STERIS
Life Sciences

Introduction to Regulatory Resources

Overview

Global government agencies oversee select industries to confirm manufacturers follow regulations designed for consumer safety. Food processing facilities, dairy farms, vaccine and drug manufacturers, and blood banks are among those industries inspected to protect consumers from unsafe products (FDA, 2021). The pharmaceutical and biotechnology industries produce life-saving drug products for "use in the diagnosis, cure, mitigation, treatment, or prevention of disease" (FDA, 2021). These industries control manufacturing and cleaning processes to the highest level to ensure the health and safety of consumers.

Government regulatory agencies and industry organizations develop guidelines to ensure pharmaceutical and biotechnology manufacturers have robust cleaning processes. This article will provide an overview of resources related to cleaning validation in the pharmaceutical and biotechnology industries.

Government Agencies

Food and Drug Administration

In 1993, the Food and Drug Administration (FDA), a regulatory agency for the United States, published a reference document titled, "Validation of Cleaning Processes" to guide the pharmaceutical and biotechnology industry on designing a consistent and effective cleaning process.

Cleaning validation is the process of proving manufacturing equipment is cleaned thoroughly and properly to reduce contaminants or residues to an acceptable level. Detailed cleaning procedures include, but are not limited to, the cleaning protocol, responsible parties, studies, sampling, and analytical methods (STERIS, 2020). A cleaning validation report must show that a cleaning process is valid through evidence of contamination control and residue reduction.

Table 1. Abbreviated list of global regulatory agencies for the pharmaceutical industry (PDA, 2021).

Health Authority	Acronym	Location
Brazil National Health Surveillance Agency	ANVISA	Brazil
National Medical Products Administration, formerly China Food and Drug Administration	NMPA, formerly CFDA	China
European Medicines Agency	EMA	Europe
Food and Drug Administration	FDA	United States
Health Products and Food Branch of Health Canada	HPFB	Canada
Health Products Regulatory Authority, formerly Irish Medicines Board	HPRA, formerly IMB	Ireland
Korea Ministry of Food and Drug Safety	KFDA	Korea
Medicines & Healthcare Products Regulatory Agency	MHRA	United Kingdom
Pharmaceuticals and Medical Devices Agency	PMDA	Japan
World Health Organization	WHO	Multinational

When developing a cleaning validation report, the FDA requires the pharmaceutical and biotechnology industries to follow current Good Manufacturing Practices (cGMPs) outlined in the Code of Federal Regulations (CFR) Title 21. cGMP regulations are the minimum requirements that the industry must follow for the manufacturing, processing, and packaging of a drug product (FDA, 2021). 21 CFR Parts 210 and 211 describe the requirements, methods, facilities, and controls necessary for manufacturing drugs (FDA, 2021).

Global Regulatory Agencies

In addition to the FDA there are global organizations and pharmacopoeias to oversee drug safety, manufacturing, and efficacy. Table 1 outlines an abbreviated list of various global regulatory authorities.

Industry Guidelines and Standards

In addition to government regulatory agencies, manufacturers may also look to industry standards for additional guidelines on specific topics.

International Standards Organization

The International Organization for Standardization (ISO) publishes guidance documents across several fields and topics (ISO, 2021). The pharmaceutical industry relies on ISO 9001:2015 for specific requirements related to the quality management system within an organization (ISO, 2021). ISO 9001 is a coveted certification obtained by manufacturer sites adhering to the criteria for a quality management system (ISO, 2021).

International Society for Pharmaceutical Engineers

Not only do manufacturers frequently clean equipment to prevent microbiological contamination, but cleaning also prevents cross contamination from one product to the next. This is crucial to ensure that active ingredients from one pharmaceutical, do not impact the next batch of product that may have a different active ingredient or concentration.

The International Society for Pharmaceutical Engineering (ISPE) offers training and resources related to managing cross contamination with a Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) Baseline. The Risk MaPP approach helps manufacturers understand the risk of cross contamination (ISPE, 2021).

United States Pharmacopeia

The United States Pharmacopeia (USP) provides several guidelines for pharmaceutical manufacturers. Whether a manufacturer is producing a sterile or nonsterile product determines the level of bioburden allowed, consequently impacting the cleaning protocols. Sterile products include injectables, such as intravenous bags used in hospitals. Since injections deliver medication directly to the patient's body, any presence of microbial contamination can have a severe impact on the patient's well-being. Non-sterile products include over the counter (OTC) products that people take orally. In nonsterile manufacturing, a low and controlled level of bioburden is presumed. (STERIS, 2020).

The following USP resources are commonly used in the industry for the manufacture of nonsterile and sterile products:

- USP 42 <1111> Microbiological Examination of nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
- USP 42 <1112> Applications of Water Activity Determination to Nonsterile Pharmaceutical Products
- USP 42 <1115> Bioburden Control of Nonsterile Drug Substances and Products
- USP 42 <60> Microbiological Examination of Nonsterile Products – Tests for Burkholderia cepacian complex
- USP 42 <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
- USP <795> Pharmaceutical Compounding – Nonsterile Preparations
- USP <797> Pharmaceutical Compounding – Sterile Preparations

Parenteral Drug Association

The Parenteral Drug Association (PDA) publishes technical reports. Technical Report Number 29, Points to Consider for Cleaning Validation, and Technical Report Number 49, Points to Consider for Biotechnology Cleaning Validation, serve the industry as further reference material. These technical reports expand on the FDA's guidance on "Validation of Cleaning Processes."

STERIS
Life Sciences

International Council for Harmonisation

With manufacturing sites in countries around the world sometimes serving both domestic and international markets, it is necessary for manufacturers to adhere to multiple global regulatory agencies. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) focuses on the alignment of guidelines globally. The ICH publishes several guidelines with input from various regulatory agencies and industry organizations to promote the standardization of quality, safety, and efficacy for manufacturers (ICH, 2021).

Summary

The pharmaceutical and biotechnology industries are required to follow federal regulations, implement industry guidelines, and inspections to ensure regulated products are safe (FDA, 2021). To ensure product safety, a thorough cleaning program to meet adequate bioburden or microbial contamination limits is mandatory. Leveraging resources such as industry guidelines, standards, and STERIS's technical expertise supports product quality and safety. STERIS Life Science has a dedicated Technical Services Team to support our Customers to meet their cleaning validation objectives.

Do you have a technical question? Reach out to the STERIS experts! https://www.sterislifesciences.com/education-and-training/meet-the-experts/ask-the-experts

Resource List

Table 2. List of resources for the pharmaceutical industry (EMA, 2021), (European Commission, 2021).

Organization	Document	Title
Food and Drug Administration	Guidance for Industry	Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice
Food and Drug Administration	21 CFR Title 21 Part 210	Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
Food and Drug Administration	21 CFR Title 21 Part 211	Current Good Manufacturing Practice for Finished Pharmaceuticals
European Medicine Agency	Eudralex Volume 4 Part I: Chapter 3	EU GMP Guide Part I: Basic Requirements for Medicinal Products: Chapter 3: Premise and Equipment
European Medicine Agency	Eudralex Volume 4 Part I: Chapter 5	EU GMP Guide Part I: Basic Requirements for Medicinal Products: Chapter 5: Production
European Medicine Agency	Eudralex Volume 4 Annex 7	Manufacture of Herbal Medicinal Products
European Medicine Agency	Eudralex Volume 4 Annex 9	Manufacture of Liquids, Creams, and Ointments
The International Organization for Standardization	ISO 9001:2015	Quality Management
United States Pharmacopeia	USP 42 <1111>	Microbiological Examination of nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use
United States Pharmacopeia	USP 42 <1112>	Applications of Water Activity Determination to Nonsterile Pharmaceutical Products
United States Pharmacopeia	USP 42 <1115>	Bioburden Control of Nonsterile Drug Substances and Products
United States Pharmacopeia	USP 42 <60>	Microbiological Examination of Nonsterile Products – Tests for *Burkholderia* cepacian complex
United States Pharmacopeia	USP 42 <61>	Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
United States Pharmacopeia	USP <795>	Pharmaceutical Compounding - Nonsterile Preparations
United States Pharmacopeia	USP <797>	Pharmaceutical Compounding - Sterile Preparations
ISPE	Baseline Guide Volume 7	Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)
Parenteral Drug Association (PDA)	Technical Report Number 29	Points to Consider for Cleaning Validation
Parenteral Drug Association (PDA)	Technical Report Number 49	Points to Consider for Biotechnology Cleaning Validation

STERIS
Life Sciences

Resource List

EMA. (2021, May 14). *Human Regulatory*. Retrieved from Guidance on Good Manufacturing Practice and Good Distribution Practice: Questions and Answers: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers

European Commission. (2021, May 14). Retrieved from EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines: https://ec.europa.eu/health/documents/eudralex/vol-4_en

FDA. (2021, May 14). *FDA Basics*. Retrieved from What Does the FDA Inspect?: https://www.fda.gov/about-fda/fda-basics/what-does-fda-inspect

FDA. (2021, May 14). *Pharmaceutical Quality Resources*. Retrieved from Current Good Manufacturing Practice (cGMP) Regulations: https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations

FDA. (2021, May 14). *Regulated Products*. Retrieved from Human Drugs: https://www.fda.gov/industry/regulated-products/human-drugs#drug

ICH. (2021, May 14). *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)*. Retrieved from https://www.ich.org/

ISO. (2021, May 14). Retrieved from ISO 9001:2015 Quality Management Systems - Requirements: https://www.iso.org/standard/62085.html

ISO. (2021, May 14). *ISO 9001 Family Quality Management*. Retrieved from https://www.iso.org/iso-9001-quality-management.html

ISO. (2021, May 14). *ISO-ICS*. Retrieved from Standards Catalogue: https://www.iso.org/standards-catalogue/browse-by-ics.html

ISPE. (2021, May 14). Retrieved from Managing Cross Contamination with Risk-MaPP Training Course: https://ispe.org/training/course/cross-contamination-risk-mapp

PDA. (2021, May 14). *Regulatory Resources*. Retrieved from Global Regulatory Authority Websites: https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites

STERIS. (2020). Microbial or Bioburden Control Program: An Overview of the Regulatory and Industry Guidelines for Non-Sterile Manufacturing. *Technical Tip #4056*. STERIS Corportaion.