storage*.

2.5.1.8 When venting waste gases from process equipment through an exhaust system, ensure the exhaust system is operational prior to venting. An acceptable option is to interlock the exhaust system with the process generating these gases to ensure the exhaust system is in operation at the time venting is required. For additional guidance, refer to Data Sheet 7-78, *Industrial Exhaust Systems*.

2.5.2 Heating, Ventilation, and Air-Conditioning (HVAC) Systems

2.5.2.1 Design the heating, ventilation, and air-conditioning (HVAC) systems in accordance with Data Sheet 1-45, *Air Conditioning and Ventilating Systems*. Where these systems are to be servicing cleanrooms, follow the guidance in Data Sheet 1-56, *Cleanrooms*.

2.5.2.2 Use noncombustible or FM Approved 4920 filters. Where combustible filter media is used, provide automatic sprinkler protection in accordance with Data Sheet 1-45, *Air Conditioning and Ventilation Systems*.

2.5.3 Reactors

2.5.3.1 Design and protect all reactors, including bioreactors, in accordance with Data Sheet 7-46, *Chemical Reactors and Reactions*.

2.5.4 Dryers

2.5.4.1 Protect dryers per Data Sheets 6-9, *Industrial Ovens and Dryers*, and 7-59, *Inerting and Purging Vessels and Equipment*.

2.5.5 Process Control Systems

2.5.5.1 Where computer-based process control systems are present, use the guidance in Data Sheets 7-45, *Safety, Controls, Alarms and Interlocks*, and 7-110, *Industrial Control Systems*.

2.5.6 Lyophilizers (Freeze Drying)

2.5.6.1 For lyophilizers, follow the guidance in Data Sheet 7-99, *Heat Transfer Fluid Systems*.

2.5.6.2 Provide backup power sources (e.g., UPS, emergency generators) in accordance with Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*.

2.5.6.3 Locate the heating/cooling equipment for lyophilizers outside of the clean/sterile core.

2.5.6.4 Protect hydraulic systems associated with lyophilizers per Data Sheet 7-98, *Hydraulic Fluids*.

2.5.6.5 If the fluid being removed from the product is an ignitable liquid, analyze per Data Sheet 7-32, *Ignitable Liquid Operations*.

2.5.7 Cooler and Freezer Storage Units

2.5.7.1 Protect walk-in coolers, refrigerators and freezer storage units for pharmaceutical raw materials, intermediates, and finished products in accordance with Data Sheet 2-0, *Installation Guidelines for Automatic Sprinklers*, in addition to the following:

A. Provide a backup power supply for the duration of a foreseeable scenario in which there is a loss of power. Refer to Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*, for additional guidance.

B. Provide refrigeration/cooling systems on an N+1 basis with the following:

1. An easily read temperature indicator that is checked on a regular basis, with a locally sounding alarm to indicate out-of-range (high or low) conditions

2. Remote temperature monitoring to a constantly attended location

C. Where N+1 (backup) systems are based on separate freezer/cooler enclosures, have a documented contingency plan to relocate storage.

2.5.8 Cell Banks (Master and Working)

2.5.8.1 Duplicate master and working cell banks.

2.5.8.2 Store master and working cell banks (including any duplicates) in separate physical locations from each other.

2.8.5.3 Establish a fully documented contingency plan for any loss or damage to any cell banks.

2.5.9 Chemical/Molecule Libraries

2.5.9.1 For research and development chemical/molecule libraries, implement the following loss prevention features:

A. Split critical individual samples into separate storage units in separate fire areas, where possible.

B. Locate automated storage systems in areas that have no other stored combustible materials, are secure from outside access, and have necessary temperature and humidity controls.

C. Provide sprinklers in accordance with the relevant data sheet. Where stored compounds can be sensitive to smoke damage, an FM Approved gaseous extinguishing system activated by high-sensitivity products of combustion detectors is acceptable in lieu of sprinklers.

2.5.10 Laboratories

2.5.10.1 For bench-scale laboratories, implement the following loss prevention features:

A. Keep the quantities of ignitable liquid to a minimum and store them in FM Approved safety cans or storage cabinets. This includes solvent waste from high-performance liquid chromatography (HPLC) operations.

B. Store ignitable liquids kept in glass bottles or plastic containers that are less than (0.7 gal [2.5 L]) in FM Approved storage cabinets where they will not be subject to mechanical damage, bumping, or falling, when not in use.

C. Do not store ignitable liquid in ordinary refrigerators. Use only devices specifically designed for such use.

2.5.11 Vivariums

2.5.11.1 For vivariums, implement the following loss prevention features:

A. Keep combustible storage out of animal areas and other areas sensitive to smoke contamination.

B. Install automatic sprinkler protection in areas used for the storage of food, bedding, and cleaning supplies; in the animal areas if plastic cages are used; and in the office areas if combustible loading is significant. Design the sprinkler protection in accordance with Data Sheet 3-26.

C. If sprinklers are installed in cage wash areas, ensure they have a temperature rating at least 50°F (10°C) above the normal room temperature when cleaning is being undertaken.

D. Provide and arrange HVAC systems in accordance with Data Sheet 1-45, *Air Conditioning and Ventilating Systems*.

2.6 Operations and Maintenance

2.6.1 Implement an asset integrity program per Data Sheet 9-0, *Asset Integrity*.

2.7 Training

2.7.1 Implement operator training programs per Data Sheet 10-8, *Operators*.

2.8 Human Factor

2.8.1 Implement programs to manage process safety at a level commensurate with the hazards present in accordance with Data Sheet 7-43, *Process Safety*, even if not required by national or local regulations. Apply these elements for all critical operations, support systems, and utilities. Focus particularly on the following areas:

- Management commitment
- Process safety knowledge
- Process Hazard Analysis (PHA)
- Management of Change (MOC)

2.8.2 Provide protection against burglary and theft in accordance with Data Sheet 9-16, *Burglary and Theft*.

2.8.3 Where enclosures such as freezers and stability chambers are not constantly attended, provide an FM Approved fire detection system.

2.8.4 Develop and maintain a documented liquid damage emergency response plan in accordance with Data Sheet 1-24, *Protection Against Liquid Damage*.

2.8.5 Develop emergency response plans and procedures per Data Sheet 10-1, *Pre-Incident Planning*. When developing these plans, give particular consideration to the following:

A. Location and access restrictions for materials that are toxic, corrosive, or radioactive, as well as other biological hazards. This may include when these materials are present but do not present a risk to entry.

B. Shutoffs for ignitable liquids, flammable gases, and process gases (including oxygen).

C. Maintenance of utilities to critical/sensitive areas, such as freezers, cell banks, and stability chambers, outside the fire area.

D. Post-event review to ensure all utilities to critical/sensitive areas are restored.

2.9 Utilities

2.9.1 Provide sufficient reliability and redundancy of process utilities to prevent interruption to critical processes or product spoilage. This may include providing N+1 reliability and/or emergency (backup) power. Critical utilities include process heating and cooling; room/building air-handling systems; humidity control; power, instrument, process, and breathing air; fuels; process and inert gases; steam and clean steam; purified water; water for injection (WFI); process waste handling; and solvent recovery.

2.9.2 When important emergency systems are taken out of service for maintenance or repair, implement a tracking/management system to ensure the outage is minimized and the proper precautions are instituted for affected users.

2.10 Contingency Planning

2.10.1 Duplicate and safeguard important business records and store them in separate locations. These records may be paper or electronic and include the following:

A. Research records such as animal studies; records of production techniques, chemical synthesis techniques, development chemicals, and master cell cultures

B. Production records (QA/QC records, stability studies, retention samples)

C. Discovery, optimization, and production information of successful products

D. Regulatory required materials, supplier information, toll converters

2.10.2 Develop a contingency plan considering the loss of QA/QC laboratories.

2.10.3 Establish a business continuity plan (BCP) for all critical product lines. Include the following:

A. Credible disruption scenarios including site-wide conflagration events, area-wide disasters (hurricane, earthquake, wildfires), loss of critical suppliers/third-party manufacturing, and pandemics

B. Amount and location of strategic safety stocks

C. Redundant capacity/alternative manufacturing locations

2.11 Electrical

2.11.1 Inspect, test, and maintain backup and emergency generators in accordance with Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*.

3.0 SUPPORT FOR RECOMMENDATIONS

3.1 Industry Overview

Pharmaceutical plants use a variety of chemical and biological processes to produce prescription drugs and over-the-counter medications. Pharmaceuticals can be for human or animal use.

Primary pharmaceutical plants manufacture active pharmaceutical ingredients (APIs). APIs are made on a campaign basis, typically in relatively small volumes, yet the finished products are often of high value. APIs can be made:

- Synthetically, through chemical reactions with solvents, catalysts and inhibitors.
- Biochemically or biologically e.g. fermentation, enzyme reactions
- By a combination of synthetic and biochemical processes

Chemical processes used can be multipurpose operations or dedicated to a single process step for a defined component. Typical equipment and unit operations include the following:

- Mixing and blending of chemicals
- Chemical reactions
- Cell growth
- Crystallization, centrifuging, filtration, drying, milling, sieving, blending and bulk packaging
- Distillation, liquid-liquid extraction, chromatographic separation
- Heat transfer using water, brine, steam, or organic fluids
- Control of vapor, liquid, and solid emissions by collection (dust collectors, scrubbers, carbon bed adsorbers) or destruction (catalytic or thermal oxidizers, fume incinerators)

Secondary pharmaceutical plants take the active ingredients manufactured by primary sites or toll converters and put them into a form that is suitable for use by the customer. Operations are numerous and can include the following:

- Blending APIs with other chemicals such as fillers, additives and even some ignitable liquids
- Granulation, where products (sometimes dissolved in ignitable liquid) are sprayed onto a nucleus in a fluidized bed granulator/dryer
- Centrifuging, filtration, drying, milling, sieving, and blending)
- Filling, tableting, compounding of products into bottles, syringes, ampoules, inhalers and vials with liquid actives
- High-purity water production (water for injection [WFI])
- Freeze-drying of finished products (lyophilization)

Some pharmaceutical products are seasonal in nature. The most notable of these being vaccines, such as the flu vaccine. In the case of the flu vaccine, inventory levels are very high just prior to flu season beginning and at the lowest levels, at the end of flu season. When evaluating occupancies where these seasonal fluctuations occur this should be taken into account.

3.1.1 Good Manufacturing Practice (GMP)

Within the pharmaceutical industry, Good Manufacturing Practice (GMP) is a series of guidelines and principles to ensure high standards of quality and purity throughout the manufacture, testing and packaging of pharmaceutical products.

The goal of GMP is to minimize the risks involved in the manufacture of a pharmaceutical product that cannot be eliminated via testing of the final product – examples of this include, but are not limited to incorrect labeling on containers, unexpected contamination, too much active ingredients and so on, all of which could have adverse effects on the end user.

GMP regulations cover many areas including cleanliness, sanitation, equipment and process verification, record-keeping, and personnel qualifications.

GMP is also known as cGMP where the “c” stands for “current”. Equipment and processes that were installed years ago, may not be in-line with current requirements. cGMP ensures that technologies and systems must be up-to-date in order to comply with the GMP regulations.

3.2 Registration and Process Validation

Registration and process validation are necessary qualification steps that are required before an ethical or generic drug is produced for human consumption. Completing these processes can delay the startup of a product, increase the cost of the construction project, and affect restart of a process that has experienced a fire or other type of property loss.

Times for registration and validation can vary. Long validations times are common when dealing with new processes and plants, whereas shorter validations times are typical for changes to existing products, processes and replacement-in-kind operations.

3.3 Key Exposures

The nature of operations and the high monetary value associated with the product within pharmaceutical plants present means there are often several loss prevention opportunities. The hazards, for the most part, are not unique or unusual. Some of the key exposures in these plants are:

3.3.1 Liquid Transfer

These may involve ignitable liquids, acids, bases, highly toxic fluids, etc. and the full range of transfer processes and vessels containing these liquids are possible. For additional information see Data Sheet 7-32.

3.3.2 Reactors

A key production step in the manufacture of APIs involves chemical reactions, often in the presence of ignitable solvents, under a wide range of process conditions, temperatures and pressures.

Where pharmaceutical reactors are used, they range in size from less than 5 gal (19 L) for high-pressure reactors to thousands of gallons (tens of m^3) for fermentation reactors. They can be a customized or standard design and are commonly fabricated from glass-lined carbon steel or stainless steel. Sometimes more exotic metals are used. Unlined carbon steel reactors are not common as they are more susceptible to corrosion and contamination. These reactors are often fitted with agitators (usually electrically driven). Older reactors may have constant speed agitators fitted however most these days are fitted with variable speed units. In rare cases Variable-speed agitation also can be achieved hydraulically rather than by using electric motors directly.

Connections to reactor vessels which include those for material transfer, access to inspection ports and piping and valving are all potential sources of leakage and should be limited to those absolutely needed.

Upon completion of the reaction, the contents are typically transferred out of the reactor vessel for additional processing. However, there are times when further processing such as crystallization, phase separation, or product isolation, is conducted in the reactor itself.

Cleaning reactors, especially those where these operations are conducted, or batch reactors is therefore important for quality control reasons and to prevent hazardous reactions if incompatible process materials are used.

Temperature control in these reactors is achieved using various media, including water, steam, and organic heat transfer fluids. Heat transfer systems can be a source of contamination if leakage occurs into the vessel. Organic heat transfer fluids can also be an additional fire source in the event of a leak.

Many reactions are carried out at reflux, where the solvent is brought up to boiling point and exits the reactor as vapor. This vapor is condensed in an overhead condenser and then returns to the reactor. Where the solvent is a ignitable liquid or where there is a contamination potential from the coolant, control of leakage is a high priority.

3.3.2.1 Biochemical and Biological Manufacture of APIs

Natural materials or fermentation process products may be used as the starting material in biochemical processes. Downstream operations are then frequently similar to synthetically produced APIs.

Products made by this process include antibiotics, vaccines, vitamins, bioconverted steroids (anti-inflammatory agents such as cortisone) and enzymes.

Biocatalysis, biotransformation, and bioconversion are all names for the use of biological substances in a biochemical process. Biocatalysts are either enzymes or whole cell organisms that act as a catalyst to carry out a chemical conversion.

Biotransformation reactions include additions, aminations, dehalogenations, epoxidations, esterifications, hydrolysis, hydroxylations, polymerizations, and reductions. These reactions may be for the synthesis, interconversion, or degradation of chemical species.

Animals may be used for the production of biologically based products. Transgenic animals (such as mice or goats) grow the cells or antibodies; the cells are then extracted from blood or animal milk, and the recovered cells are used to create a finished product.

Cell cultures may be used as the starting material in biological processes. The important differences between cell culturing and fermentation are that the process can take much longer (two or three times longer) than fermentation, and PET roller bottles are used during the production phase. Cells in media are put into small PET plastic bottles. The bottles are then stacked on side in roller racks (shelf units with rollers for each bottle that keep the bottle spinning around its axis). There may be a 3,000 to 5,000 ft^2 (279 to 465 m^2) room with 7 ft (2.1 m) high shelf storage of plastic bottles located in the middle of the clean production facility. This is a significant combustible load not found in other biotech operations.

Recombinant DNA and other genetically modified cells may be used as the starting material in biological processes. Master cells are used to produce working cells. Master calls are reproduced in a scaled process going from vials to Petri dishes or flasks to bioreactors.

Ignitable liquids, though not commonly used, could include ethanol, acetone, dimethylformamide, and dimethylsulfoxide.

A typical biotechnology process can include the following steps:

- Media preparation
- Fermentation or other cell growth process
- Cell separation or harvesting: ultrafiltration, centrifugation, homogenizing
- Purification: ion exchange chromatography
- Virus inactivation: organic solvent/detergent mixtures
- Purification: membrane filtration
- Purification: size exclusion chromatography
- Formulation
- Sterile filtration, filling, lyophilization

The process generally consists of adding the raw materials, the media, and nutrients to water in a bioreactor, adjusting the pH, allowing the reaction to take place over a period of time (usually days to weeks), then inactivating and purifying the product.

Some common exposures to loss in this industry include the following:

- Spoilage due to service interruption; lack of (or lack of control of) heat, cooling, agitation, electricity, natural gas, instrument and sparge air, and other utilities
- Contamination due to foreign material, internal or external fire, etc.
- Cleanroom construction due to the use of plastic- and foam-insulated wall and ceiling components
- Master cultures or cell banks that may be one of a kind or difficult to replicate

Damage or loss of master cultures can have a serious impact on the ability to create product, so attention to details that maintain critical utilities and eliminate the exposure to fire, contamination, and other nonthermal damage is important. It is critical to have sufficient built-in safeguards to avoid a significant loss of production if a cell bank is lost (see Section 2.1.4.2).

For large scale biochemical manufacturing there are some additional areas for consideration:

A. Large fermentation reactors may require overpressure protection due to the generation of CO_2 as a reaction product.

B. The consequences of overheating in a fermentation reactor should be considered, as should a situation where the outlets could be blocked by fermentation products within the reactor.

C. The use of steam (usually direct steam injection) in the sterilization process could create vacuum conditions, causing the collapse of the vessel as the steam condenses. The need for vacuum breakers is something that should be considered.

D. Interlocks may also be needed to prevent the quick cool down of large steam filled vessels, which could create sudden vacuums that may not be handled by the vacuum vents.

E. Sterile (and oil-free) air for the fermenter and seed vessels may require special compressors. These compressors are usually not available at short-notice. These compressors also use significant lube oil, and localized automatic sprinkler protection may be warranted, especially if adjacent compressors are not cut off from one another. (See Data Sheet 7-95, *Compressors*.) If the compressors use combustible filters, spares should not be stored nearby.

F. Fermentation “broth” may be a raw material for additional downstream processes. Often the broth is treated, (filtrations, extraction of solvents etc.) before being moved to the next process. This may increase the downtime if additional processes are affected.

3.3.3 Isolation

”Isolation” is a general term that refers to one or a series of physical separation processes using extraction, centrifuging, and/or filtering. The isolated product could be an intermediate used in subsequent steps, or an API sent to a secondary operation for subsequent blending and packaging.

These separation processes include filtering to separate liquids and solids, drying of the solid material and recycling or disposal of the liquid product. These processes are often seen when the desired API may be formed as a solid particle in the reaction steps or may require additional steps to achieve crystallization. The liquid streams may be aqueous or organic. Many of the organic streams are ignitable.

3.3.4 Ion Exchange and Chromatography

Some pharmaceutical processes use this technique. It may be known as high performance liquid chromatography (HPLC) and is a common process used to analyze or purify materials.

In this process, a liquid stream, usually a volatile or hazardous solvent, is passed through one or a series of ion exchange columns containing a packed resin bed having specific adsorption and chemical properties. A component from the liquid stream is preferentially adsorbed onto the resin bed. The adsorbed component may be the desired product or an undesired material that needs to be removed from the product stream. The remainder of the stream passes through the column. If it does not contain product, it may be recycled back into one of the upstream processes, sent to a recovery step, or discarded as waste. If the stream is the product, it could be sent for further processing or finishing operations.

Saturated resin beds need to be regenerated or eluted. Whether the saturate is the product or waste, the process is the same. The resin bed is flushed using a fresh solution (an ignitable solvent, other organic material, steam, etc.) that has a higher affinity for the saturate than the resin bed. The regeneration fluid is then sent for further processing.

The solvent from the chromatography process, along with any used in the regeneration of the solvent beds is collected as waste. Typically draining via gravity through a small tube into an open container. Depending on the size of the waste container this waste material could be a fire hazard. In addition, the material could be potentially toxic.

3.3.5 Drying and Coating

These operations are typically found both in primary and secondary pharmaceutical plants. Multiple-unit operations may be performed to obtain the final dose form.

Various dryer types are seen in the pharmaceutical industry including equipment that performs two-unit operations, such as filtering and drying or blending and drying. Dryers can be directly or indirectly heated, with indirect heating being preferred for pharmaceutical products that are sensitive to heat. The heating medium can be steam, hot water, organic heat transfer fluid, or indirectly heated air or nitrogen. Dryers can be batch or continuous. Dryers can also be operated under vacuum conditions to enable drying at lower temperatures.

Cleaning of dryers may introduce other hazards such as the use of ignitable solvents that may not be part of the normal operation. Cleaning may require opening and entering the equipment or may be cleaned in place (CIP). CIP does not necessarily introduce additional fire or explosion hazards but can result in sources of breakdown or contamination. These need to be recognized in any hazard studies.

Dryers can include the following:

A. Batch tray: These dryers are the simplest and most basic. A wet cake or material is placed into trays in the dryer unit. Hot air or nitrogen passing across the material dries it. The major hazards include overheating of the product to the point where it catches fire, or vapor explosions if the evaporated material is an ignitable solvent (Figure 1).

Fig. 1. Batch tray dryer

B. Continuous belt: Hot gas passes through or across a continuous belt or conveying screen with and product on it. The major hazards include belt warping or fire caused by overheating or friction at rotating or rubbing parts.

C. Spray: The major hazard is overheating of the product where it has accumulated on the interior surfaces of the dryer. This material can create a hot-spot or can detach and fall to the bottom of the dryer, The result being a fire or explosion.

D. Conical: A conical rotating dryer consists of cones that rotates end over end at low speed to tumble and dry the product. Hazards include both combustible dust and flammable vapor in the unit and ancillary equipment (Figure 2).

Fig. 2. Conical dryer

E. Fluidized bed: These direct-heated dryers use hot air, (nitrogen can also be used) to suspend the powder to be dried. This provides uniform drying of the solids. Hazards can include combustible dusts or hybrid mixture (dust and vapor) in the head space of the dryer. Fluid beds are commonly used for combined operations such as agglomeration and drying, wet granulation and drying, or coating and drying. They are also used for powder layering and pelletizing applications.

F. Rotary: A horizontal, cylindrical dryer with a jacketed shell. Hazards include both combustible dust and flammable vapor issues in the unit and ancillary equipment (Figure 3).

Fig. 3. Rotary dryer

Coatings may be applied to obtain desired properties and may involve the use of ignitable liquid.

3.3.6 Lyophilization

Lyophilization is a freeze-drying process used for many drugs. Some products are thermolabile or unstable at elevated temperatures in aqueous solution (instability is a quality issue in this case). The lyophilization process creates a more stable, powder product that can be later reconstituted prior to patient use. The process is vulnerable to spoilage in the event of an interruption.

The typical treatment cycle is that the product to be processed is first prepared as an aqueous solution or suspension that is then cooled rapidly to a low temperature, often approaching -58°F (-50°C). The freezing chamber is sealed, and the frozen material is then subject to heat under a high vacuum. The liquid portion sublimes and the resulting dry product is often less than 1% moisture. The product is then packaged under sterile and low-humidity conditions.

The solvent for the solution might be an ignitable liquid. If so, the vaporization/ sublimation of the liquid should not create a flammable atmosphere in either the lyophilizer or any off-gas handling equipment.

Some lyophilizers process the solution in the final vial. Vials are loaded into the process chambers with loose fitting tops, which are set by compressing the stack of trays at the end of the process. These units will

commonly have a hydraulic system (see Data Sheet 7-98). Hydraulic spray fires, even from small volumes in some lyophilizer units, have the potential to cause significant damage and extended downtime.

To provide reliable electrical power, lyophilizers frequently have emergency power supplied by batteries and backup emergency generators (see Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*).

3.3.7 Ventilation

Ventilation is installed for many reasons including personnel comfort, safety, product quality, and to prevent ignitable liquid, flammable gas, and combustible dust hazards.

Systems designed to meet personnel safety or product quality requirements are often specified as “x” number of air changes per hour and can have higher volumetric requirements than systems designed for flammable hazards. These systems can be used to meet the flammable vapor hazard requirements provided there are low-point pickups and there is no recirculation of the air. If there are only limited flammable materials involved, air recirculation could be acceptable with FM Approved vapor detection systems interlocked to put the system in full exhaust mode.

Laboratory fume hoods have minimum air flow rates that are specified by codes. These are to protect personnel and would be sufficient for the quantities of ignitable liquid or flammable gas normally handled. Noncombustible ducts for fume hoods should be routed directly outside. Exhaust openings need to be located away from intake points for building ventilation systems.

3.3.8 Waste Gas Handling

Gaseous by-products can range from being relatively harmless to gases that are toxic, corrosive and/or flammable, that need to be removed. In some cases the by-product may be a large volume of gas (e.g., carbon dioxide) that could pressurize a reactor and associated equipment, leading to mechanical failure of the vessel, if not removed.

These gaseous by-products may be recycled in the process or vented outside, either directly or through some type of gas cleaning or treatment system. Venting directly to atmosphere is limited to non-toxic, non-hazardous gases such as carbon dioxide. Limited amounts of a flammable gas such as hydrogen may be vented directly to atmosphere; however, these need to be routed to a safe area such as above a high roof.

Scrubbers are most commonly used to remove corrosive and/or toxic components from waste gas streams. Scrubbers are usually vertical vessels containing packed beds to allow a large surface area for good liquid-gas contact.

The scrubbing solution can be water, alkaline streams (e.g., caustic, sodium hypochlorite, etc.) or acidic streams (e.g., sulfuric or hydrochloric acid). The equipment used is frequently of combustible construction. Where scrubbers are located indoors and of combustible construction, sprinkler protection for the area may be needed.

The major hazards associated with scrubber systems include the combustible construction, and the effect on operation if the ability to scrub off gases is lost. Often, the process will be shut down due to local pollution control regulations.

Some gaseous streams that are flammable and have a sufficiently high calorific value can be burned on site. These gases can be routed to:

Boilers (or sometimes gas turbines), where the gases are burned as supplementary fuel.

Incinerators, where flammable gas streams are burned; sometimes these incinerators are equipped with waste heat recovery boilers that provide steam or hot water for other processes.

A flare stack, where the gases are ignited, and flared-off.

See Data Sheet 6-11, Data Sheet 7-2, and Data Sheet 7-78, for further guidance.

3.4 Special Occupancies

3.4.1 Chemical/Molecule Libraries

Automated storage libraries (ASL) are used to store small chemical samples that are part of a new product development (R&D) cycle. The libraries are not usually used for production sample storage. The samples may be produced in onsite development labs or purchased from outside sources. Samples may be liquid or solid and may be only a few micrograms each.

Sample storage consists of two basic types:

A. Samples are stored in a small glass or plastic bottle with a cap or rubber stopper. Multiple sample containers are then stored on a metal or plastic tray in the ALS unit. Sealed bottles with caps reduce the susceptibility of the compounds sealed inside to smoke and/or water damage.

B. The other configuration uses “microplates” for storage of liquid solutions. Microplates are plastic plates or sheets, typically with 88 small wells containing samples. The microplates are sealed by the thin plastic sheet, but are susceptible to smoke and/or water damage.

Fire hazards include:

- Ignitable liquids in the samples. These quantities are usually negligible.
- The electric motor that is used for storage and retrieval of the samples – a small electric motor fire or insulation breakdown may create enough combustion products to contaminate all samples
- Potentially large quantities of plastic.

A significant exposure is the fact that the samples themselves may be one of a kind or expensive to purchase from a supplier. The monetary value of the storage may be difficult to determine and includes not only the purchase/development cost, but also the effect of a loss on on-going development programs.

3.4.2 Laboratories: R&D, Production, Quality Control

Pharmaceutical development and production requires the use of laboratories on an extensive scale. The basic loss prevention features for all laboratories include separation from higher hazard operations (production) using noncombustible construction with separate ventilation systems, automatic sprinklers, and good housekeeping, including control of hazards related to ignitable liquids and flammable gases.

Laboratory areas, including the interiors of fume hoods, are “unclassified” as defined in Article 500 of NFPA 70, *National Electrical Code*.

Pressurized liquid dispensing containers (PLDCs) may be seen in labs. These range in size from 5 to 55 gal (19 to 208 L) and are usually of stainless-steel construction. These containers are pressurized using an inert gas, typically up to 15 psig (103 kPa), with the vessel rated for 60 psig (415 kPa) or higher. They may deliver their contents to a dispensing system or directly to lab instrumentation. There are several FM Approved PLDCs listed in the Approval Guide under the classification “flammable liquid dispensing systems.” Devices of this type with plastic construction and with plastic liners or bladders, are not FM Approved.

Production and quality control labs are usually small, with limited amounts of analytical equipment and associated liquids and gases.

R&D labs are used to conduct development testing of various types on a small scale, usually less than 1 gal (4 L) in vessel volume. They are usually in dedicated buildings and may use high-value test and analysis equipment not typically seen in other labs. Ignitable liquids in larger quantities may be present as part of the test equipment.

3.4.3 Storage Facilities (Excluding Chemical/Molecule Libraries)

Pharmaceutical storage is commonly located in conventional warehouses with palletized and rack arrangements and may consist of final products, raw materials and intermediates.

Pharmaceutical storage can often present high unit values, susceptibility to contamination from products of combustion or foreign materials, a need for temperature and humidity control, and security considerations associated with potential burglary or theft.

Due to the high values, separate storage areas for raw materials, intermediates, and final products should be considered to minimize time element losses where there are long production cycle times. Even where cycle times are short, consider splitting high property value concentrations to reduce exposure to a single loss event.

Walk-in coolers storing final products with a high unit value can create a potential for significant financial exposure from a small combustion incident. The best loss prevention advice is a high level of equipment maintenance, strict control of ignition sources, and use of noncombustible construction and storage containers. However, where combustible packaging or construction is present, fast-response fire protection systems may be required. This includes high sensitivity smoke detection (HSSD) and/or extinguishing components. Response of a gaseous clean agent system may result in less damage than sprinkler protection could achieve, especially in cases where water may result in loss of the product. Water discharge in freezers may impact the operation of manual or automatic material handling systems and should be considered in developing contingency plans.

Where humidity and temperature control is needed to maintain product, intermediate or raw material quality, utility reliability must be evaluated.

3.4.4 Vivariums

Vivariums are facilities in pharmaceutical plants where animals used for production or research are housed. Common animals are small mammals and rodents, but other species are also seen. The animals are genetically well defined, having been raised for specific purposes. Often, many generations of animals are needed, and loss of one generation (or related documentation) due to disease, fire, flood, etc., can set a development program back to its beginning. Depending on the criticality of the animals or the testing, replacement animals may be housed at separate locations or facilities.

Vivariums also have attached laboratories and work rooms related to animal examination. Auxiliary operations in the building can include offices, cage wash areas, and rooms for the storage of food, cleaning materials, and bedding. These are usually located outside the “clean” areas. The storage rooms present the largest concentration of combustibles in the building. Automatic sprinkler protection is usually needed, and these areas are usually separated from the vivarium by fire-rated construction.

Vivarium atmosphere is controlled to maintain temperatures and humidity within a close tolerance, arranged so individual rooms have independent air circulation. The building conditioning system may have multiple units to prevent contamination or cross contamination. Evaluation of the important features of HVAC systems is key to minimize the potential for a disruptive incident.

Fire alarm arrangements require extra consideration, as loud noises such as fire alarms can impact the animals and research results.

3.4.5 Cleanrooms

Pharmaceutical plants commonly have areas referred to as cleanrooms. These cleanrooms are not necessarily to the same as semiconductor cleanrooms.

Table 1 highlights some of the major differences between semiconductor and pharmaceutical cleanrooms.

Table 1. Pharmaceutical vs. Semiconductor Cleanrooms

	Pharmaceutical	*Semiconductor*
Size	*Many Small Rooms 500 to 1000 ft^2 (45 to 90 m^2)*	*Few Large Rooms 5000 ft^2 and up (450 m^2 and up)*
Construction	Mixed materials	Mixed materials
	No raised floors and no under floor air plenums	Raised floors and air plenums
	Washable surfaces	Highly susceptible to liquid damage
Equipment	Small scale	Large scale
	"Off the shelf" equipment	Custom-designed equipment
	Isolation technology (glove boxes)	
HVAC Systems	Differential pressure	Positive pressure
	Once through	Recirculation
Utilities	Ordinary reliability	Reliability is critical (built in spares)
	Breathing air may be needed	

Pharmaceutical cleanrooms have a cleanliness rating (Table 2). This is based on the number of particles equal to or greater than 0.02 in. (0.5 mm) in 1 ft^3 (0.03 m^3) of air. For example, a class 10 cleanroom based has a maximum of 10 particles greater than 0.02 in. (0.5 mm) in every 1 ft^3 (0.03 m^3) of air.

Table 2. Cleanliness Ratings Used in Farious Countries

Origin of Standard	*Cleanliness Ratings*					
USA (209D)[1]	1	10	100	1000	10000	100000
USA (209E)[2]	M1.5	M2.5	M3.5	M4.5	M5.5	M6.5
Britain[3]	C	D	E or F	G or H	J	K
France[4]	-	-	4000	-	400000	4000000
Germany[5]	1	2	3	4	5	6
EU[6]	-	-	A and B	-	C	D
ISO[7]	3	4	5	6	7	8
Australia[8]	0.035	0.35	3.5	35	350	3500
Japan[9]	3	4	5	6	7	8

Note 1. US Federal Standard 209D (1988). *Clean Room and Work Station Requirements, Controlled Environments.* Replaced by 209E.
Note 2. US Federal Standard 209E (1992). *Clean Room and Work Station Requirements, Controlled Environments.* Replaced by ISO 14644.
Note 3. British Standard BS 5295 (1989). *Environmental Cleanliness in Enclosed Spaces.* Superseded by ISO 14644.
Note 4. French Standard ANFOR X44101 (1981). Superseded by ISO 14644.1.
Note 5. Vereinigte Deutsche Ingenieure (VDI) VDI 2083.1 (1991). *Cleanroom Technology, Part 1: Fundamentals, Definitions and Determination of classes.*
Note 6. Pharmaceutical Inspection Convention (2009). *Guide to Good Manufacturing Practice for Medical Products.*
Note 7. ISO 14644-1 (1999). *Cleanrooms and Associated Controlled Environments, Part 1: Classification of Air Cleanliness.*
Note 8. Standards Australia AS 1386 (1989). *Cleanroom and Clean Workstations, Part 1: Principles of Clean Space Control.* Superseded by AS/NZS ISO 14644.1:2002.
Note 9. Japanese Industrial Standards JIS-B-9920(2002). *Air Cleanliness Evaluation Methods for Cleanrooms.*

3.4.6 Protection

The goal for all building and equipment construction is to reduce the impact of smoke damage which can lead to large losses in pharmaceutical occupancies.

Noncombustible construction methods are preferred in pharmaceutical occupancies to reduce the generation of smoke. Where unavailable other FM Approved materials are recommended, per this data sheet.

Data Sheet 1-57 provides guidance on plastic modular construction components that can be used in this occupancy including FM Approved plastic materials and acceptable alternatives. Note, however, that smoke production from these panels could be significant even though they don't propagate fire beyond the initial ignition point. This should be considered wherever plastic panels are installed or proposed.

There are also constructions other than rigid panels that include thin plastic facing materials (like paint coatings or wallpaper) on a mineral board backing material. Such a facing, alone, in the absence of other combustibles, would not likely warrant the installation of sprinklers.

The goal of recommending FM 4910 materials is to reduce the amount of combustibles in processing and manufacturing areas susceptible to non-thermal damage. These materials have been evaluated for fire propagation, smoke contamination, and contamination by corrosive products, in accordance with FM Approvals Cleanroom Flammability Tests. These materials have successfully been used in semiconductor cleanrooms for several years but are rarely seen in pharmaceutical occupancies.

Where combustible construction or combustible occupancy is used, sprinkler protection or water spray systems are the preferred protection measures.

In areas where there is combustible occupancy, or in areas where combustible materials are staged, difficulties can arise in determining how much combustible material is needed to warrant the installation of sprinkler protection. Table 3 shows typical protection requirements for the various areas found in pharmaceutical occupancies.

Table 3. Protection Requirements

Area	*Typical Classification*	*Fire Protection Needed*
Finished Product Warehouse	None	Always
QC/QA Labs	None	Always
Packaging	None	Always
Sterile Filling (point)	ISO 5 / Class 100 / A-B	Never
Sterile filling	ISO 7 / Class 10,000 / C	Rarely
Non-sterile filling	ISO 8 / Class 100,000 / D	Depends: see below
Mixing / Blending / Processing	ISO 8 / Class 100,000 / D	Depends: see below
Raw Material Warehouse	None	Always

Evaluation of areas where the need for fire protection may not readily be apparent (e.g., in non-sterile filling and mixing/blending/processing areas) should be conducted to allow a full understanding of the hazards withing the area, and whether they need full automatic fire protection to be provided.

In some areas, sealed concealed sprinklers may have been installed to meet US Food and Drug Administration (FDA) cleanliness requirements as a result of local interpretations of the regulations.

Sealed concealed sprinklers use a gasket around the ceiling plate of the sprinkler to seal the small gap formed between the ceiling plate and the tile. Where these sprinklers are required by others, FM Approved sealed concealed sprinklers should be used. In some cases, concealed sprinklers that are FM Approved for light hazard occupancies have been modified by the addition of the gasket, creating an un-Approved unit.

Pre-action systems are sometimes seen as being an advantage in the prevention of liquid damage. The inherent delay in their normal operation, is seen to reduce the impact of water leaks and the resultant damage. While this can be good with respect to leakage potential, Data Sheet 1-56, *Cleanrooms*, recommends avoiding them when protecting cleanrooms or other non-storage occupancies.

Additionally, dead legs of water will accumulate above the pendant sprinklers, resulting in a situation that could compromise Good Manufacturing Practice (GMP) in a pharmaceutical plant.

3.4.7 Toxic and Potent Compounds

Toxic and potent compounds are common in the pharmaceutical industry as raw materials, intermediates, or final products. Minimizing their impact on personnel and the environment may result in situations where solutions are in conflict with property protection. (e.g. venting). There are methods that can be implemented where both causes are served. Such methods include the following:

A. Routing the material through scrubbers, neutralizers, or incinerators.

B. Vent panels on building walls in conjunction with damage limiting construction

C. Reducing the hazard using inherently safer design. This can reduce or control property damage incidents and indirectly reduce the exposure from release of these materials.

D. Simplification or error tolerance. This may reduce the likelihood of an incident but may not be acceptable to the authority having jurisdiction where any release, no matter how infrequent, may be unacceptable.

3.4.8 Escaped Liquids

Liquid leaks from piping are a major loss driver in pharmaceutical occupancies. Running liquid pipes over the top of sensitive occupancies should be avoided. Where possible liquids should be fed into these areas from the floor upwards.

Floor sealing, containment, drains, liquid alarms and leak detection are all recommended options for situations where it is not possible to avoid running liquids over the tops of these areas.

Standard operating procedures and startup instructions should be clear on managing areas and equipment where these hazards are present. Additionally, as part of their process safety systems, Management of Change protocols are key to mitigate issues should any changes to liquid piping be needed.

3.4.9 Routine Spares

Routine spares within pharmaceutical plants are typically consumables such as plastic conveyor belts (seen on filling lines), filters and hoses and are not considered to reduce the equipment downtime in the event of a breakdown. These routine spares are expected to be put into service under normal operating conditions over the course of the life of the equipment. For additional guidance see Data Sheet 9-0, *Asset Integrity*.

3.5 Loss History

FM pharmaceutical occupancy losses with a total gross value greater than US$1 million for the period 2004-2019 were reviewed. The breakdown by peril is shown in Figure 4 (percentage based on the number of incidents). Significant losses were associated with natural hazards (31%), fire (22%), equipment (16%), and escaped liquids (13%).

Calculated by number of events, 50% of all equipment losses were due to service interruption (Figure 5); however, calculated by cost, service interruption only accounted for 32% of the equipment losses. The costliest equipment losses were caused by pressure vessel breakdown.

The cause of the largest number of natural hazards losses was flooding, followed closely by wind and hail events (Figure 6).

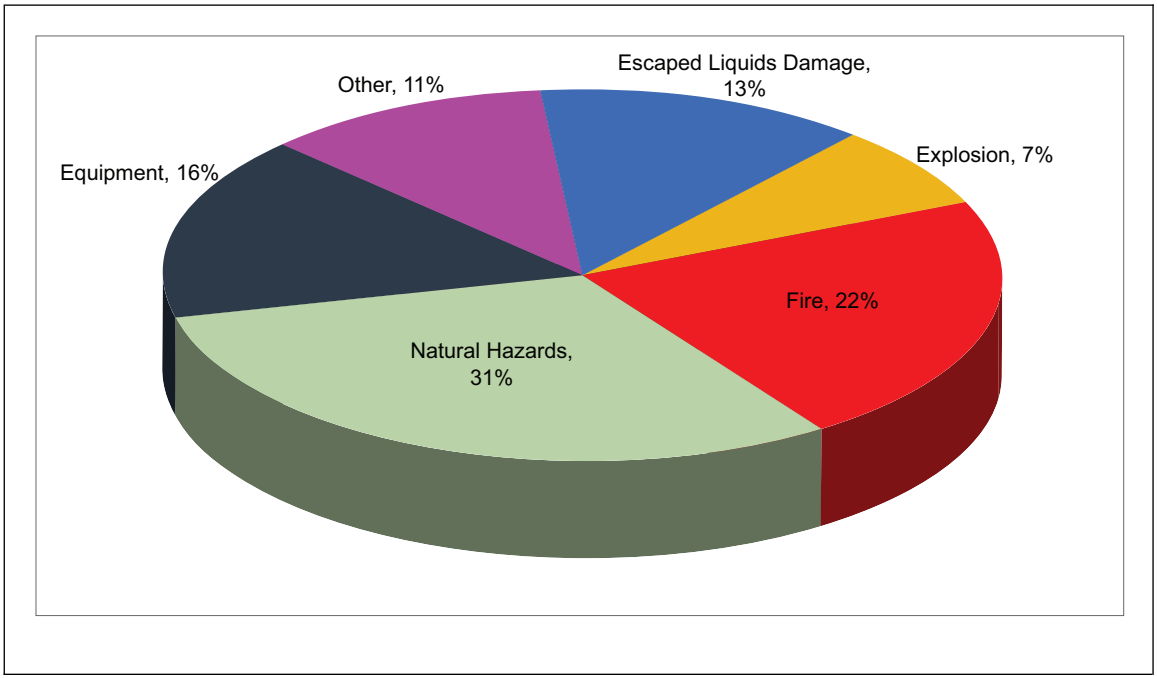

Fig. 4. Pharmaceutical losses by peril (percentage by number over US$1 million)

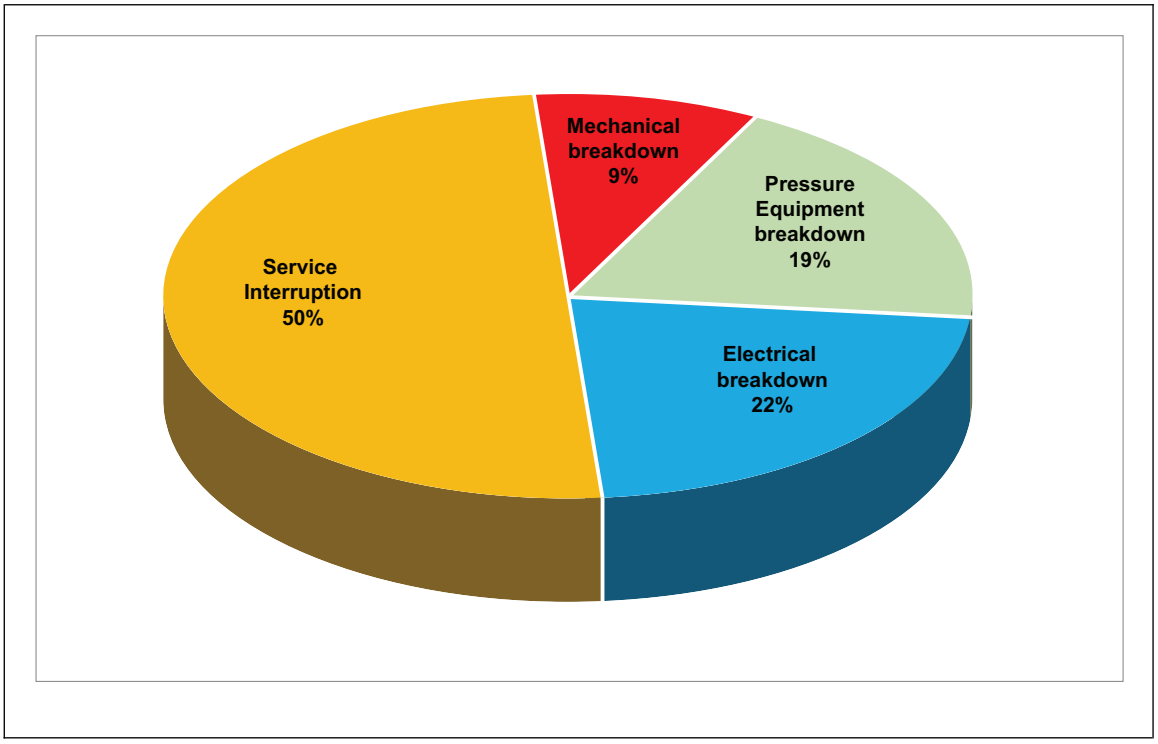

Fig. 5. Pharmaceutical equipment losses (percentage by number of losses over US$1 million)

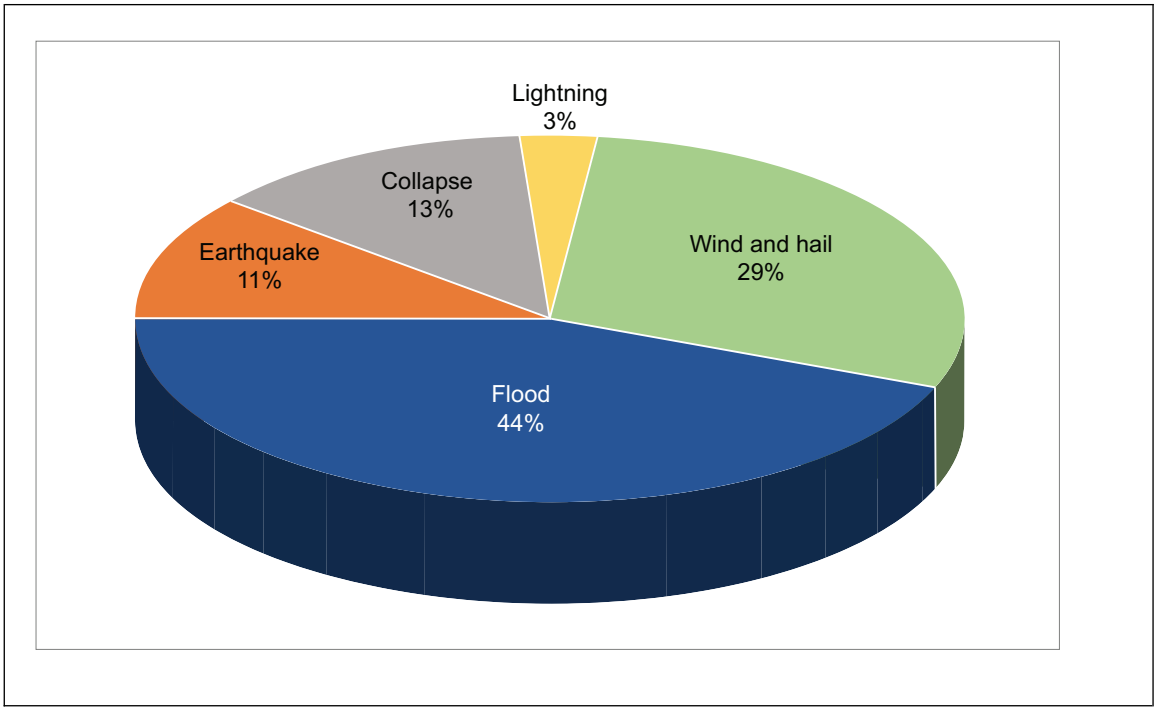

Fig. 6. Pharmaceutical natural hazard losses (percentage by number of losses over US$1 million)

During the period 2004-2019, there were 180 losses associated with active pharmaceutical facilities where the gross loss cost exceeded US$1 million (see Table 4). The total gross loss cost was US$2.2 billion, with an average loss of US$12.24 million (indexed to 2019 values).

Of the losses attributed to service interruption, the majority were related to hurricanes or winter storms interrupting power supplies at pharmaceutical occupancies. The average service interruption loss was US$3.78 million.

Table 4. Pharmaceutical Losses by Peril, 2004-2019

Peril	*Number of losses*	*Gross Loss Amount, US$ million**
Collapse	8	75.96
Earth movement (non-EQ)	1	4.60
Earthquake	7	55.83
Electrical breakdown	7	24.60
Escaped liquids damage	25	249.13
Explosion	13	135.72
Fire	43	384.45
Flood	27	238.70
Impact	3	8.16
Lightning	2	10.30
Mechanical breakdown	3	6.26
Pressure equipment breakdown	6	97.58
Service interruption	16	60.47
Theft	1	51.23
Wind and hail	18	800.24
TOTAL	180	2203.23

*All amounts indexed to 2019 values. Only losses over US$1 million are included.

4.0 REFERENCES

4.1 FM

Data Sheet 1-45, *Air Conditioning and Ventilating Systems*
Data Sheet 1-56, *Cleanrooms*
Data Sheet 1-57, *Plastics in Construction*
Data Sheet 5-23, *Design and Protection for Emergency and Standby Power Systems*
Data Sheet 6-9, *Industrial Ovens and Dryers*
Data Sheet 6-11, *Thermal and Regenerative Catalytic Oxidizers*
Data Sheet 7-2, *Waste Solvent Recovery*
Data Sheet 7-13, *Mechanical Refrigeration*
Data Sheet 7-32, *Ignitable Liquid Operations*
Data Sheet 7-43, *Process Safety*
Data Sheet 7-45, *Safety Controls, Alarms and Interlocks*
Data Sheet 7-46, *Chemical Reactors and Reactions*
Data Sheet 7-49, *Emergency Venting of Vessels*
Data Sheet 7-59, *Inerting and Purging Vessels and Equipment*
Data Sheet 7-61, *Facilities Processing Radioactive Materials*
Data Sheet 7-76, *Combustible Dusts*
Data Sheet 7-78, *Industrial Exhaust Systems*
Data Sheet 7-88, *Outdoor Ignitable Liquid Storage Tanks.*
Data Sheet 7-95, *Compressors*
Data Sheet 7-98, *Hydraulic Fluids*
Data Sheet 7-99, *Heat Transfer Fluid Systems*
Data Sheet 8-9, *Storage of Class 1, 2, 3, 4 and Plastic Commodities*
Data Sheet 9-0, *Asset Integrity.*
Data Sheet 9-16, *Burglary and Theft*

FM Approvals Approval Standard 4880, *Class 1 Fire Rating of Insulated Wall or Wall and Roof/Ceiling Panels, Interior Finish Materials or Coatings and Exterior Wall Systems*

FM Approvals Approval Standard 4882, *Class 1 Interior Wall and Ceiling Materials or Systems in Smoke Sensitive Occupancies.*

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4.2 Other

American Petroleum Institute (API). *Fire Test for Soft-Seated Quarter-Turn Valves*. API 607.

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U.S. Code of Federal Regulations. *Current Good Manufacturing Practices in Manufacturing, Processing, Packing or Holding of Drugs, General*. 21 CFR,

US Federal Standard 209D (1988). *Clean Room and Work Station Requirements, Controlled Environments*.

US Federal Standard 209E (1992). *Clean Room and Work Station Requirements, Controlled Environments*.

APPENDIX A GLOSSARY OF TERMS

Active pharmaceutical ingredient (API): The biologically active ingredient in a drug. Also called pharmaceutical actives or chemical actives. (See also excipient)

Aseptic filling: A processing technique where products are filled and packaged into previously sterilized containers, under sterile conditions.

Biosimilar: A product that is highly similar to an already approved medicine or drug. Biosimilars have the same pharmaceutical quality, safety and efficacy as the original drug, but are typically manufactured once the original patent on a drug expires. A biosimilar is not the same as a generic version of a biological medicine or drug.

BLEVE: Boiling liquid expanding vapor explosion. It occurs when, for example, a drum of liquid is exposed to a fire, which causes the contained liquid to vaporize, overpressure and fail the drum, with the immediate vaporization of the released liquid. If the liquid is ignitable, a large fireball will be created.

Breakthrough therapy designation: A designation for a drug for the treatment of a life-threatening or serious condition and where preliminary clinical evidence indicates the drug provides a significant improvement over existing therapies.

Campaign: The process of making different chemicals in a particular process system by producing chemical A for X period of time, and then cleaning out the process system and producing chemical B for Y period of time, etc. The period of time could be days, weeks or months.

cGMP: Current good manufacturing practice. Regulations enforced by regulatory bodies. cGMPs provide for systems that assure proper design, monitoring and control of manufacturing processes at facilities. (See Section 3.0.)

Clean: As applied to pharmaceutical operations, this means free from dirt, stain and other impurities. (See Table 1.)

Combustible dust: Combustibility of a dust is established by tests that expose the material to ignition sources of various intensities, such as a spark, a match flame, a Bunsen burner, or a Meker burner. A combustible dust is not always an explosible dust. Dust explosibility is established by ASTM tests E1226 or E1515, or the national/international equivalent (e.g., ISO 6184/1). Any sample of dust with a median particle size smaller than 500 microns is possibly explosible unless testing proves otherwise. Dust with a median particle size greater than 500 microns can be assumed to be non-explosible as long as particles smaller than 500 microns have not been segregated during material handling.

Cytotoxic: Compound that is toxic to cells. Chemotherapy drugs used to treat cancer are cytotoxic.

DIERS: Design Institute for Emergency Relief Systems. See Data Sheet 7-49, *Emergency Venting of Vessels*, for details.

Ethical pharmaceutical: A prescription medicine on which the patent held by the developing company is still valid (also see generic pharmaceutical).

Excipient: The inactive substances in a drug that act as the medium or vehicle for the API or other active substances. Uses include providing stability to the active ingredients, preventing denaturation, facilitating drug absorption/solubility, adding bulk to the formulation, and/or aiding in handling during manufacturing of the API. They can be referred to as “fillers,” “bulking agents,” or “diluents.”

FM Approved: Products and services that have satisfied the criteria for FM Approval. Refer to the Approval Guide, an online resource of FM Approvals, for a complete listing of products and services that are FM Approved.

Ignitable liquid: In this document the term is used to describe any liquid that will burn.

FRP: Fiber-reinforced plastic.

Generic pharmaceutical: A prescription medicine on which the patent has expired, allowing it to be produced by many manufacturers (also see ethical pharmaceutical).

GMP: Good manufacturing process. See also the definition of cGMP and Section 3.0 for additional information.

GRP: Glass-reinforced plastic.

HAZMAT: Hazardous material. Could refer to an ignitable, corrosive, or toxic liquid; a flammable, corrosive, or toxic gas; or a combustible, corrosive, or toxic solid.

Inherent safety: Process whereby hazards are minimized by intensification, substitution, attenuation, limitation of effects, and simplification/error tolerance (see Data Sheet 7-43).

Master cell bank (MCB): MCBs are the original modified biological material. There are also Research Cell Banks (RCBs) and Master Working Cell Banks (MWCBs). MWCBs are copied from MCBs and are used for production. They are often kept in “straws” or milliliter-sized vials. They can be stored in liquid nitrogen flasks of 5 gal (19 liter) capacity, or liquid nitrogen-cooled freezers of 35 to 70 ft^3 (1 to 2 m^2) volume.

Nutraceuticals: Nutraceuticals are biological substances specifically derived from plants.

Orphan: A status assigned to a drug or medicine intended for use against a rare condition or disease. The orphan designation allows the drug or medicine to benefit from incentives during development and others, such as protection from competition, once on the market.

Parenteral: Medication that is administered by a route that bypasses the gastro-intestinal tract, such as a drug given by injection.

PLDC: Pressurized liquid dispensing container. NFPA uses the term pressurized bulk solvent storage container (PBSSC).

Potent compound: See toxic compound.

Primary pharmaceutical plant: A facility where APIs are produced.

Qualification: Qualification is the act of proving and documenting that equipment and ancillary systems are properly installed, work correctly and comply with specified requirements. Qualification is a part of validation, but the individual qualification steps alone do not constitute process validation. It can be divided into Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ).

Registration: A regulatory process for the approval, sale and marketing of a new pharmaceutical product within a country. A “Registration Dossier” accompanies the product and contains all the technical data (administrative, quality, nonclinical and clinical) of the specific product that is to be approved/registered/marketed within that specific country.

Secondary pharmaceutical plant: A facility where the APIs manufactured by the primary plant (or by third parties) are converted into a form that is suitable for use by a patient.

Sterile: As applied to pharmaceutical operations, this means free from bacteria and other microorganisms. (See Table 1.)

Thermolabile: Subject to loss of characteristic properties on being heated to or above 55°C (131°F), a characteristic of many immune bodies, enzymes, and vitamins.

Toll converter: A third-party company that carries out one or more of the steps in the manufacturing process of a finished pharmaceutical commodity. The toll converter could be a primary or a secondary pharmaceutical facility. For instance, a primary plant may produce an intermediate in-house, then send it to a toll converter who processes it further to produce the active product. The toll converter might return the processed material to the plant, or to one of the pharmaceutical facility’s other plants, for further processing. Or, the toll converter might formulate, package, and distribute the product on behalf of the pharmaceutical plant.

Toxic compound: A substance that is poisonous and/or may produce an injurious or deadly effect on introduction into a living organism.

USP/NF: The United States Pharmacopeia (USP) and National Formulary (NF) are standards for potency and purity for most common drug products. They have been published since 1833 and 1887, respectively, and were combined for the first time in 1980. Revisions take place every 5 years.

Validation: A systematic approach to collecting and analyzing sufficient data to provide a high degree of assurance along with documented evidence, that a specific method or process will consistently produce a product within defined specifications, when operated with specific parameters. When this approach is applied to a machine or equipment it is referred to as Qualification.

Vivarium: An enclosed area for keeping and raising animals for observation and research.

WFI: Water for injection.

WIP: Work in process.

APPENDIX B DOCUMENT REVISION HISTORY

The purpose of this appendix is to capture the changes that were made to this document each time it was published. Please note that section numbers refer specifically to those in the version published on the date shown (i.e., the section numbers are not always the same from version to version).

July 2021. Interim revision. Relocated inspection guidance for sealed concealed sprinklers to Data Sheet 2-81, *Fire Protection Systems Inspection, Testing and Maintenance.*

October 2020. Full revision. The following significant changes were made:

A. Reorganized the document to provide a format that is consistent with other data sheets.

B. Updated references to other data sheets where applicable protection options are covered in more detail.

C. Updated guidance on the use and acceptance of sealed, concealed sprinklers.

D. Added protection guidance for escaped liquids and piping of liquids.

E. Added guidance on construction materials for pharmaceutical occupancies, for modular and prefabricated construction.

F. Updated protection guidance for vivariums and chemical/molecule libraries.

G. Updated protection guidance for lyophilizers.

H. Added guidance for completion of cyber safety evaluations.

I. Updated loss history.

July 2013. The following changes have been made:

- Replaced references to “flammable” and “combustible” liquids with “ignitable” liquids throughout the document.
- Reorganized the document where necessary to provide a format that is consistent with other data sheets.
- Added references to other FM Global data sheets where sprinkler protection options are covered in more detail.
- Changed terminology for animal facilities (to “vivariums”).
- Updated the loss history.
- Updated the illustrative losses.

September 2010. Minor editorial changes were made.

January 2008. Minor editorial changes were made.

January 2007. Clarification was made to section 3.4.5.

January 2004. Minor editorial changes were done for this revision.

January 2002. First published.