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Challenges in the Medical Devices Manufactured Using Chemical Processing Like Compounding, Buffering

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A B S T R A C T

The aim of this paper is to describe the chemical and drug substances in medical devices and to identify controls in the pharmaceutical and chemical industry connections to the medical devices industry in terms of requirements and properties of various chemicals in relation to common processes. This paper provides a simple glimpse into the issues facing the pharmaceutical and chemical industry during composite and buffered processes. The paper is helpful to validate the overall risk-based approach in order to prevent future complications that may lead to product non-conformities.

Keywords: Chemical, Drug, Pharmaceutical, Therapeutic, Industry

1. Introduction

1.1 Introduction of Chemical and Drug Substances in Medical Devices

The pharmaceutical sector is an important component of global health systems, consisting of several public and private organisations, which discover, create, produce and sell medicines for human and animal health (Gennaro 1990). The pharmaceutical industry largely focuses on the basic study and development (R&D) of medication for illness and condition prevention or cure. Drugs have a wide variety of pharmacological and toxicological action (Hardman, Gilman and Limbird 1996; Reynolds 1989). New advances in research and technology promote the discovery and development of revolutionary drugs with greater therapeutic activity and reduced side effects. Through growing its strength and accuracy, molecular biologists, medicinal chemists and pharmacists boost the advantages of medicinal items. These innovations raise new issues for the health and safety of pharmaceutical employees (Agius 1989; Naumann et al. 1996; Sargent and Kirk 1988; Teichman, Fallon and Brandt-Rauf 1988).

2. The pharmaceutical sector is influenced by several dynamic technological, social and economic influences. Certain pharmaceutical firms compete in both domestic and international markets. Their operations are also regulated by laws, rules and policies pertaining to drug development, registration, supply and quality management, promotion and sales (Spilker 1994). In the pharmaceutical sector, university, government and industry scientists, clinicians and pharmacists as well as the general public influence. In hospitals, clinics, pharmacies and private practice, health care professionals (for example, doctors, dentists, nurses, pharmacists and veterinarians) can prescribe or suggest medicines. The media, activist organizations and private interests are affected by government legislation and prescription health policies. These diverse factors interact with each other in order to affect drug discovery, growth, processing, marketing and sales.

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1.2 Drug Development

The pharmaceutical industry is primarily driven by scientific research and production of toxicological and clinical expertise (see FIGURE 1.1). There are significant differences between large drug research and production, manufacturing and quality control, marketing and sales organizations and smaller organizations which concentrate on a specific aspect. In all these operations, the majority of global pharmaceutical firms will specialize in one aspect, though, depending on local market conditions. In order to find and create novel medicines, medical, public and private entities pursue experimental research. The biotechnology industry is making a big contribution to groundbreaking drug discovery (Swarbick and Boylan 1996). Collaborative arrangements are also signed between academic institutions and major pharmaceutical firms to investigate the promise of new medicines.

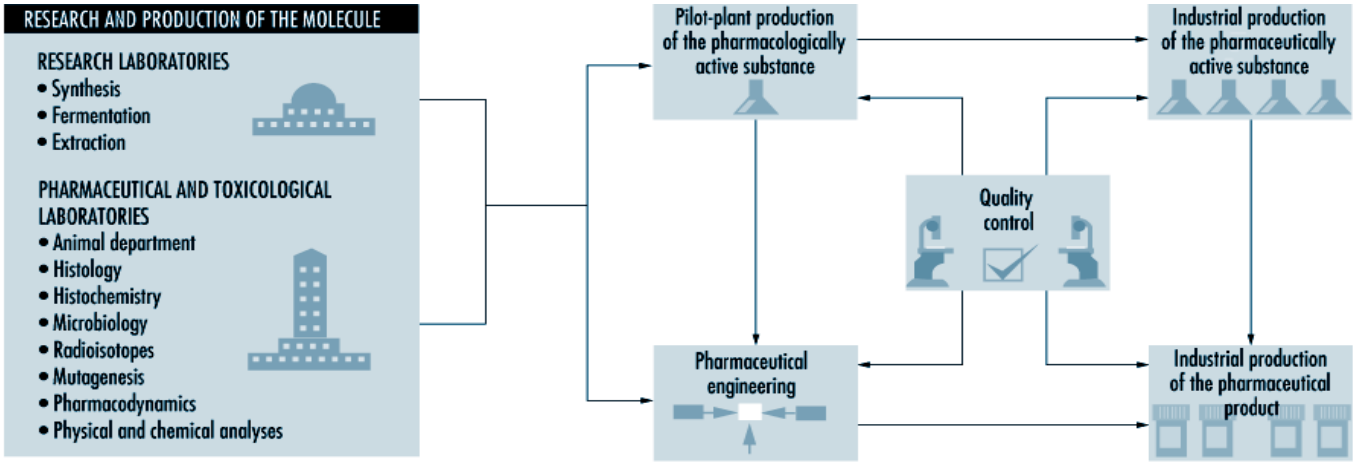


Figure 1.1 Drug developments in the pharmaceutical industry

1.3 Pharmaceutical Operations

Prescription processing activities can be classified as basic processing of bulk drug substances and pharmaceutical dosage process in the type products. Figure 1.2 demonstrates manufacturing.

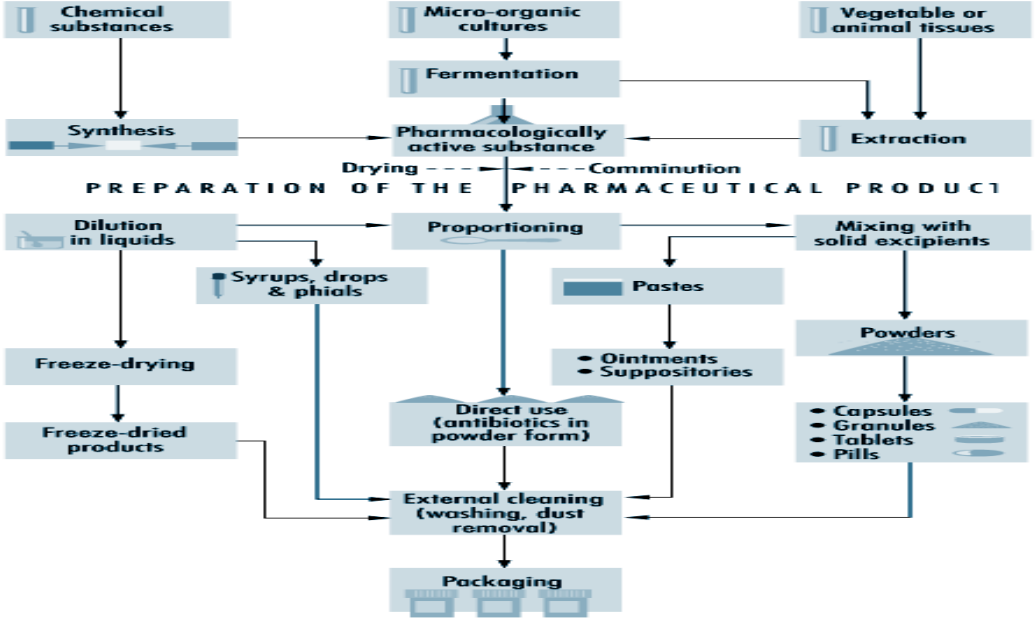


Figure 1.2 Manufacturing pharmaceutical industry

Three main process forms can be used in simple mass processing of pharmaceutical products: fermentation, organic chemical synthesis and organic and natural extraction (Theodore and McGuinn 1992). This manufacturing operation may be batch, continuous, or a mixture of these processes. Fermentation produces antibiotics, steroids and vitamins, while organic synthesis produces several new compounds. Historically, most opioid ingredients have

originated from natural sources like seeds, animals, fungi and other species. Because of their complex chemistry and minimal potency, natural drugs are pharmacologically diverse and difficult to commercialize.

2. Categories of Pharmaceutical Agents

Central nervous system	Renal and cardiovascular system	Gastrointestinal system	Anti-infectives and target organs	Immune system	Chemotherapy	Blood and blood-forming organs	Endocrine system
Analgesics • Acetaminophen • Salicylates Anaesthetics • General and local Anticonvulsants • Barbituates • Benzodiazepine Migraine preparations • Beta adrenergic blocking agents • Serotonin receptor antagonists Narcotics • Opates Psychotherapeutics • Antianxiety agents • Antidepressants Sedatives and hypnotics • Barbituates • Benzodiazepine	Antidiabetics • Biguanides • Glycosidase inhibitors • Insulins • Sulphotryforeas Cardioprotective agents • Adrenergic blockers • Stimulants • Angiotensin inhibitors • Antiarrhythmics • Calcium channel blockers • Diuretics • Vasodilators • Vasodepressors	Gastrointestinal agents • Antacids • Antiflatulents • Antidiarrhoeals • Antiemetics • Antispasmodics • Laxatives • Prostaglandins	Systemic anti-infectives • AIDS therapies • Amebicides • Anthelmintics • Antibiotics • Antifungals • Antimalarials • Sulphonamides • Cephalosporins, penicillins, tetracyclines, etc. Respiratory agents • Antitussives • Bronchodilators • Decongestants • Expectorants Skin and mucous membrane agents • Acne preparations • Allergans • Anti-infectives • Burn preparations • Emollients Urinary tract agents • Anti-inflectives • Antispasmodics Vaginal preparations • Antifungals	Analgesics • Non-steroidal anti-inflammatory agents·(NSAIDs) Biological response modifiers • Alpha proteinase inhibitors • Antitoxins • Immune serums • Toxoids • Vaccines Antifibrosis therapy Immunodilators and immuno-suppressives Multiple sclerosis management	Antineoplastics • Adjunct therapy • Alkylating agents • Antibiotics • Antimetabolites • Hormones • Immuno-modulators	Blood modifiers • Anticoagulants • Antiplatelet agents • Colony • stimulating factors • Haemantinics • Haemostatics • Plasma fractions Vasodilators Cerebral· vasodilators	Diagnostics • Adreno cortical steroids • Glucocorticoids • Gondotropins • Hypothalamic dysfunction • Thyroid function test Hormones • Adreneal cortical steroid inhibitors • Anabolic steroids • Androgens • Oestrogens • Gonadotropins • Growth hormone • Progesterone • Somatostatin Prostaglandins

During pharmaceutical processing, active drug compounds and inert materials are mixed to form dosages of drugs (i.e., pills, capsules, liquids, powders, creams and oints) (Gennaro 1990). Medicines can be graded by method of development and medicinal benefits (EPA 1995). Strictly administered means (e.g., injection, skin) and dosages are used to administer drugs, while staff may be exposed to drugs by unintentionally airborne particles or vapors or by unintentional ingestion of infected foods or liquids. Toxicologists and industrial hygienists are creating occupational exposure limits (OELs) to provide advice on reducing worker exposures to opioid substances (Naumann et al. 1996; Sargent and Kirk 1988). Drugs specifications (such as binders, fillers, flavours and bulk agents, preservatives and antioxidants), which include the desired physical and pharmacological qualities of the dosage-form items, are combined with active drug substances (Gennaro 1990). Many pharmaceutical necessities have little or limited medicinal benefit and are relatively healthy for the staff during drug discovery and processing. These chemicals include additives and preservatives, colouring agents, aromatics and diluters, emulsifiers, suspenders, ointment bases, pharmaceutical solvents and excipients.

3. Fermentation

The original concept of fermentation is 'the processing by microbial species, effectively effective, versatile bio-factories, of organic materials into relatively simple substances.' Throughout their development and lifespan, microorganisms create a large range of different molecules necessary to be viable and multiplicated. The adaption of the organically modified setting.Microorganisms that are typically used within the pharmaceutical industry include: prokaryotes such as Bacteria (e.g. Escherichia coli, Staphylococcus aureus) and Streptomycetes (e.g. Streptomyces spp, Actinomyces spp), eukaryotes such as Filamentous Fungi (e.g., Nigrosporaspp, Aspergillus spp,) and Yeast (e.g. Saccharomyces cereviciae, Pichia pastoris).

Fermentation

Fermentation is a biochemical mechanism used for the processing of a chemical substance by chosen microorganisms and micro-biological technologies.Three essential phases include batch fermentation processes: inoculum and preparation of plants, fermentation and commodity restoration or

isolation (Theodore and McGuinn 1992). Figure 1.3 displays a graphical diagram of a fermentation method. The inoculum preparation continues with a microbial strain spore sample. The strain is selectively breeding, purifying and delivering the target substance using a battery of microbiological techniques. The microbial strain spores are triggered in warm environments with water and nutrients. Crop cells are grown in controlled environmental conditions using a collection of agar plates, tubes and flasks to create a thick suspension.

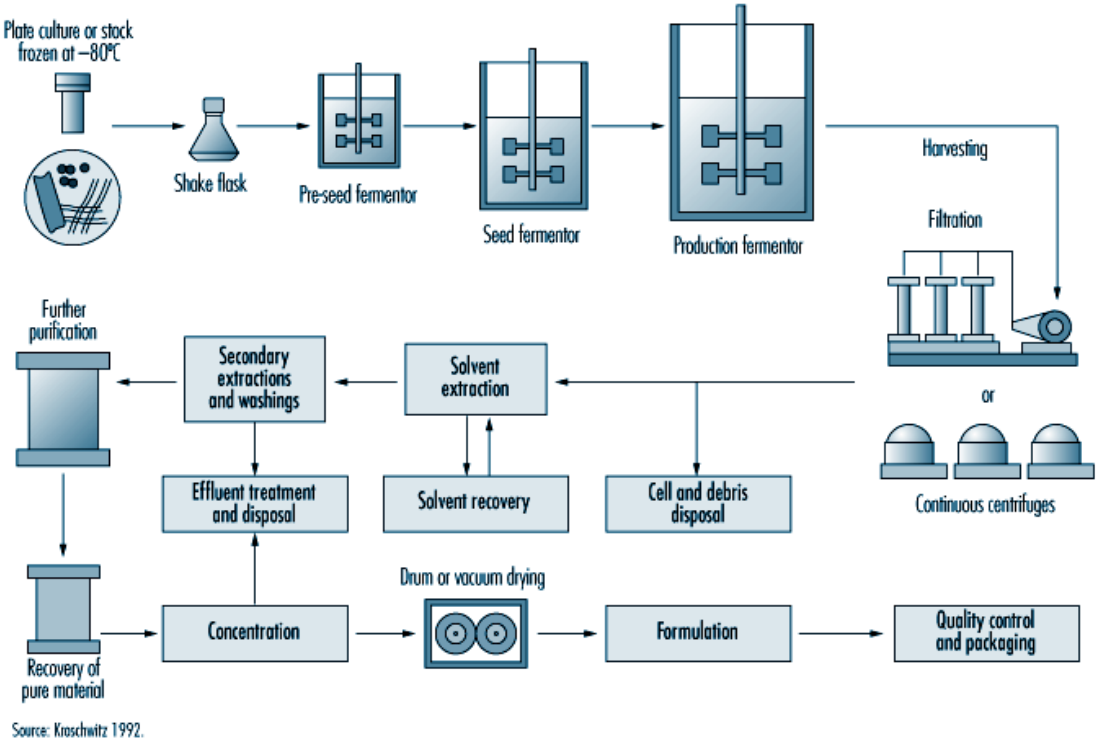


Figure 1.3 Diagram of a fermentation process

For further development, the cells are moved to a seed tank. The seed tank is a small fermentation vessel to maximize inoculum development. The seed tank cells are filled with a steam sterilized fermenter. To start fermentation, sterilized nutrients and distilled water are applied to the vessel. The fermenter material is heated, stirred and aired via perforated pipe or spreader during aerobic fermentation to ensure an optimal air flow rate and temperature. The fermentation broth is filtered after the biochemical processes have been performed to eliminate the micro-organisms or mycelia. Different steps such as solvent extraction, precipitation, exchange of ions and absorption will retrieve the drug product which may be present in filtrate or in mycelia.

4. Solvent Used in Pharmaceutical Industry

4.1 Solvents

5. Solvents are organic compounds that can typically dissolve, suspend or remove other materials without altering solvents or other materials chemically. Solvents Solvents can be organic, which means that the solvent contains carbon, or inorganic, which means the solvent does not contain carbon. "rubbing" alcohol, for example, is an organic solvent and water is an inorganic solvent. Examples of types of organic solvents that can easily dissolve several materials include hydrocarbon and oxygenated solvents.

4.2 Work of solvents in pharmaceuticals

Solvents may perform one or more pharmaceutical manufacturing roles. They have molecules for the creation of such medications. Solvents are used for preparation and purification of other medicines. Solvents can also provide a substrate for reaction. Solvents work in many ways to help many of the drugs that we use today. Solvents play an important role in the medicinal firm in the formulation of a vast range of health products, such as penicillin, aspirin, cough syrup, and topical ointments.

4.3 Solvents used in the pharmaceutical industry

Solvents used to remove a substance (table 1.1) will normally be extracted. Small portions, based on their solubility and process equipment design, stay in the process wastewater. Precipitation is a procedure for disconnecting the drug from the aqueous broth. The medicinal substance is drained from the broth and isolated from solid residues. In this process, copper and zinc are common precipitating agents. Exchange of ions or adsorption by chemical reaction

with solid matter, such as resins or activated charcoal, eliminates product from the broth. The pharmaceuticals are extracted from the stable phase by a solution that can be evaporated.

Table 1.1 Solvents used in the pharmaceutical industry

Solvents	Processes		
Acetone	C	F	B
Acetonitrile	C	F	B
Ammonia (aqueous)	C	F	B
n-Amyl acetate	C	F	B
Amyl alcohol	C	F	B
Aniline	C		
Benzene	C		
2-Butanone (MEK)	C		
n-Butyl acetate	C	F	
n-Butyl alcohol	C	F	B
Chlorobenzene	C		
Chloroform	C	F	B
Chloromethene	C		
Cyclohexane	C		
o-Dichlorobenzene (1,2-Dichlorobenzene)	C		
1,2-Dichloroethane	C		B
Diethylamine	C		B
Diethyl ether	C		B
N,N-Dimethyl acetamide	C		
Dimethylamine	C		
N,N-dimethylaniline	C		
N,N-dimethylformamide	C	F	B
Dimethyl sulphoxide	C		B
1,4-Dioxane	C		B
Ethanol	C	F	B
Ethyl acetate	C	F	B
Ethylene glycol	C		B
Formaldehyde	C	F	B
Formamide	C		
Furfural	C		
n-Heptane	C	F	B
n-Hexane	C	F	B
Isobutyraldehyde	C		
Isopropanol	C	F	B
Isopropyl acetate	C	F	B
Isopropyl ether	C		B
Methanol	C	F	B
Methylamine	C		
Methyl cellosolve	C	F	
Methylene chloride	C	F	B
Methyl formate	C		
Methyl isobutyl ketone (MIBK)	C	F	B
2-Methylpyridine	C		

Petroleum naphtha	C	F	B
Phenol	C	F	B
Polyethylene glycol 600	C		
n-Propanol	C		B
Pyridine	C		B
Tetrahydrofuran	C		
Toluene	C	F	B
Trichlorofluoromethane	C		
Triethylamine	C	F	
Xylenes	C		

Appendix A. C = chemical synthesis, F = fermentation, B = biological or natural extraction.Source: EPA 1995.

5. Hazardous Industrial Chemicals and Drug-related Substances

Many different biological and chemical agents in the pharmaceutical industry are found, developed and used (Hardman, Gilman and Limbird 1996; Reynolds 1989). Certain methods are similar in the pharmaceutical, biological, and organic synthetic industries; however, the larger variety, smaller scale and special uses in the pharmaceutical sector are distinct. Since the primary aim is to manufacture pharmacologically active medical products, a substantial amount of pharmaceutical R&D and processing agents are harmful for staff. Proper protection mechanisms must be enforced to protect employees from synthetic chemicals and medicinal goods in many R&D, processing and quality control operations (ILO 1983; Naumann et al. 1996; Teichman, Fallon and Brandt-Rauf 1988).

In a variety of various applications, the pharmaceutical industry employs biological agents (e.g., bacteria and viruses) such as vaccine manufacturing, fermentation procedures, blood products derivation and biotech. This profile does not discuss biological agents because of their particular pharmaceutical uses. However, other sources are available conveniently (Swarbick and Boylan 1996). Chemical agents can be listed as industrial and medicinal chemicals (Gennaro 1990). There may be untreated, intermediate or finished products. Special cases exist where industrial or medication compounds are used for laboratory R&D, quality assurance and testing, engineering and maintenance or where they are manufactured as by-products or waste.

5.1 Industrial Chemicals

Industrial chemicals are used in the discovery, production and manufacture of active pharmaceutical substances and finished pharmaceutical products. Organic and inorganic chemicals are primary compounds and are used as reactants, reagents, catalysts and solvents. The use of industrial chemical materials relies on the particular processes and activities of production. Many of these products can be unsafe for employees. As worker exposure to industrial chemicals could be dangerous, government, technological and specialist associations have developed occupational exposure limits including threshold limit values (TLVs) (ACGIH 1995).

5.2 Drug-Related Substances

Pharmacologically active compounds can be labeled as natural and synthetic products. Natural products originate from plant and animal origins, and microbiological and chemical processing produces synthetic pharmaceutical products. Natural products are essential antibiotics, steroid and peptide hormones, vitamins, enzymes, prostaglandins and pheromones. Study in science is primarily focused on synthetic medicines due to the recent progress in molecular biology, biochemistry, pharmacology and IT.

6. Hazardous Situations with Chemical and Drug Substances Used with Medical Devices

6.1 Ergonomics and material handling

The shipping, storage, treating, refining and packing materials in the pharmaceutical industry include a wide variety of raw materials and small packets containing pharmaceutical goods. Metal and fiber containers, lined paper and plastic bags are transported in bulk goods for chemical manufacturing (e.g. tank trucks, train cars). Owing to the limited size of activities, pharmaceutical manufacturing uses lower amounts of raw materials. Load handling systems (e.g. fork-lift vans, pallet lifts, vacuum hoists, and drum jackets) support the handling of material during warehousing and industrial activities. When carrying materials and tools, heavy handwork may cause ergonomic hazards if there are no mechanical devices available. Strong industrial manufacturing and facilities maintenance experience eliminate material handling accidents by upgrading equipment construction and efficiency and the workspace and minimizing container size and weight (Cole 1990). Engineering control mechanisms (e.g. ergonomic construction of devices, products and appliances) and

management procedures (e.g. staff rotating, preparation for workers) minimize the risk of chronic injuries wounding as manufacturing and shipping is extremely routine.

6.2 Machine Guarding and Control of Hazardous Energy

Uncontrolled rotating machine parts causes mechanical risks in pharmacy and manufacturing machinery. Exposed "crush and nip points" can trigger a serious injury to staff in open machinery. The vast number of diverse designs of machinery, cramped working environments and repeated encounters with staff and equipment exacerbates technical hazards. The mechanical risk reduction is accomplished by interlocking guards, power levers, emergency stop systems and operator instruction. The equipment could be trapped with loose hair, long sleeved shirts, jewelry or other things. Mechanical dangers are identified and controlled during manufacturing and packing operations. Dangerous electrical, pneumatic and thermal power must, before operating on the active equipment and services, be released or regulated. Jobs are secured by lock-out/tagout protocols from harmful energy sources.

6.3 Noise Exposures

The production equipment and utilities will produce high sound levels (e.g., compressed air, vacuum sources and ventilation systems). Due to the enclosed nature of pharmaceutical working area units, employees are frequently placed in the proximity of machinery during processing and packing. Jobs watch and communicate with machines for manufacturing and storage, which increases their noise sensitivity. Methods for architecture minimize sound volumes by adjusting, locking and damping sources of noise. Rotation of staff and use of hearing protectors (e.g., ear muffs, plugs) decrease the sensitivity of personnel to elevated noise levels. Comprehensive auditory conservation systems locate sources of noise, reduce the level of sound at work and educate staff on noise sensitivity and the proper use of hearing safety equipment. Noise management and diagnostic monitoring (i.e. audiometry) determine the worker's noise sensitivity and the associated hearing loss. This helps to recognize noise issues and determine the appropriateness of corrective intervention.

6.4 Solvent Vapour and Potent Compound Exposures

Unique concern can occur when employees are exposed to poisonous solvent vapors and strong medicines such as airborne powders. During various manufacturing practices worker exposure to solvent vapors and powerful compounds can occur, which must be detected, measured and regulated to ensure that employees are safe. Engineering sensors are the preferred way to monitor these exposures because of their quality and reliability (Cole 1990; Naumann et al. 1996). Enclosed equipment for packaging and storage of products prohibit worker contamination, and these precautions are supplemented by LEV and PPE. Increased containment of plant and processes is needed to monitor extremely volatile solvents (e.g. benzene, chlorinated hydrocarbons, ketones) and potent compounds. Positive pressure breathers (e.g. air-powered and air-supplied purifiers) and PEPs are necessary for handling and processing of highly toxic solvents and poisonous compounds. Unique issues are raised by operations in which high solvent vapor levels are produced (e.g. compounding, granulation and tablet coating) and dust (e.g. drying, milling, mixing). Locker and shower facilities, decontamination procedures and good hygiene practices (for example, washing and showering) are required to avoid or mitigate the consequences of exposure to workers both inside and outside the workplace.

6.5 Process Safety Management

Via sophisticated chemistry, toxic materials and operations of bulk chemical processing, process safety systems are applied in the pharmaceutical industry (Crowl and Louvar 1990). In multi-stage organic synthesis reactions, extremely toxic materials and methods may be used to manufacture the target drug product. These chemical reactions must be tested for their thermodynamics and kinetics, as they growing include extremely volatile and reactive chemicals, lachrymators and compounds flammable or explosive.

Process safety management consists of physical substance and reaction hazard testing, toxic research research evaluation of process chemistry and technical standards, proactive maintenance and functional integrity of process equipment and functionality, staff preparation execution, and the production of operating orders and emergency response procedures. Product safety management Unique process safety engineering features include choosing suitable pressure-rated vessels, installing separation and removal systems, and supplying pressure relief ventilation with catch tanks. Process safety monitoring activities in the pharmaceutical and chemical industry are close when bulk pharmaceutical products are manufactured as organic chemical products (Crowl and Louvar 1990; Kroschwitz 1992).

7. Different Controls of Chemicals and Drgs Substances Required During Production and Handling

7.1 Fermentation

Fermentation creates substantial quantities of solid waste containing mycelia and spent cakes (EPA 1995; Theodore and McGuinn 1992). Filter cakes contain mycelia, filter components, and nutrient, intermediate and residual products with small quantities. These solid wastes are usually non-hazardous but, depending on the particular chemical method of fermentation, contain solvents and minor quantities of residual chemical. If fermentation batches are contaminated with a viral phage, which attacks the micro-organisms throughout the fermentation phase, environmental problems can occur. Though phage infections are uncommon, they produce vast quantities of waste broth and generate a major environmental issue.

Spent fermentation broth includes high-biochemical oxygen demand (BOD), chemical demand (COD) and complete suspended solids (TSS) with pH values ranging from 4 to 198, as well as all sugars, starches, protein, nitrogen, phosphates and other nutrients. After the effluent is equalized to enhance the stable function of the treatment system, microbiological wastewater treatment broths may be handled. The sterility of machinery and products during fermentation is preserved by steam and limited quantities of industrial chemicals like phenols, detergents and disinfectants. Huge amounts of moist air, which include carbon dioxide and odors, may be handled by fermenters before it is released to the atmosphere.

7.2 Organic Synthesis

Chemical synthesis waste is complicated because of the variety of harmful products, reactions and device activities (Kroschwitz 1992; Theodore and McGuinn 1992). Organic processes of synthesis can produce liquid or slurry acids, bases, aqueous or solvent liquors, cyanides and metal waste. Filter cakes containing inorganic salts, organic byproducts and metal complexes can include solid wastes. Waste solvents are typically recovered by distillation and extraction in organic synthesis. Which helps solvents to be reused in other applications and decreases the amount of toxic liquid waste to be disposed of. Distillation residues (still bottoms) need to be processed before disposal. Typical treatment methods require the elimination of solvents by steam stripping and the microbiological treatment of other organic compounds. The air pollution management equipment can control volatile organic and hazardous material emissions during organic synthesis operations (e.g., condensers, scrubbers, venturi impingers).

The synthetic wastewater will include aquatic liquors, rinse water, pump discharges, scrubbers and cooling systems and fugitive leaks and discharges (EPA 1995). This waste water can contain many organic and inorganic compounds with varying chemical compositions, biodegradability and toxicity. Aquatic mother liquors from crystallizations and wash layers from extractions and machine washing can include trace quantities of raw materials, solvents and byproducts. The waste water is rich in BOD, COD and TSS and varies between 1 and 11, with a differing acidity and alkalinity and pH.

7.3 Biological and Natural Extraction

The key causes of solid and liquid wastes are used raw materials and solvents, cleaning water and spills (Theodore and McGuinn 1992). Organic and inorganic chemicals in these waste streams can be found as residues. Typically, waste water has a low BOD, COD and TSS, with pH levels between 6 and 8 that are relatively neutral.

7.4 Pharmaceutical Manufacturing of Dosage Forms

Dosage products pharmaceutically produce solid and liquid waste during cleaning and sterilization and by leakage and spill and rejected products (Theodore and McGuinn 1992). Drying, milling and mixing produce air and fugitive emissions of dust. These pollutants may be regulated and recycled for the manufacture of dosage type goods, but quality control procedures can prohibit this where other residues remain. When solvents are used for wet granulation, compounding and tablet covering, VOCs and harmful air pollution as process or fugitive contaminants can be emitted to the atmosphere or at the workplace. Inorganic salts, sugars, syrups and fragments of substances can be in waste waters. The waste waters are usually low in BOD, COD and TSS, with neutral pH values. Such anti-parasitary or anti-infection medications can be harmful to marine species and require careful handling of liquid waste for humans and animals.

8. Different Controls and Measures During Production and Handling of Chemical and Drug Substances

Preventing and protecting fires, explosive prevention, process containment of dangerous chemicals, machine risks and elevated noise levels, dilution and local exhaust ventilation (LEV), the use of respirator devices and personal protection equipment (PPE) and staff training in occupational hazard; dusts and local exhaust ventilation (PPE); Relevant challenges require removal of less harmful products wherever possible during drug growth and processing. Reduces the risk for disclosure of the worker to reduce content movement, unsealed or exposed packaging and sampling operations.

The construction of engineering facilities, infrastructure and process machinery will avoid contamination in the atmosphere and minimize exposure to employees to dangerous substances. Modern pharmaceutical facilities and process machinery mitigate environmental, health and safety danger through pollution control and hazard containment. Via increased separation, containment and cleanliness of pharmaceutical installations and process facilities, health and safety and quality control targets for employees are accomplished. Preventing worker exposure to toxic chemicals and prescription products is strongly consistent with the desire to stop workers contaminating raw materials and finished products unintentionally. Complementary activities include healthy operating conditions and sound production practices.

Resource recycling uses waste products and during sorting, reclaims materials by removing waste impurities from desired materials. Fermentation-related solid waste (e.g. mycelia) may be added as a dietary supplement to animal feed or as soil and fertilizer. Inorganic salts from organic synthesis operations of chemical liquors can be retrieved. Separation and distillation also recycle used solvents. Air pollution control systems (e.g. condensers, compression and cooling equipment) substantially decrease leakage into the atmosphere of volatile organic compounds (EPA 1993). These systems accumulate solvent vapors by condensation that allows solvents to be reused as raw materials or for vessels and equipment for cleaning. Scrubbers neutralize or absorb the ammonia, caustic and soluble gasses and vapors and release sewage disposal devices from their effluents.

Recycled solvents may be reused as media for performing reactions and extractions, and cleaning operations. Different solvent forms should not be combined, since this limits their recycling capacity. During manufacturing, certain solvents should be isolated (e.g., chlorinated and non-chlorinated,

aliphatic and aromatic, aqueous and flammable solvents). Until solvent recovery, dissolved and suspended solids are removed from or isolated from solvents. The structure and properties of waste solvent and recycled raw materials was established in laboratory research. Many new waste management and control technologies for solid, liquid and gas waste are being developed.

9. Different Guidelines for Stability Study of Medical Devices with Chemical and Drug Substances

The architecture and features of pharmaceutical installations and process facilities affect the health and safety of workers. Building products, process machinery and housekeeping jobs have a significant effect on office cleanliness. Fugitive vapors and dust emissions are regulated by Dilution and LEV systems during manufacturing activities. Where flameproof liquids and vapors are present fire and explosion prevention and safety mechanisms (e.g., electrical and dustproof appliances and supplies, extinguishing devices, fire and smoke detectors, and emergency alarms) shall be required. Storage and handling devices (e.g. storage tanks, compact bins, pumps and piping) are installed for the transportation of fluids to pharmacy facilities. In enclosed equipment and vessels, individual bulk containers (IBCs) and packed drums and sacks, hazardous solids are treated and handled. Insulation or containment of machinery, process equipment and hazardous chemicals ensures health and safety for employees. The mounting of barrier guards on moving parts of the system controls mechanical threats.

Process equipment and services can be manually or automatically operated. Chemical operators read instruments and process control devices and utilities near the process equipment in manual plants. Process facilities, services and control instruments are managed by distributed networks in integrated systems that can be run from a remote location, such as a control center. Sometimes as goods are charged or delivered, items are released and packed and maintenance or non-routine conditions exist. Manual procedures are often used. Written manuals for explaining normal operating practices and health and safety risks and checking steps should be prepared.

Workplace systems are regularly reviewed to shield workers from health and safety risks and to reduce emissions in the environment. Many processing procedures and machinery in the pharmaceutical industry are validated to ensure product consistency (Cole 1990; Gennaro 1990; Swarbick and Boylan 1996). Related validation procedures should be introduced in order to ensure efficient and consistent workplace compliance controls. Method instructions and healthy operating procedures are regularly updated. Preventive maintenance detects when procedure and engineering equipment fail, thereby avoiding problems. Education and surveillance advises and educates staff on natural, health and safety risks, promotes safe workplace and breathing habits and personal safety devices. Inspection services investigate the maintenance of healthy working environments and working procedures. This involves testing of respirators and ensuring that staff are correctly selected, worn and preserved. Audit plans revise monitoring processes for natural, health and safety risks to be detected, assessed and managed.

10. Process Failure Mode and Effects Analysis of The Chemical Process

Link to the EU Hit Directive: (Abbreviation for Chemical Registration, Assessment, Authorisation and Restriction)

REACH (EC 1907/2006) attempts to enhance human health and conservation of the environment through clearer and earlier recognition of the substances' inherent properties. This takes place through four REACH procedures, including the registration, inspection, licensing and restriction of chemicals. REACH also seeks to boost EU chemicals industry's creativity and productivity.

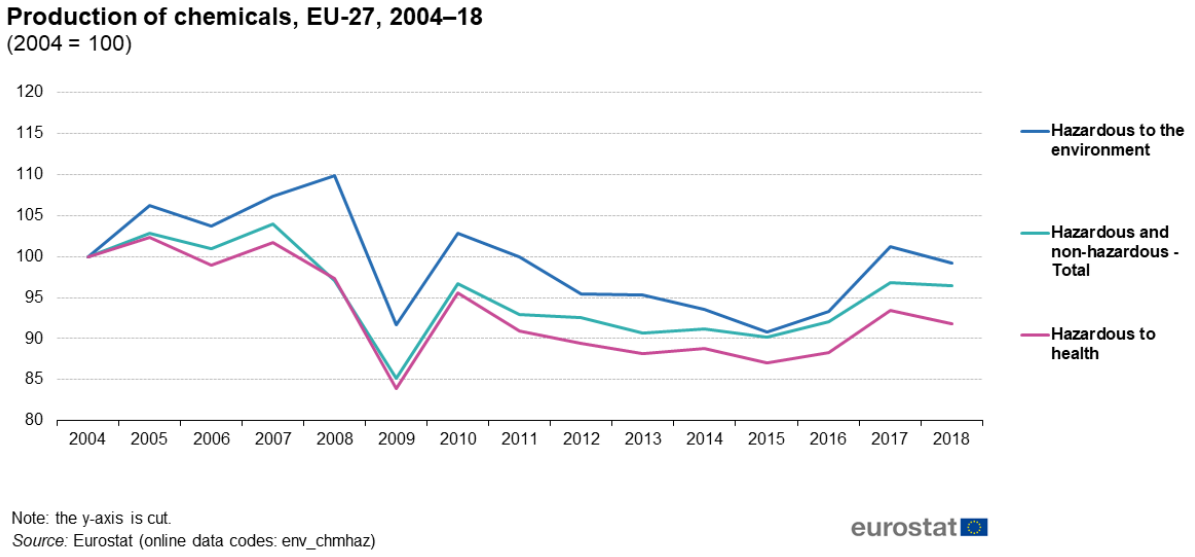
'No details no market': the Scope Legislation puts on industry responsibility for handling chemical risks and supplying safety records for chemicals. Manufacturers and importers are expected to collect and record the information in a central database in the European Chemicals Agency (ECHa) in Helsinki on the characteristics of their chemical substances, which will allow their safe handling.

REACH scheme: it maintains the necessary databases to run the system, coordinates the comprehensive review of suspicious chemicals and establishes a public archive on which users and experts are able to locate information on hazards.

The Law also calls for the phasing-in of the most toxic chemicals (the so-called 'extremely necessary substances') where sufficient substitutes have been found. One of the big factors for establishing and implementing the REACH Rule are that for years a vast amount of drugs, often in very high numbers, have been imported and put on the market in Europe, although inadequate evidence is available about the risks to human health and the environment. These knowledge holes must be filled to ensure that the industry can determine the threats and hazards of the chemicals and to define and enforce risk control strategies for the safety of humans and the environment.

The Scope provisions, which came into effect in 2007, was gradually in force over 11 years. Companies may find REACH details on the DG Development websites or on ECHA's websites and can contact the national assistance offices.

Chemicals Production and Consumption Statistics:



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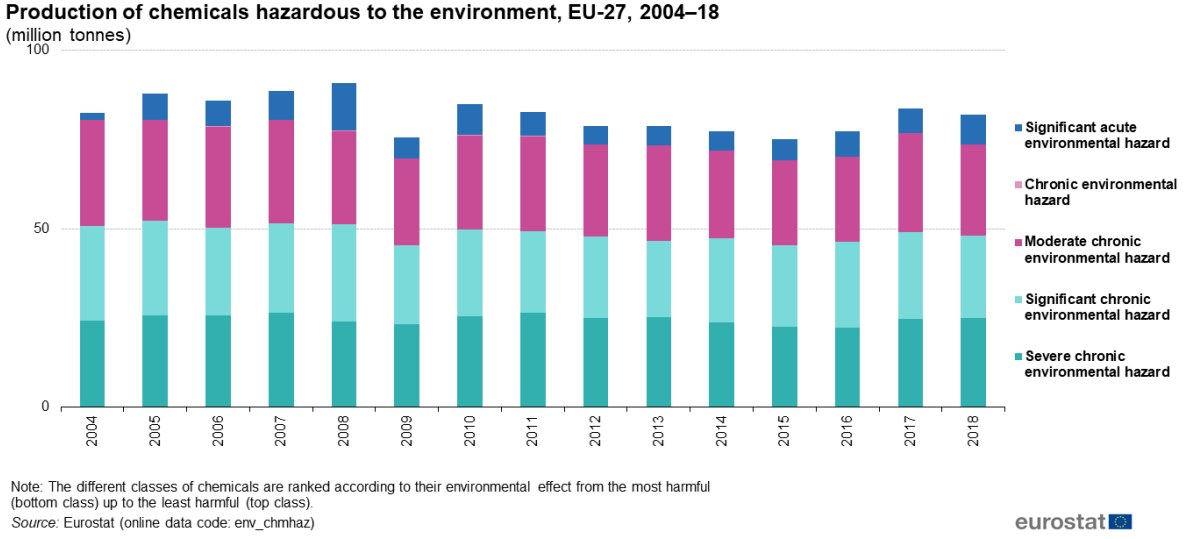

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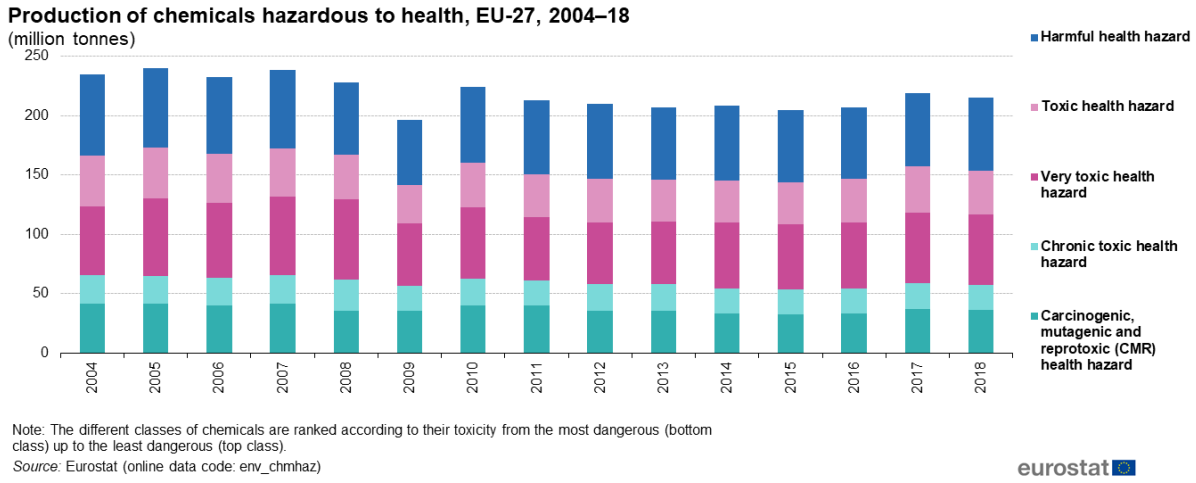
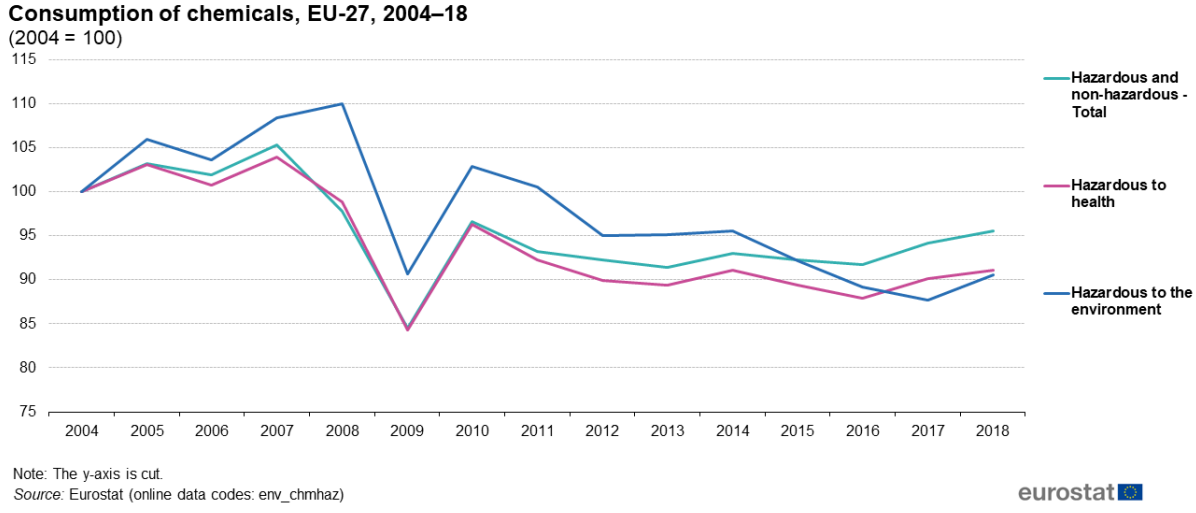
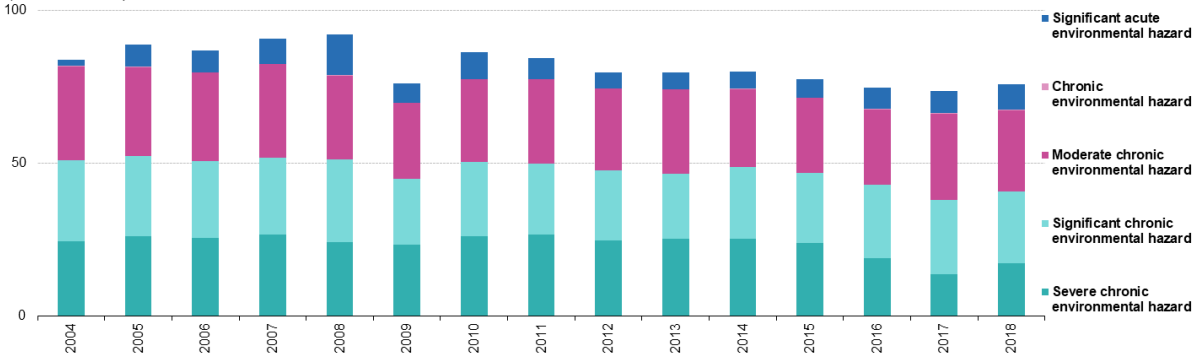


Source: https://ec.europa.eu/



Source: https://ec.europa.eu/

Consumption of chemicals hazardous to the environment, EU-27, 2004–18
(million tonnes)

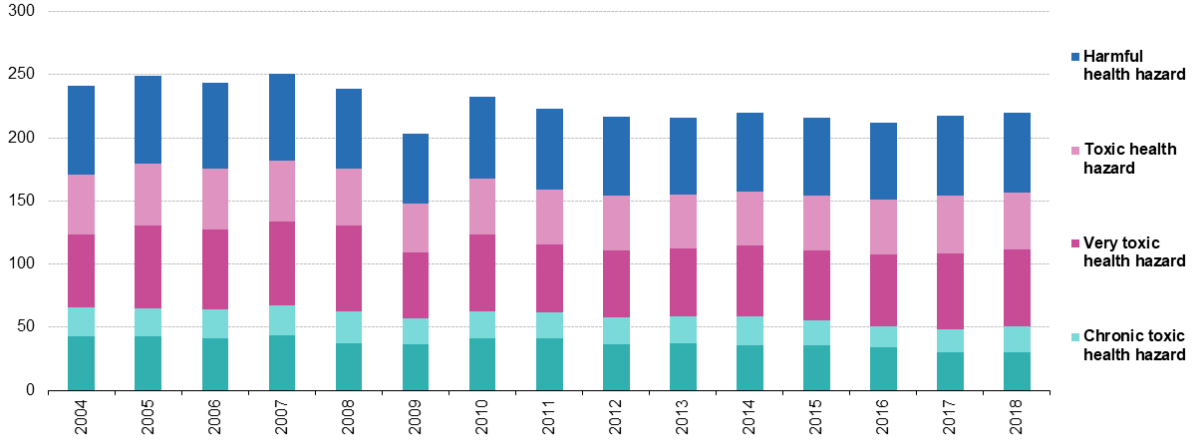


Note: The different classes of chemicals are ranked according to their environmental impact from the most harmful (bottom class) up to the least harmful (top class).
Source: Eurostat (online data code: env_chmhaz)

eurostat

Source: https://ec.europa.eu/

Consumption of chemicals hazardous to health, EU-27, 2004–18
(million tonnes)



Note: The different classes of chemicals are ranked according to their toxicity from the most dangerous (bottom class) up to the least dangerous (top class).
Source: Eurostat (online data code: env_chmhaz)

eurostat

Source: https://ec.europa.eu/

References of the applicable standards: following are the chemicals used in the medical device industry which are harmonised by European Council:

EN ISO 10993-18:2009 Biological evaluation of medical devices - Part 18: Chemical characterization of materials (ISO 10993-18:2005)

EN ISO 11140-1:2009 Sterilization of health care products - Chemical indicators - Part 1: General requirements (ISO 11140-1:2005)

EN ISO 11140-3:2009 Sterilization of health care products - Chemical indicators - Part 3: Class 2 indicator systems for use in the Bowie and Dick-type steam penetration test (ISO 11140-3:2007, including Cor 1:2007)

EN 13624:2003 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of fungicidal activity of chemical disinfectants for instruments used in the medical area - Test method and requirements (phase 2, step 1)

EN 13727:2012 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of bactericidal activity in the medical area - Test method and requirements (phase 2, step 1)

EN 14348:2005 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of mycobactericidal activity of chemical disinfectants in the medical area including instrument disinfectants - Test methods and requirements (phase 2, step 1)

EN 14561:2006 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of bactericidal activity for instruments used in the medical area - Test method and requirements (phase 2, step 2)

EN 14562:2006 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of fungicidal or yeasticidal activity for instruments used in the medical area - Test method and requirements (phase 2, step 2)

EN 14563:2008 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of mycobactericidal or tuberculocidal activity of chemical disinfectants used for instruments in the medical area - Test method and requirements (phase 2, step 2)

EN ISO 15883-4:2018 Washer-disinfectors - Part 4: Requirements and tests for washer-disinfectors employing chemical disinfection for thermolabile endoscopes (ISO 15883-4:2018)

EN ISO 15883-4:2009 Washer-disinfectors - Part 4: Requirements and tests for washer-disinfectors employing chemical disinfection for thermolabile endoscopes (ISO 15883-4:2008)

Link with country specific regulations:

Different country-specific regulations typically define the risk based method to be considered during assessment using this paper

Link with clinical evaluation:

In conjunction with the recent EU MDR Legislation on Medical Instruments and the relevant policy criteria on health, biological and technical protection and compliance parameters, this paper will assist the clinical assessment process by presenting some additional details on procedures that may lead to an unreasonable danger to the medical equipment in question.

Link with first party audit:

The internal auditor cannot arrange its own method from the point of view of the effect of certain systems on end product compliance, during the internal audit of the relevant business. This would allow companies to recognize vulnerabilities and possibilities for detecting future substance non-conformities around controls in the system.

Link with second party audit:

Since second-party audits usually concentrate on the provider's capacity to threaten the compliance of the product requirement with the regulatory requirements, the second-party auditor may use the paper to question the processes undertaken by the provider.

Link with third party audit:

The licensing agency, the informed body, auditing organisations' auditors ought to question procedures in relation to apparent non-conformities during a third-party audit. This paper will be used to assess the holes (even if they are minor in nature)

11. Conclusion

This paper is dealing with chemicals and medication compounds, the other processing systems often include mechanical assemblies, electronics, and so on. Essentially, the compatibility of the other technology should be taken into account when achieving the difficulties of chemical processes such as

compounding and buffering. This paper will be found in other fields that are not in the medical device but use chemicals as part of the commodity or for its manufacturing.

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