USFDA WARNING LETTERS ISSUED TO PHARMACEUTICAL INDUSTRIES FOR cGMP VIOLATIONS PERTAINING TO STERILE PRODUCTS: ANALYSIS AND GUIDANCE

Thesis Submitted for the Award of the Degree of

DOCTOR OF PHILOSOPHY

in

Pharmaceutics

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2025

DECLARATION

I, hereby declare that the presented work in the thesis entitled "USFDA warning letters issued to pharmaceutical industries for cGMP violations pertaining to sterile products: Analysis and guidance" in fulfilment of degree of **Doctor of Philosophy (Ph. D.)** is outcome of research work carried out by me under the supervision of **Dr. Monica Gulati (UID 11045)**, working as Professor, in the Pharmaceutics of Lovely Professional University, Punjab, India. In keeping with general practice of reporting scientific observations, due acknowledgements have been made whenever work described here has been based on findings of other investigator. This work has not been submitted in part or full to any other University or Institute for the award of any degree.

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CERTIFICATE

This is to certify that the work reported in the Ph. D. thesis entitled **"USFDA warning letters issued to pharmaceutical industries for cGMP violations pertaining to sterile products: Analysis and guidance"** submitted in fulfillment of the requirement for the award of degree of **Doctor of Philosophy (Ph.D.)** in **School of Pharmaceutical Sciences**, is a research work carried out by **Gambhire Hanumant Pandurang**, **Registration No.** 41900056, is bonafide record of his original work carried out under my supervision and that no part of thesis has been submitted for any other degree, diploma or equivalent course.

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ABSTRACT

Sterile products are intended for direct administration into the human body and are thus critical for human health. Due to high demand of sterile products including vaccines owing to recent pandemic of COVID-19, the focus on manufacture of sterile products has enhanced. Due to this, the regulatory authority from the US, US Food and Drugs Administration (US FDA) has also increased its focus on quality of such products through strict compliance of cGMP requirements. US FDA issues warning letter upon any noncompliance observed during the inspection of sterile product facility resulting in imposition of import ban and recall of sterile products from market. The non-compliant firm incurs financial loss as well as loss in customer faith on their entire product range. Besides, the resulting shortage of sterile products results in unavailability the product to the public. For analysing the causes for such cases, warning letters were accessed from US FDA website and sorted for sterile products manufacturers. A total of 120 warning letters were found to be related to sterile products. A review of WLs over the past 14 years and 9 months shows that pharmaceutical companies must improve their quality systems and enhance its knowledge of handling sterile products. Firms must work towards the direction of exercising greater control over aseptic practices, specifically to maintain product sterility and environmental monitoring. Any finding of a sterility violation is expected to shake the confidence of the regulator and result in a shutdown of the export to US market. Based on analysis of WLs issued to sterile products, a comprehensive guideline document is drafted which may serve as a document to follow to avoid cGMP violations pertaining to sterile products.

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Gambhire Hanumant Pandurang

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LIST OF ABBREVIATIONS

Abbreviated form	**:**	**Full form**
AHU	:	Air Handling Unit
ANDA	:	Abbreviated New Drug Application
API	:	Active Pharmaceutical Ingredient
APQR	:	Annual Product Quality Review
ATCC	:	American Type Culture Collection
BCG	:	Bacillus Calmette-Guerin
BFS	:	Blow-Fill-Seal
BLA	:	Biologics License Application
BMR	:	Batch Manufacturing Record
CA	:	Canada
CAGR	:	Compound Annual Growth Rate
CAPA	:	Corrective Action and Preventive Action
CDER	:	Center for Drug Evaluation and Research
CFR	:	Code of Federal Regulations
cGMP	:	Current Good Manufacturing Practice
CMO	:	Contract Manufacturing Organization
COVID	:	Coronavirus Disease
DHS	:	Dry Heat Sterilization
ECA	:	European GMP Auditor Association
EM	:	Environmental Monitoring
FAR	:	Field Alert Reports
FDA	:	Food and Drug Administration
FL	:	Florida
FY	:	Financial Year
GIDC	:	Gujarat Industrial Development Corporation

Abbreviated form	:	Full form
GMP	:	Good Manufacturing Practices
HEPA	:	High-Efficiency Particulate Air
HVAC	:	Heating Ventilation and Air Conditioning
IBEF	:	India Brand Equity Foundation
IOM	:	Investigations Operations Manual
IQVIA	:	International Quality and Value Institute Advisors
ISO	:	International Organization for Standardization
ITC	:	International Trade Centre
LAF	:	Laminar Airflow
LLC	:	Limited Liability Company
Ltd.	:	Limited
LVP	:	Large Volume Parenteral
MDR	:	Medical Device Regulation
MIDC	:	Maharashtra Industrial Development Corporation
NAI	:	No Action Indicated
NDA	:	New Drug Application
OAI	:	Official Action Indicated
OIDC	:	Omnibus Industrial Development Corporation
OOS	:	Out of Specification
OTC	:	Over-the-Counter
PAI	:	Pre-Approval Inspection
PDA	:	Parenteral Drug Association
PDF	:	Portable Document Format
PSI	:	Pounds Per Square Inch
QAMS	:	Quality Assurance Management System
QC	:	Quality Control

Abbreviated form	:	Full form
QRM	:	Quality Risk Management
RABS	:	Restricted Access Barrier System
SAL	:	Sterility Assurance Level
SIDCO	:	Small Industries Development Corporation
SOP	:	Standard Operating Procedure
SVP	:	Small Volume Parenteral
TS	:	Terminal Sterilization
TSIIC	:	Telangana State Industrial Infrastructure Corporation
TTC	:	Trans Thane Creek
UAE	:	United Arab Emirates
UID	:	Unique Identification Number
UK	:	United Kingdom
US	:	United States
USA	:	United States of America
USFDA	:	United States Food and Drug Administration
USP	:	United States Pharmacopeia
VAI	:	Voluntary Action Indicated
WL	:	Warning Letter

LIST OF APPENDICES

Chapter 1 Introduction

The US FDA is governing authority accountable for protecting the community health related to both humans and animals by controlling and supervising medications, medical devices, tobacco, foods, and cosmetics supplied in the US region. To ensure the quality of all of these, the US FDA, issues warning letters to warn their manufacturers if there are any regulatory violations. The issue of adherence to norms laid out by US FDA becomes more pronounced while dealing with sensitive items like sterile products. The sterile products must strictly adhere to the cGMP regulations. The industry involved in the production of sterile products has been receiving a number of WLs from the US FDA whenever any lapse in the guidelines to be followed is detected. This trend has increased in recent years, which is a major concern for the pharmaceutical industry worldwide. Because sterile products may come directly in contact with the human blood, any compromise in the quality of such products poses a very high risk to the patients. In light of this, any WLs received in context to sterile products assume much higher significance.

1.0. Sterile Products:

A sterile product means a medicinal product or a device that is free from any viable microorganisms and has been assembled, handled, or repackaged by qualified personnel in strict adherence to aseptic technique and quality control procedures. Various sterilization methods are used during the manufacture of different sterile products. These include filtration, steam, dry-heat, ionizing radiation, and gas sterilization techniques. Sterile products are classified into the categories mentioned in the Figure 1 given below.[1]

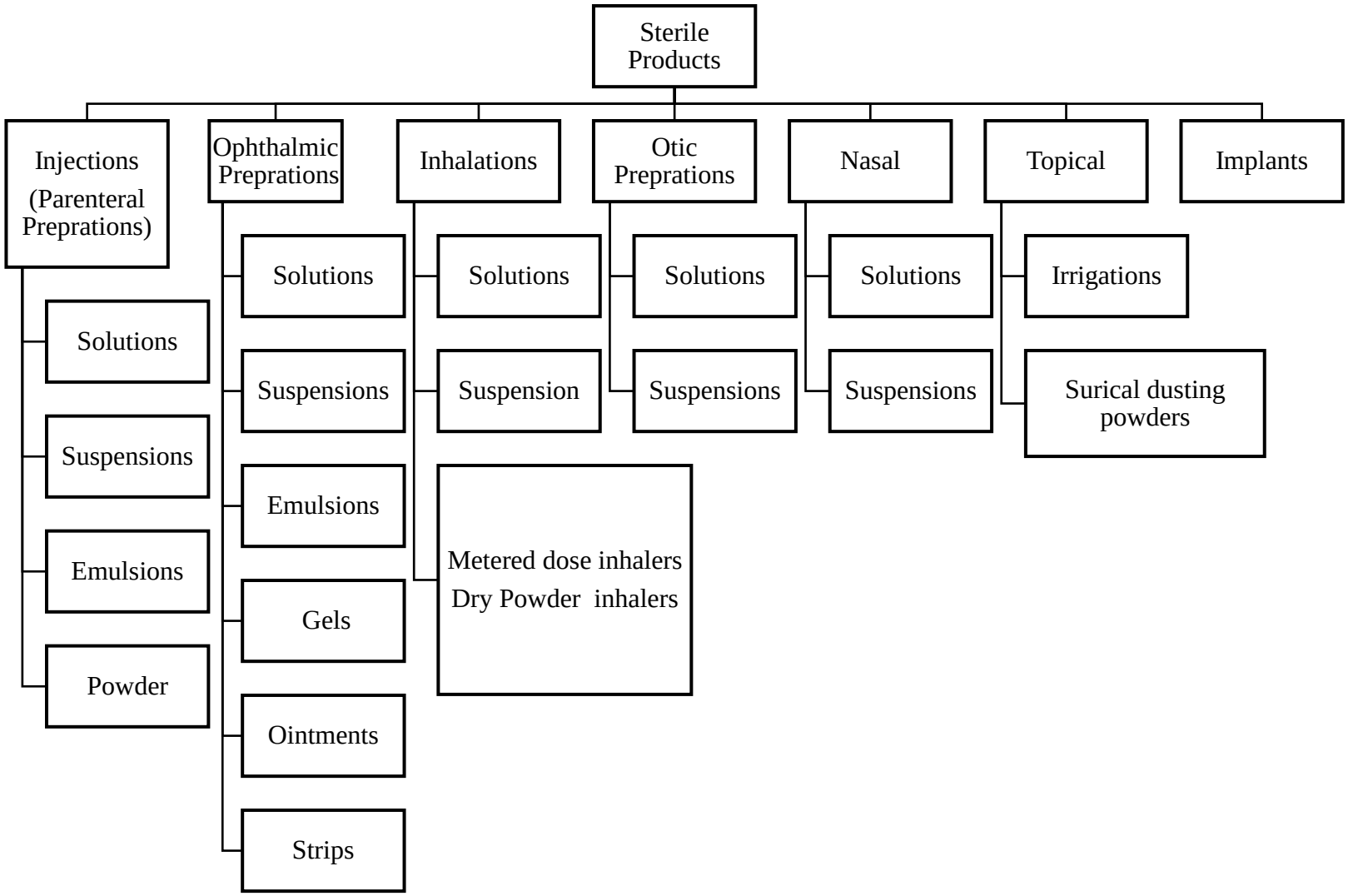


Figure 1: Standard classification of sterile products for pharmaceutical use

1.1. Injection (Parenteral Preparations)[1]:

Among the sterile products, injectable formulations are the most important class and are intended for parenteral administration or preparation or dilution of a parenteral article before administration. Injectable dosage forms, also called parenteral dosage forms, include both aqueous and non-aqueous products. Injections or parenteral solutions are classified as:

- Small Volume Parenteral (SVP) - An injection that is packed in containers including ampoules, vials, syringes, bottles and cartridges of volume 100 mL or less are classified as SVPs
- Large Volume Parenteral (LVP)- These are formulations meant for parenteral use, designed to provide fluid, vitamins, and essential electrolytes to the body, wherein the volume is more than 100 mL

1.2. Standard methods for Sterilization

USP General Chapter <1211> "Sterilization and Sterility Assurance of Compendia Articles" classifies sterilization methods as detailed in the Figure 2 given below.

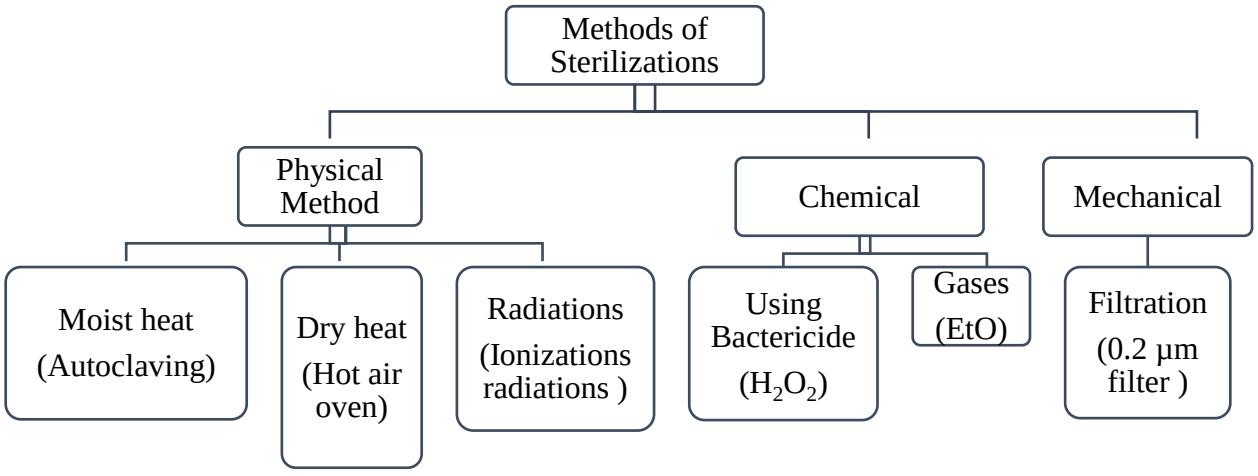


Figure 2: Common methods of sterilization techniques

1.2.1. Steam Sterilization (SS) or Autoclaving- This is the most commonly used and basic sterilization method. In this method, heat sterilization with the saturated steam under pressure is used in an autoclave, at a temperature generally between 100 to 121° C for 15 to 30 minutes, 15 Pounds per square inch (PSI) of pressure.[2] The autoclaving method is used for sterilizations of utensils, garments, rubber stoppers, aluminium seals and for terminal sterilization of thermostable finished liquid products.

1.2.2. Dry-Heat Sterilization (DHS) - Typically, the dry-heat sterilization process is used as a "batch process" and in this process, hot air is filtered and used to sterilize the glassware, glass vials, utensils, and terminal sterilizations of thermostable drugs including oil-based injectables in hermetically sealed containers.[3] The hot air is evenly distributed inside the whole chamber by a fan system. The DHS process is generally carried out at temperature between 160 to 170 °C for 2 to 4 hours.

1.2.3. Gas Sterilization (GS) - Most of the time GS method is used as an alternate option for autoclaving sterilization, where heat sterilization is not possible due to heat sensitivity of the items being sterilized. Ethylene oxide (EtO) is the most commonly used gas for GS. It is employed for sterilization of polymeric containers, hospital utensils, active pharmaceutical ingredients, etc.[4] Other gasses used for the sterilizations purpose include Chlorine dioxide gas, vaporized peracetic acid and nitrogen oxide.

1.2.4. Ionizing Radiation- Certain specific products like medical devices are not able to withstand heat sterilization due to the presence of certain thermolabile components and cannot be sterilized by GS because of their incompatibility with the EtO.[5] Ionizing radiation method, also called cold sterilization method utilizes cobalt 60 gamma rays or electron rays and is generally used for sterilizations of glassware, polymeric containers closures, active pharmaceutical ingredients etc.

1.2.5. Filtration- Filtration is commonly used to sterilize heat-labile solutions and microbial-retaining materials. [6] This is also categorized as cold sterilization process. The principle of this process is based on physically removing the contained microorganisms from liquid products. The sterile filter membrane is used for filtering out any viable microbes from the parenteral formulations. The filter membrane is defined as a membrane capable of retaining 100% of microorganisms of the biological indicator, *Pseudomonas diminuta* (ATCC-19146) under pressures 30 psi or higher. The filter membranes are rated as 0.22 µm or 0.2 µm depending on the manufacturer's practice.

1.2.6. Aseptic Processing- Terminal sterilization of filled containers or packaged products is the preferred method to minimize the risk of microbial contamination. However, some products cannot be terminally sterilized due to heat/gas/radiation sensitivity or higher viscosity where filtration is not feasible. Those products are manufactured by using aseptic processing methods. These aseptic processes are described below in the below Figure 3.

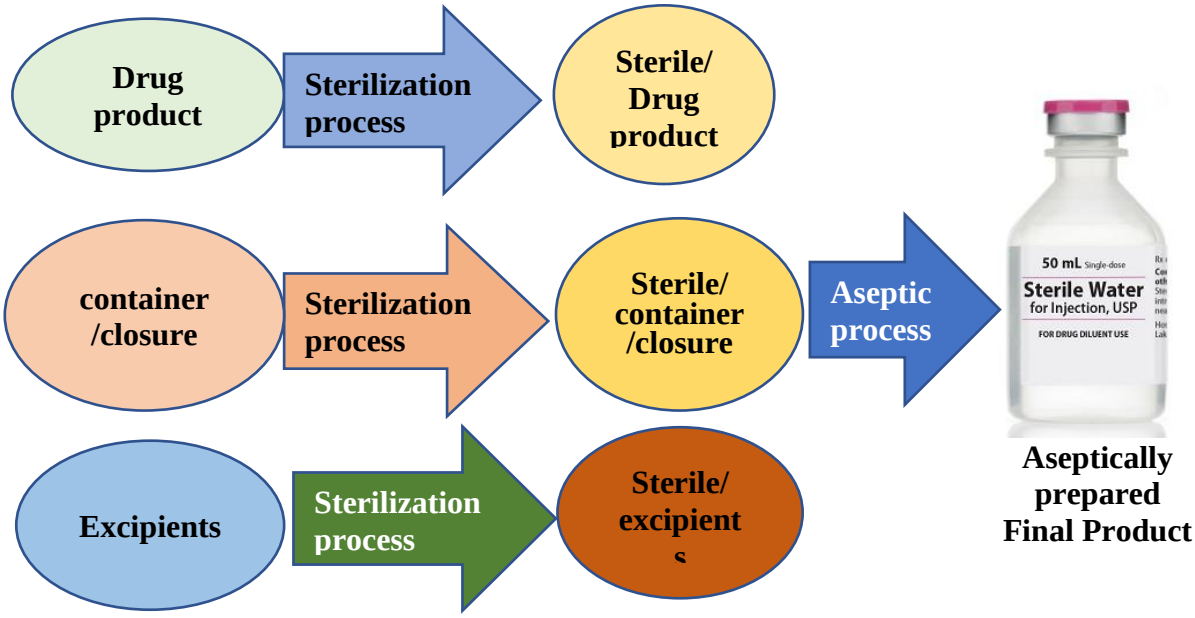


Figure 3: Aseptic process for sterile products

1.3. Current Good Manufacturing Practice

The key regulatory standard for pharmaceutical quality assurance for medicinal products is cGMP. Consumers expect every dose of medicine they take to meet quality standards so that it is safe and effective. cGMP regulations for drugs contain minimum requirements for the methods, equipment and controls applied in the production, processing and packaging of the drug product. The cGMP regulations make sure that a product is safe for use, and that it has the ingredients and strength according to the label claims.

1.4. Warning Letters (WLs)

A "WL" is an official letter issued by US FDA to a manufacturer or other organization that has violated a rule in a federally regulated activity. The cGMP provides "standard operating protocols (SOPs)" system, which ensures the appropriate drug design, monitoring, and controls of the manufacturing process and available facilities of the manufacturing unit.

As part of the cGMP compliance, agency investigators conduct inspections of drug substances as well as drug manufacturing sites for complete monitoring. The investigation officers of the US FDA primarily conduct their inspections in three steps.

1. Pre-Approval Inspection (PAI): The PAI is conducted after a company applies for a license from the US FDA, before marketing a new product. PAI is conducted to help assure the US FDA that the manufacturing facility listed in the drug application is capable of producing the drug and that the data submitted is accurate and complete
2. Routine and follow up inspection: This inspection is conducted for monitoring the regulated facility of the unit. During a routine inspection, observations are recorded on FDA Form 483. FDA may wish to conduct a follow-up inspection to confirm that corrective actions have been taken to satisfactorily address the concerns raised earlier.
3. An inspection may be conducted "For-cause" to investigate particular concerns that came to be known by US FDA. This inspection is performed due to:

- Significant Form 483 observations made during a routine inspection
- Serious problems reported to US FDA by consumers or employees
- Product recall

If non-conformances are found during the inspection, the inspector will document and communicate a finding on Form 483. The observation is commonly referred to as the "483" observation.[7] After issuance of 483 observations, the manufacturer is directed to respond within 15-calendar days after receiving the notice. The manufacturer should provide an explanation regarding existing non-conformity; its impact on product quality and efficacy and about appropriate corrective actions, which involve solving or avoiding recurrence. However, after such correction, if the resolution of observation is considered inadequate and still they have a significant impact on the product quality, then the US FDA will issue a warning letter to the drug product manufacturer.

1.5. US FDA Inspection

Upon submission of the response to the Form 483 observations, FDA classifies the actions as below: [8]

1.5.1. No Action Indicated (NAI): This statement typically indicates that no significant issues were identified during the inspection processes or that any identified issues were deemed minor and did not require further action. It is a common statement used in reports to signify that no major problems were observed and that the inspected entity complies with applicable regulations or standards.

1.5.2. Voluntary Action Indicated (VAI): If the response is deemed acceptable but the company's corrective actions are insufficient to address all observed objectionable conditions, the US FDA may classify the case as VAI. This means that the company has taken voluntary actions to address the issues, but further regulatory action may be needed if the corrective actions are found inadequate.

1.5.3. Official Action Indicated (OAI): If the response is deemed unacceptable to address the observed objectionable conditions, US-FDA may classify the case as OAI. Further regulatory action may be needed, such as WLs, fines, or even product recall.

1.6. Impact of the cGMP non-Compliance

The US FDA issues a Form 483 after an inspection if any observed objectionable conditions or practices may violate "cGMP" regulations. Form FDA-483 is a notification to the company of the issues that have been observed and a request for a written response outlining the corrective actions that have been taken or are planned. In case, the observed issues are serious or repeated, the US FDA may take further actions such as issuing WLs, imposing fines, or even recall of products or shutting down the facility. These actions can significantly impact the company's reputation, financial health, and operating ability. In addition to the regulatory consequences, losing the consumer confidence in the product can damage the company's reputation. Therefore, companies must comply with cGMP regulations and address any observed issues promptly to maintain the credibility of their products and trust of their customer.

1.7. Research Gap:

Review of existent literature on warning letters to pharmaceutical industries for cGMP violations pertaining to sterile products reveals the following research void: -

- In recent years, there has been a significant increase in the number of warning letters referring to 'sterility assurance' of drug products
- There is a need for a paradigm shift in quality culture and transparent dealing with regulators while interacting during the inspections. Firms need to exercise more control on sterilization practices as well as microbiological contamination
- Any observation about breach of sterility assurance shakes the confidence and trust of regulator and may lead to stoppage of the business for USA market

Though the gaps that lead to issuance of warning letters and Import alerts appear to be oversight, lack of thorough understanding of US FDA expectations and at times, business taking priority over compliance, is also observed. There is no report available in literature where the FDA warnings letters to pharmaceutical industries for cGMP violations pertaining to sterile product have been systematically analyzed. Therefore, no guidance has ever been provided to the pharmaceutical industry to take steps in order to avoid the issuance of WLs for such products.

1.8. Research Questions

Based on the research gap identified, the following research questions will be taken up -

1) How frequently are the warning letters being received by pharmaceutical industries for cGMP violations pertaining to sterile products?
2) What are the common causes of issuance of these WLs?
3) How does the pharmaceutical industry respond to these warning letters?
4) What is the learning for pharmaceutical industries from these warnings letters?

1.9. Research Hypotheses

For addressing the four research questions, a testable hypothesis has been proposed.

The hypothesis is that if logical suggestions are provided to the pharmaceutical industry based on the analysis of warning letters issued by US FDA regarding aseptic processing of sterile products, and they are implemented by the concerned industries, the frequency of issuance of such letters is expected to reduce considerably.

1.10. Research Objective

The objective of research is:

- To analyze the US FDA warning letters issued to pharmaceutical industries for cGMP violations pertaining to sterile products
- To identify the cause and effect of increased number of warning letters issued by the FDA year after year in spite of clarity in the guidance issued by the agency for aseptic processing of the sterile products
- To evaluate the economic impact of the issuance of warning letters on the concerned organization
- To summarize the recurring observations which will help as guidelines for all such organizations to avoid similar non-compliances

Chapter 2 Review of Literature

As discussed in the introductory chapter, sterile products are considered high-risk dosage forms because they come in direct contact with blood when administered.[9] During the COVID-19 pandemic, the demand for sterile products such as vaccines and life-saving parenterals including biologics increased in huge proportion.[10] This surge has not yet subsided and the market for parenteral formulations continues to grow.[11] For manufacturing of sterile products, applicable cGMP regulations must be carefully followed.[12] In this regard, increase in the number of WLs is of great concern to the manufacturers of sterile products, regulatory authorities and entire society.

A number of studies have been conducted on WLs issued by the US FDA for drug products, including a recently published review article where the authors discussed all WLs issued between 2019 and 2021.[13] It has been reported therein that China and India received the second highest number of WLs from the US FDA in 2019 after the United States. During the years 2019 to 2021, 46 WLs related to sterile product cGMP violations were reported. Such high number of WLs indicates that manufacturers need to focus on their quality systems to ensure compliance with the guidelines.

In the year 2018, the US FDA issued 422 WLs, of which 91 (21.5%) were issued by CDER. Of these, 61 (67.0%) were WLs for non-compliance with cGMP regulations, of which 45 (73.8%) were for finished drugs and 16 (26.2%) were for APIs. More than half of the WLs were related to cGMP.[14] These WLs indicated numerous types of violations of federal regulations, the lack of sterility assurance being the most commonly cited observation mentioned in these WLs.

There are several available studies on WLs issued by the US FDA. However, there are no specific reports on WLs associated with sterile products. This chapter provides a summary

of the literature on WLs related to sterile products. The details on cGMP regulations, sterilization types, US FDA sterile product inspection systems and procedures, Form 483, and WL procedures are also briefly discussed. In addition, this chapter also analyses WLs related to sterile products reported in the literature.

2.1.cGMP Regulations

The US FDA regulates the quality of drugs by closely observing how drug manufacturers adhere to cGMP regulations.[15] cGMP regulations set minimum requirements for production facilities, procedures, packaging and quality control of products. Regulations ensure that the manufactured products are safe to use. During facility inspection, US FDA inspectors assess whether a company has the required equipment, facilities including trained manpower and technology to manufacture the drug it intends to sell and whether it is following the recommended guidelines.

cGMP deals with both manufacturing and quality control. The basic requirements of cGMP are:

1. The manufacturing procedures should be pre-defined and demonstrated to be capable of constantly producing pharmaceutical products of the required quality and meeting their specifications
2. Critical steps of manufacturing processes and significant process changes are validated using pre-approved protocols
3. All necessary required facilities complying with cGMP are available, which include:
    a. Competent and skilled employees
    b. Adequate buildings and spaces
    c. Appropriate equipment for manufacturing products
    d. Raw materials, containers/closures and labels
    e. Approved SOPs and guidelines
    f. Appropriate storage facility and transportation system

4. Instructions and procedures are available in instructional form in simple language that is specifically applicable to the concerned procedures
5. Operators are trained to perform procedures correctly
6. Batch records are documented on-line throughout production process
7. Any significant deviations during production process are logged and investigated to identify root cause
8. Production records are kept in a comprehensible and accessible form, enabling the complete history of batch to be traced

Part of the US FDA CFR Title 21 interprets relevant laws, including the Federal Food, Drug and Cosmetic Act and the Public Health Services Act, pharmaceutical or quality regulations for drugs.

Drug manufacturers must adhere to the following sections of cGMP CFR:

- 21 CFR Part 210, which relates to cGMP practices in the "manufacturing, processing, packaging, or holding of drugs"
- 21 CFR Part 211, which relates to minimum cGMP for preparation of drug products

The subsections of 21 CFR 210/211 which are the most relevant to sterile products are presented in table 1:[16]

Table 1: Subsections of 21 CFR 210/211 relevant for sterile products

S. No.	Parameter	Guideline	Reference Section of CFR
2.1.1.	**BUILDINGS AND FACILITIES**		
1.	Prevention of contamination by flow of material	"The flow of components, drug product containers, closures, labelling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination."	Excerpt from 211.42(b)
2.	Dedicated space for critical activity, suitable EM, sanitation, HEPA air filtration in sterile workplaces.	"Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixup during the course of the following procedures: Aseptic processing, which includes as appropriate: (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable; (ii) Temperature and humidity controls; (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;	Excerpt from 211.42(c)

S. No.	Parameter	Guideline	Reference Section of CFR
		(iv) A system for monitoring environmental conditions; (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions."	
3.	Adequacy of environmental control	"Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product."	Excerpt from 211.46(b)
4.	Use of AHU (Air Handling Units) system for sterile area	"Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas."	Excerpt from 211.46(c)
5.	Proper equipment design, size and location	"Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."	211.63
6.	Inertness of equipment used for processing	"Equipment shall be constructed so that surfaces contact components, in process materials, or drug products shall not be reactive,	211.65(a)

S. No.	Parameter	Guideline	Reference Section of CFR
	of drug products	additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."	
7.	Adherence to available written protocols for prevention of microbiological contamination	"Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."	211.113(b)
2.1.2.	**PERSONNEL TRAINING, QUALIFICATION, & MONITORING**		
1.	Availability of adequate quality control unit	"There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labelling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company."	211.22(a)

S. No.	Parameter	Guideline	Reference Section of CFR
2.	Responsibility for quality control	"The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product."	211.22(c)
3.	Personnel training	"Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in cGMP as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them."	211.25(a)
4.	Personnel qualification and training	"Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug	211.25(b)

S. No.	Parameter	Guideline	Reference Section of CFR
		product has the safety, identity, strength, quality, and purity that it purports or is represented to possess."	
5.	Adequate number of qualified personnel	"There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product."	211.25(c)
6.	Garments for prevention of contamination	"Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination."	211.28(a)
7.	Hygienic practices	"Personnel shall practice good sanitation and health habits."	211.28(b)
8.	Entry restrictions in critical areas	"Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas."	211.28(c)
9.	Prevention of contamination due to personnel illness	"Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from	211.28(d)

S. No.	Parameter	Guideline	Reference Section of CFR
		direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products."	
2.1.3.	**COMPONENTS AND CONTAINERS/CLOSURES**		
1.	SOP (Standard Operating Procedures) availability	"There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed."	211.80(a)
2.	Handling of containers/closures/components	"Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."	211.80(b)
3.	Testing of samples for microbiological tests before use	"Samples shall be examined and tested as follows: Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall	Excerpt from 211.84(d)

S. No.	Parameter	Guideline	Reference Section of CFR
		be subjected to microbiological tests before use."	
4.	Cleaning and appropriate processing of containers and closures	"Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated."	211.94(c)
5.	Availability of microbiological controls and written procedure for container closures	"Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures."	211.94(d)
2.1.4	**ENDOTOXIN CONTROL**		
1.	Appropriate cleaning and sanitizations of equipment	"Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identify, strength, quality, or purity of the drug product beyond the official or other established requirements."	211.67(a)

S. No.	Parameter	Guideline	Reference Section of CFR
2.1.5.	**TIME LIMITATIONS**		
1.	Establishment of hold time for intermediate bulk and filled units for prevention of microbiological contamination	"Time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."	211.111
2.1.6.	**VALIDATION OF ASEPTIC PROCESSING AND STERILIZATION**		
1.	Collection of samples	"Samples shall be collected in accordance with the following procedures: (1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component. (2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures. (3) Sterile equipment and aseptic sampling techniques shall be used when necessary. (4) If it is necessary to sample a component from the top, middle, and bottom of its	211.84(c)

S. No.	Parameter	Guideline	Reference Section of CFR
		container, such sample subdivisions shall not be composited for testing. (5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample. (6) Containers from which samples have been taken shall be marked to show that samples have been removed from them".	
2.1.7	**LABORATORY CONTROLS**		
1.	Adequate facility for laboratory	"Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit."	211.22(b)
2.	SOPs for cleaning of equipment	"There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed."	211.56(b)

S. No.	Parameter	Guideline	Reference Section of CFR
3.	SOPs for sanitation	"There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed."	Excerpt from 211.56(c)
4.	SOPs for sampling and testing of in-process materials and drug products	"To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."	Excerpt from 211.110(a)
5.	Adequate laboratory controls	"Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure	211.160(b)

S. No.	Parameter	Guideline	Reference Section of CFR
		that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include: (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration. (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.	

S. No.	Parameter	Guideline	Reference Section of CFR
		(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified. (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used."	
6.	Validation of test methods	"The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented."	Excerpt from 211.165(e)
7.	Approval of documents	"All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed."	Excerpt from 211.192

S. No.	Parameter	Guideline	Reference Section of CFR
2.1.8	**STERILITY TESTING**		
1.	Sampling for sterility testing	"Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled."	210.3(b)(21)
2.	Specifications for drug product and input materials	"For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release."	Excerpt from 211.165(a)
3.	Maintenance of documents record and periodic review	"Written records required shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures."	Excerpt from 211.180(e)
2.1.9	**BATCH RECORD REVIEW: PROCESS CONTROL DOCUMENTATION**		
1.	SOPs for production and process control	"There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are	211.100(a)

S. No.	Parameter	Guideline	Reference Section of CFR
		represented to possess. Such procedures shall include all requirements. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit."	
2.	QAMS (Quality Assurance Management System) documentations and deviations	"Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."	211.100(b)

The above requirements are critical for aseptic products and any deviation from any of these, if observed during the inspections, call for the issuance of Form 483 and then in case of unsatisfactory response from the firm, it results in the issuance of WLs.

2.2.Types of Sterilization

As stated in Parenteral Drug Association (PDA) Technical Report No. 1 (revised 2007), entitled "Validation of the Moist Heat Sterilization Process Cycle Design, Development, Qualification, and Ongoing Control",[17] there are two general methods for ensuring sterilization of sterile products. These include:

- Terminal sterilization (TS)
- Aseptic processing (AP) or Aseptic technique

There is a difference between the manufacturing of sterile products by AP and TS.[18] TS is to be used only if the product and packaging components can withstand exposure to heat or radiation or the required dose of ethylene oxide (EtO).

2.2.1 Terminal Sterilization

Terminal sterilization processes typically involve filling of liquid product in container and stoppering/sealing under classified area considered to control microbial and particulate contamination of the product. This preliminary control of biological load (bioburden) reduces the demands on subsequent sterilization processes. The product is sterilized in its final packed container. TS method is the preferred methods for providing a high sterility assurance level (SAL) to a drug product. For this reason, sterile drug products are prepared with aseptic technique only when TS is not possible due to heat, radiation or EtO sensitivity.[16]

Various methods of TS are detailed below:

2.2.1.1 Moist Heat Sterilization (Autoclaving): Moist heat sterilization is also known as autoclaving, which happens to be the most common method used in pharmaceutical industries for sterilizations of equipment, garments, components as well as finished liquid (aqueous) drug products. Sterilization of the pharmaceutical products with the application of moist heat is carried out by employing saturated steam under specific pressure in a specially designed autoclave.

The basic principle of sterilization by this method is the denaturation of structural proteins and enzymes of microorganisms.[19] Aqueous-based products such as 0.9% NaCl injection

and 5% dextrose injection (D5) are common examples of the products sterilized by moist heat sterilization.

2.2.1.2 Ethylene Oxide (EtO) sterilization: The use of gas to sterilize pharmaceutical products is an alternative to heat-based methods to overcome their limitations. EtO process is generally used when the material to be sterilized is not capable of withstanding the high temperatures reached during the processes of steam or dry-heat sterilization.[20] EtO is most commonly used gas in the process of gaseous sterilization. Plastic containers and closures for ophthalmic use, pre-filled syringes and ophthalmic products like Tetracaine Ophthalmic Solution in blister pack are generally sterilized by EtO sterilization.[21] Some other gases like ozone, oxides of nitrogen, and chlorine dioxide are also occasionally used. The major drawback of using EtO for sterilization is its absorption into certain polymers leaving a significant residue that is reported to be hazardous to the user and even to the environment.

2.2.1.3 Irradiation: The radiation sterilization was developed considering the fact that certain products like medical devices are not able to withstand heat sterilization and EtO sterilization in such cases is questionable.[22] Though radiation sterilization is particularly useful for sterilization of medical devices, it is also used for certain drug substances and final dosage forms. It utilizes ionizing radiation including gamma irradiation, X-rays or electron radiation, gamma radiation being the most popular form. The major advantages of sterilization by irradiation are its low chemical reactivity, low residues, and less number of variables to control. Certain Active Pharmaceutical Ingredients (APIs) such as Loteprednol Etabonate, Difluprednate and plastic containers as well as closures for ophthalmic use are generally sterilized by gamma irradiation method.[23]

2.2.1.4 Dry-Heat Sterilization (DHS): DHS method is based on the principle of protein denaturation of the cellular components of microorganisms and is used for heat-stable products.[24] Certain APIs like Dexamethasone and oil based products such as Artemether Injections in glass ampoules are generally sterilized by dry heat sterilization method.

The batch of the products required to be sterilized is kept in the specially designed oven supplied with heated, HEPA filtered air circulated uniformly at the required temperature

for a specific period as per the type of product. Using this method, "sterility assurance of 12 log reduction" is achievable. Although this method is effective, its use is restricted by certain limitations such as long sterilization time, warping or charring of heat-sensitive material, damage of rubber and plastic closure systems and relatively inferior penetration of heat to denature the cell wall of microorganisms as compared to the moist heat sterilization.

The types of sterilization cycles used in terminal sterilization are:

A. Overkill method (12 Log reduction method)

- The overkill method is used when the product can withstand excessive heat or a high dose of EtO/gamma rays[25]
- With the Overkill method, the achieved level of sterility assurance is twice the required one, i.e. a reduction of 12 logs in microorganisms is achieved
- This approach is adopted for the products sterilized by autoclaving/EtO/gamma rays
- The method is intended to deliver a high SAL irrespective of the number of microorganisms present in the input loads
- In the Overkill method, greater exposure to heat/dose may affect the sterilized product in terms of physicochemical characteristics/stability

B. Bioburden Based Cycle

- Bioburden is the number of contaminating viable microorganisms found in a given amount of material prior to sterilization[26]
- A bioburden-based cycle is adopted when the product is sensitive to excessive heat/EtO/radiation
- Bioburden assessment is required to evaluate the viable microorganisms in the inputs raw materials and packaging materials involved in the drug product
- In this method, cycle is developed so that the microbial load is killed without affecting the drug product
- Routine monitoring and knowledge of product bioburden is required to set the cycle[27]

2.2.2 Aseptic Technique AT):

Aseptic technique poses a "higher risk of microbial contamination" of the product than TS method due to involvement of manual interventions during the processing[28]. In the AT, the product components such the bulk solutions, containers and closures are separately sterilized and assembled under high quality environmental conditions. AT involves many more variables than TS. Manual handling of sterile drugs and containers closures prior to filling may lead to the inherent risk of sterility failure. In traditional aseptic processing, employees (operators, batch processing supervisors) are considered as significant source of contamination, especially in production lines where operators must regularly enter classified areas of the filling line (Class 100, ISO 5 or Class A).[29]

Advanced technologies such as "Restricted Access Barrier Systems" (RABS) and "Blow Fill Seal Systems" (BFS) are considered to minimize human intervention in classified areas of the filling line.[30] This is reported to reduce exposure to contamination because the fewer the interventions required, the lower the risk of contamination.[31] However, another system i.e. "isolator system" entirely separates this aseptic filling line from the outside environment and reduces operator interactions in critical areas. The use of a "Bio Fluorescence Particle Counter" (BFPC) in isolators and Class A areas during aseptic operations where open containers are used, reduces the risk of contamination in critical areas.[32]

While performing any activity in sterile manufacturing, strict control of processing parameters is required to minimize the microbial contamination. Environmental and personnel monitoring programs should be used to prevent potential risks.[16] Environmental monitoring should be conducted in areas where control is considered the weakest. The results thus obtained provide information about the risk areas in the design of the facility, along with HVAC system.[33]

A report by Weber et al., in 2018 discussed an advanced technology for real-time continuous environment monitoring, thereby reducing manual intervention and future replacement of Grade A settling plates and near-field active air sampling.[34] This

replacement of traditional manual monitoring with bio fluorescence particle counting systems was reported to provide better process understanding, product safety and minimizes operator handling, ensuring product quality and real-time process validation. The use of this kind of advanced technology may help to reduce the frequency of WLs related to sterile products due to reduction of contamination accruing from manual operations.

2.3. US FDA inspection system

The US FDA ensures the quality of medicinal products by monitoring compliance to the cGMP regulations.[35] cGMP regulations contain minimum requirements for the production and packaging of the products. In short, cGMP regulations ensure the product quality and safety. The US FDA believes that the manufacturer should have internal policies/SOPs for ensuring compliance of cGMP regulations to implement a quality system.[36]

Types of US FDA cGMP Audit/Inspections:

Under the US FDA Compliance Programs, the US FDA performs the following inspections (audit) to evaluate a drug manufacturer's cGMP compliance: [37]

1. Pre-approval audit
2. Audit after approval of product
3. Drug manufacturing audit [Routine cGMP (surveillance) audit]

2.3.1 Pre-Approval audit (PAI)

The US FDA approves new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) before import of medicinal products into the US market.[38] The equipment and controls to be used in the manufacture, processing, packaging and testing of medicinal products must be such as to ensure and maintain their identity, strength, quality and purity. A PAI is conducted to allow the US FDA to confirm that the manufacturing facility listed in the drug application is able to produce the drug as per the information given in the dossier.

2.3.2 Post Approval Audit

During the post approval audit, US FDA reviews any production changes and confirms that approved applications are updated accordingly.[39] Process validation reports are reviewed, and auditors visit shop floors to inspect the actual production runs. The goal is to ensure that the company fulfils the commitments made during the application approval process. The auditor reviews the process validation report for approved products during the post-approval inspection. The auditor visits shop floors and closely monitors the production runs during the audits.

2.3.3 Routine cGMP audit

Routine inspection activities aim to assess a company's compliance with cGMP requirements.[40] Full inspections are conducted when there is limited knowledge of a firm's compliance, doubts about compliance, or follow-ups to previous regulatory actions. The goal is to determine if the company follows applicable cGMP standard or not.

2.3.4 US FDA Inspection Action Classification

After submitting an FDA Form 483 observation response, FDA classifies the actions as shown in Figure 4.

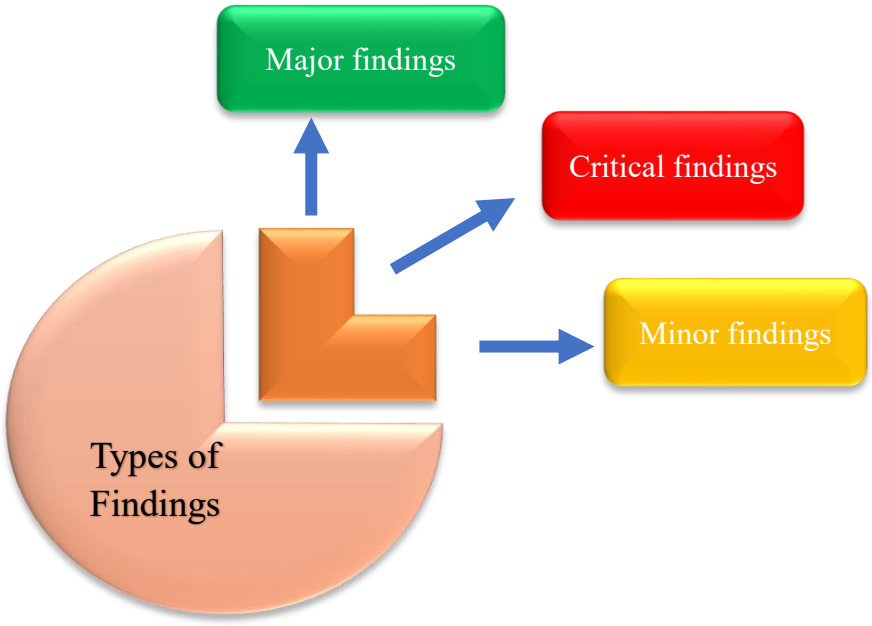


Figure 4: Types of findings during the US FDA inspections

- **Minor Findings – "No Action Indicated (NAI)":** During the inspection, no cGMP violations were identified or the violations were determined to be significant that did not require further action. NAI indicates compliance with critical parameters like data integrity, environmental monitoring, and sterility, aligning with cGMP regulations [41]
- **Critical Findings – "Voluntary Action Indicated (VAI)":** An adverse condition is discovered and documented, and the US FDA does not take any regulatory action (advisory, administrative, or judicial) because the deviation does not meet thresholds for regulatory action. VAI states that there are minor observations such as air sampling SOPs that could be improved, but do not have any effect on the quality of distributed medicinal products or cGMP violations [42]
- **Major Findings: "Official Action Indicated (OAI)":** Non-compliance situations are identified, and regulatory action is recommended. OAI classification is based on documented evidence and typically occurs when US FDA-483 is issued regarding critical issues. OAI indicates major observations, such as issues with data integrity, sterility, and filter integrity, or where the firm has violated the cGMP regulations resulting in potential compromise in the safety of product [43]

2.4. Impact of cGMP Non-Compliance

Following an on-site inspection by the US FDA, companies may receive a Form 483 for failure to meet cGMP requirements under US regulations.[44] The US FDA may take regulatory (advisory, administrative, or judicial) action in cases of clear violations of these regulations, but the most damaging aspect is the public consumption of such product and the loss of consumer confidence.[45] The types of actions that the US FDA can take for violations of US regulations include :

- Warning letters (WLs)
- Withdrawals of ANDA/NDA approvals
- Recall of products (RP)
- Import alert (IA)
- Civil penalties (CP)

- Prosecution under the FD&C Act

An overview of the process of US FDA inspections and issuance of WLs is presented in Figure 5

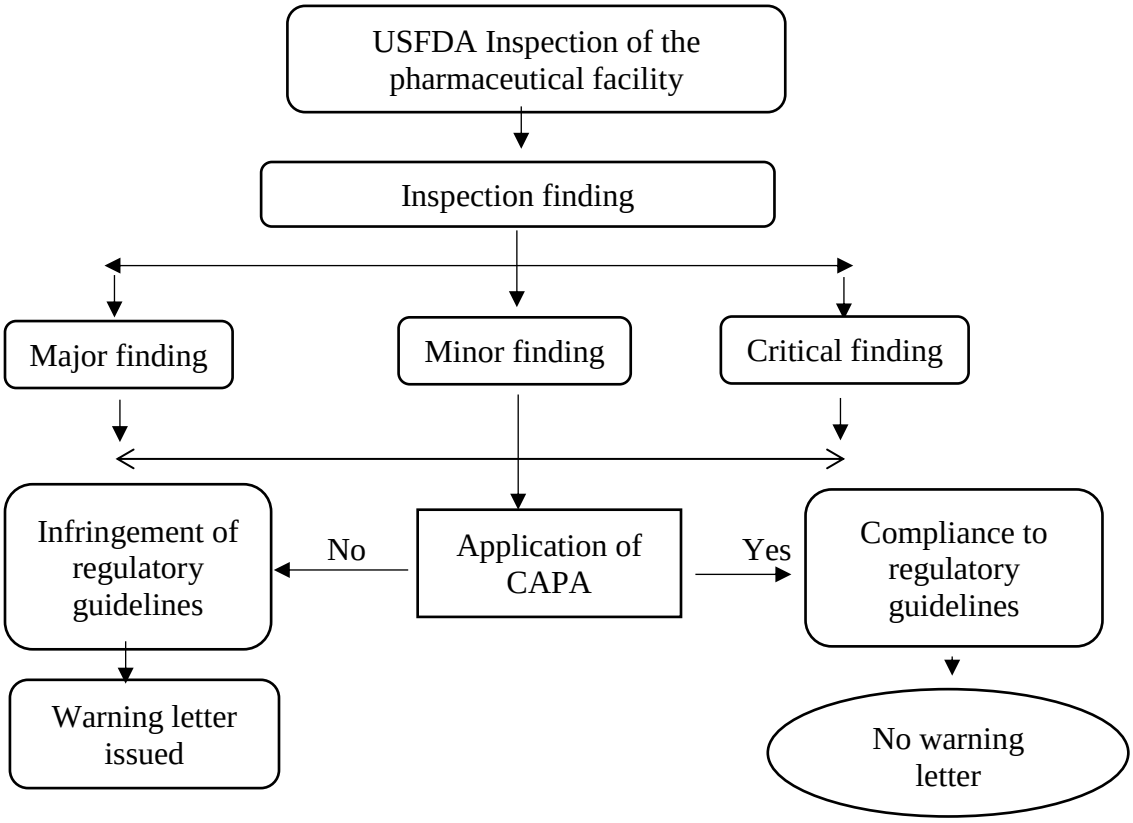


Figure 5: US FDA inspection process and issuance of WLs

2.5.Form US FDA 483 [FDA 483 or 483]

Form 483 is used by US FDA inspection team to document the results of their findings during audits.[46] The concerned company responds formally within the stipulated time to the issued Form 483. The US FDA expects the concerned firm to respond within 15 business days from the receipt of the Form 483. A prompt and satisfactory response to the issued Form 483 helps the companies avoid US FDA WL, pending product approval or regulatory action.[47]

Typical 483 observations related to sterile products are as follows:

- Media fill SOPs not fully followed
- Poor investigations of product filter integrity failures
- Absence of written procedures for aseptic practices
- Data integrity issues specifically for sterility, bioburden analysis
- Cleaning, sanitizing, and maintenance
- Environmental monitoring

2.6.US FDA Inspections of sterile drug products

According to the Compliance Program Guidance Manual, inspection of sterile products manufacturers are conducted as full or Abbreviated Inspections.[48] A full inspection includes monitoring or compliance inspections and assessing cGMP compliance. It typically includes examining at least four systems (facility/equipment, materials, production and laboratory), with the quality system being mandatory. The aim is to comprehensively evaluate the organization's adherence to cGMPs and ensure the production of safe and sterile drugs. The Abbreviated Inspection program applies when the firm has risk assessment programs in place that in turn, assures effective design and control or the firm has proven record of accomplishment for the cGMP compliance (history for the successful last two inspections).[49]

The following important features of each system are covered during the "Abbreviated Inspection program":

2.6.1. Facilities and Equipment

These include:

- Cleaning and disinfection procedures
- Measures to prevent contamination including the layout of facilities and equipment and the air handling system
- Ensuring proper material flow within the facility
- Quality control measures for classified areas, including maintaining appropriate air pressure balance and utilizing high-efficiency particulate air (HEPA) filtration
- Trending data analysis to support the effectiveness of clean room quality

- Documentation of thorough investigations conducted in response to any discrepancies encountered

2.6.2. Materials

These include:

- Control of microbiological endotoxin in incoming raw, packaging materials and product contact components like filters, tubing
- Ensuring the quality of water supply, its maintenance, and qualification
- Proper operation of systems providing required water and process gases
- Conducting documented investigations into Out of Specification (OOS), deviations, and discrepancies

2.6.3. Production

These include:

- Observing operator behaviour and aseptic techniques during manufacturing
- Managing production line operations and interventions
- Providing personnel training in aseptic techniques
- Addressing major production line repair or maintenance issues
- Conducting risk assessments on microbial and bacterial endotoxin controls, including critical step hold times
- Validating equipment, container closures, and supplies sterilization
- Designing media fills and evaluating these results
- Quality management system documents deviations, discrepancies, and OOS results

2.6.4. Laboratory

These include:

- Examining deviations, Out of Specification (OOS), and discrepancies
- Taking steps to make sure that test procedures and controls are followed including validated procedure
- Assuring that laboratory employees are properly trained and qualified
- Trending water system test results and utilizing systems for EM isolate recovery, identification, and trending

The US FDA Drug Manufacturing Inspection Compliance Program is a system-based approach to inspection, and is quite consistent with the robust quality system. US FDA authorities are instructed to perform the inspection based on six systems categorised as:[50]

(1) Quality system (QS)
(2) Production system (PS)
(3) Facilities and equipment system (FES)
(4) Laboratory control system (LCS)
(5) Materials system (MS)
(6) Packaging and labelling system (PLS)

Below presented Figure 6 shows the relationship of the quality system and the manufacturing systems as mentioned above. The basic foundation of the compliance program is the quality system, which, in turn is linked to the manufacturing systems that are also closely integrated among themselves.

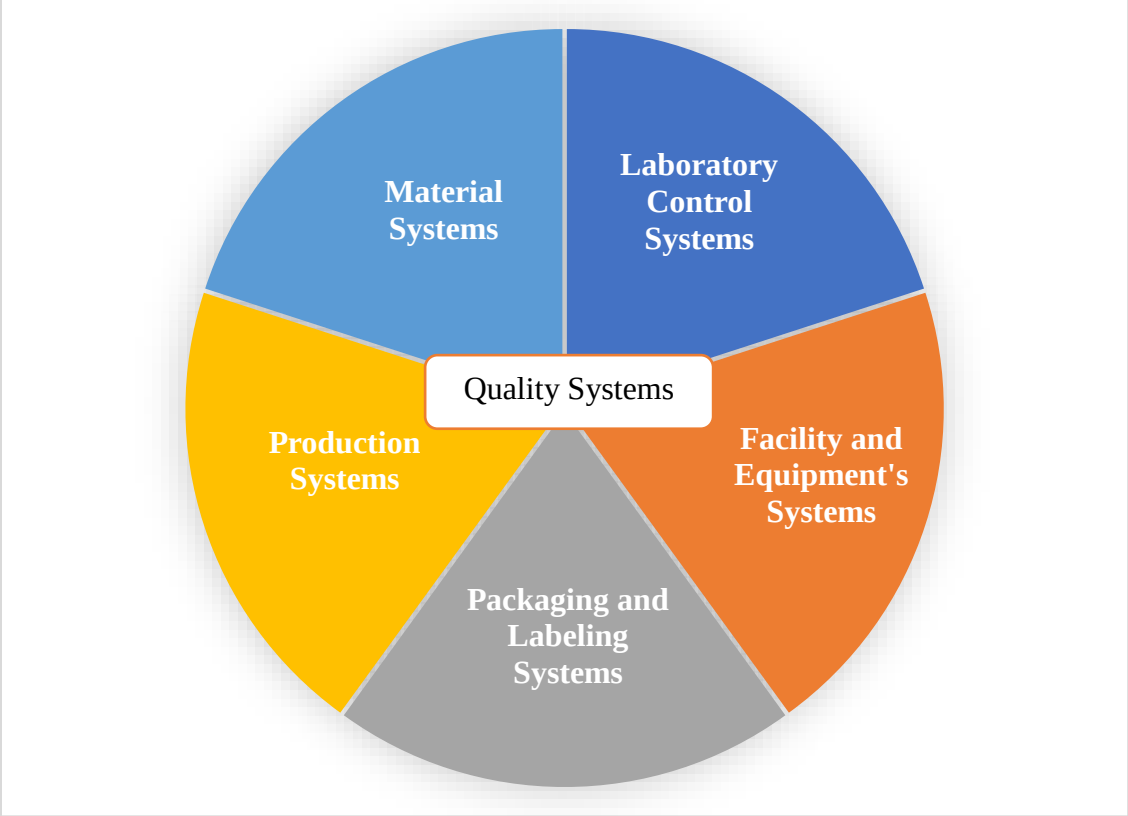


Figure 6: The Six-System Inspection Model

The number of US FDA inspections for sterile drug-manufacturing facilities has risen due to increased focus on pre-inspections, regular GMP inspections, and compliance follow-ups. Effective and efficient inspection coverage is vital in successfully administrating the FDA's foreign inspection program.[51]

2.7.WLs procedures

WL procedures are described in Chapter 4 “Advisory Measures” of the US FDA Regulatory Procedures Manual. In keeping with its duties to protect the public health, the FDA seeks to give the company in question a chance to take voluntary and prompt corrective action before starting its enforcement actions. The WL is issued to the company for serious cGMP violations that would affect the quality of the product and the safety of the patients.[7]

2.8.WL s analysis and key findings

The COVID-19 pandemic presented challenges for the US FDA in conducting in-person facility inspections for drug quality and manufacturing compliance. Joshua Oyster et al., conducted a study in 2022, analysing WLs issued by the FDA during the pandemic.[52] The study reported significant disruptions in routine inspections, forcing the FDA to rely on remote reviews of manufacturing aspects such as environmental monitoring, cleaning protocols, sterility control, and contamination prevention. To ensure an uninterrupted pharmaceutical supply chain, the FDA had to adopt this approach and utilize alternative tools. The reduced frequency of direct inspections and the reliance on remote methods during the pandemic have resulted in long-term changes to the FDA's approach (inspections based on risk approach). These changes are likely to shape the FDA's future strategies and methods to maintain drug quality and compliance in the years ahead.[53]

ECA (European GMP Auditor Association), the leading association for pharmaceutical quality regulation in Europe, reported about metal particles in a sterile product due to the use of an inappropriate equipment in aseptic manufacturing. The incidence came into light due to customer complaints. An investigation into the matter revealed that the tray units caused the problem and no corrective measures were taken to prevent particles from being introduced into the medication. In FDA's opinion, the SOPs for handling the unit's reservoir were inadequate. Based on their review, the authors concluded that if the regulatory agencies like ECA and US FDA expect to have a CAPA (corrective and preventive action) plan and implement best cleaning practices, preventive maintenance should be focused.[54] Involvement of senior management was deemed essential to ensure timely availability of resources and continuous quality improvement.

Osterreich et al., studied trends in WLs in fiscal year 2023. According to the study, the number of WLs increased in fiscal year 2023 compared to fiscal year 2022.[55] This was attributed to the continued increase in inspections in the post COVID-19 period.

Kumar et al., in 2023 studied the violations related to documentation cited in WLs issued to Indian pharmaceutical industries for the period of 2010 to 2022.[56] The study focused on identifying the most common documentation deficiencies and the impact on the Indian pharmaceutical industry. The documents destruction, non-availability of raw data, and inadequate batch manufacturing records (BMR) were reported to be the top reasons for these violations. Authors concluded that improvement of documentation practices needs to be adopted by the Indian pharmaceutical industry to sustain its significant role in the pharmaceutical global scenario.

The analysis of WLs presented in the FDA warning letter report 2023for fiscal year 2023 reveals that 21 CFR Part 211.84 i.e. “incoming inspection of raw materials, excipients and API components" is the most common point of violations by industry.[57] Out of the 71 issued WLs, 49 WLs were found to be pertaining to violations of Section 211.84 more than ever before. Although 21 CFR part 211.84 has always been among the sections frequently cited in WLs, it was reported to be particularly high in fiscal year 2023 with a share of 69%.

Kavyashree et al.,in 2020 studied WLs issued for cGMP violations related to medical devices. [58] Authors studied 669 WLs issued from the period of January 2008 to November 2018. From 2008 to 2013, there was a descending trend in the issuance of WLs. The number of WLs issued in 2014 was 101, followed by 106 in 2015, which was attributed to the enhanced focus of the US FDA on data integrity issues. The number was subsequently found to be decreased to 53, 27, and 19, respectively, in 2016, 2017, and 2018. The highest number of WLs were issued to manufacturers located in the USA (379), followed by those in Canada (52), and China (37). Section 820.30 (Design controls) of Title 21 CFR was found to be most violated section with 603 infringements. This indicated that increased awareness of both the stake holders i.e. the regulatory authorities and the concerned industries has led to overall improvement as indicated by the significant decrease in the number of WLs.

Report by Anderson on medical device CAPA concerns and the corresponding costs of US FDA non-compliance consequences indicated that significant additional expenditure was

incurred by a medical device manufacturer because of noncompliance with US FDA standards and failures in medical device quality.[59] Understanding and implementation of the fulfilment of their CAPA requirements by the medical device manufacturers will not only help them save on economic losses but also avoid the risk of losing market share, facing legal action and, in the facing worst situations like recall of the product from the market.

In an interesting study, Ajaj et al., in 2023 reported the quantitative analysis of WLs associated to the product misbranding of COVID-19 medications.[60] Analysis of WLs shows that highest number of WLs was related to advertisements on Facebook followed by those on Twitter, YouTube, and Instagram respectively. Advertisements on Facebook had to the most WLs issued while Twitter had the largest proportional amount of misinformation regarding agents for the management of COVID-19, followed by Facebook and then Instagram. Most WLs were issued in 2020. In view of misbranding of medications regarding COVID-19, many social media sites adopted policies to limit inaccurate information.

The WLs that compounding pharmacies received for cGMP violations between 2017 and 2022 were reported by Dmour.[61] The significant violations in the studied 141 WLs associated were further classified as 130 cases of contaminated pharmaceutical products followed by 103 of misbranded drugs, 42 of unapproved new drug products, 22 of failure to report adverse events, and 11 of the failure to report drugs. Additional noncompliance pertaining to the compounding of sterile products was also assessed by author, with a focus on the qualifications of staff, quality control protocols, equipment, etc. It is concluded in the report that a compounding pharmacy can minimize the compromise in patient safety by following the effective SOPs, which can reduce the number of WLs.

A report by Saini et al., in 2022 on Forms 483 and WLs issued by US FDA to various pharmaceutical manufacturers focused on misbranding of prescription drugs such as opioids and products related to the COVID-19 pandemic which led to maximum recurrently, cited violations.[62] The most common cases for issuance of Form 483 in the last four years were attributed to absence of written procedures, noncompliance to SOPs and inadequate investigations.

Rathore et al., in 2023 cited a number of manufacturing issues/problems in the pharmaceutical industry that led to issuance of WLs.[63] These issues included lot-to-lot variability during production and inadequate microbial-inspection, leading to microbial contamination in sterile and non-sterile-drugs. This study identified facility-related problems like poor aseptic technique and insufficient monitoring of environmental conditions, which increased the risk of microbial contamination. Equipment-related issues were also reported that included improper cleaning and maintenance practices, lack of cleaning validation, and inadequate equipment sterilization. It was concluded that implementation of proper aseptic techniques, rigorous environmental monitoring, and strong cleaning and maintenance practices are essential for preventing microbial contamination. Validating cleaning procedures and ensuring adequate equipment sterilization further contribute to maintaining product integrity.

According to a recent US FDA blog, quality issues constitute a major challenge for the pharmaceutical sector. [64] The most notable feature of the year 2021, as per the blog was the continued decline in issuance of Forms 483 that reached a level of less than 30% of their trend since 2016. The trend is shown in Figure 7

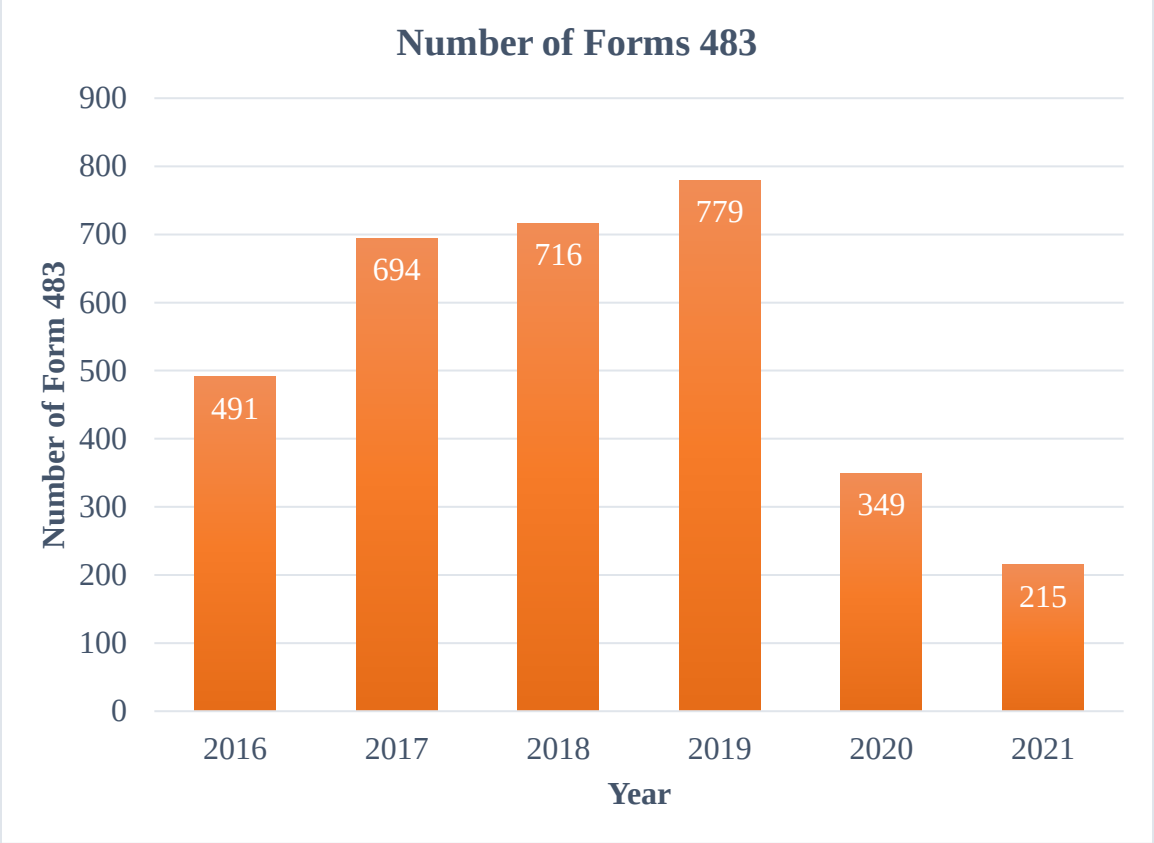


Figure 7: Year wise Forms 483 in the US FDA system (2016-2021)

Bablani and Janodia in 2020 published a comprehensive review on WLs issued to Indian pharmaceutical and medical device companies. [65] The study spanned 14 years and reported a gradual increase in WLs issued to these manufacturers. Most (85.87%) of the reported violations in these WLs were related to lack of compliance with cGMP guidelines. This suggests that the manufacturers could comply to the requisite measures leading to issuance of WLs.

Meghana reported about WLs related to manufacturing quality of drugs in the period ranging from FY 2018 – 2020. [66] Author concluded that in the given period the number of WLs issued by US FDA to Indian pharmaceutical industries was more when compared to any other country. Herein also, author suggests implementing the cGMP regulations effectively for avoiding the issuance of WLs.

According to Barreto-Pettit who has reviewed recalls due to deficiencies in US FDA cGMP compliance for sterile medicines, the majority of sterile drug recalls were due to cGMP violations related to aseptic processing.[67] Figure 8 shows recall trends of sterile drug product.

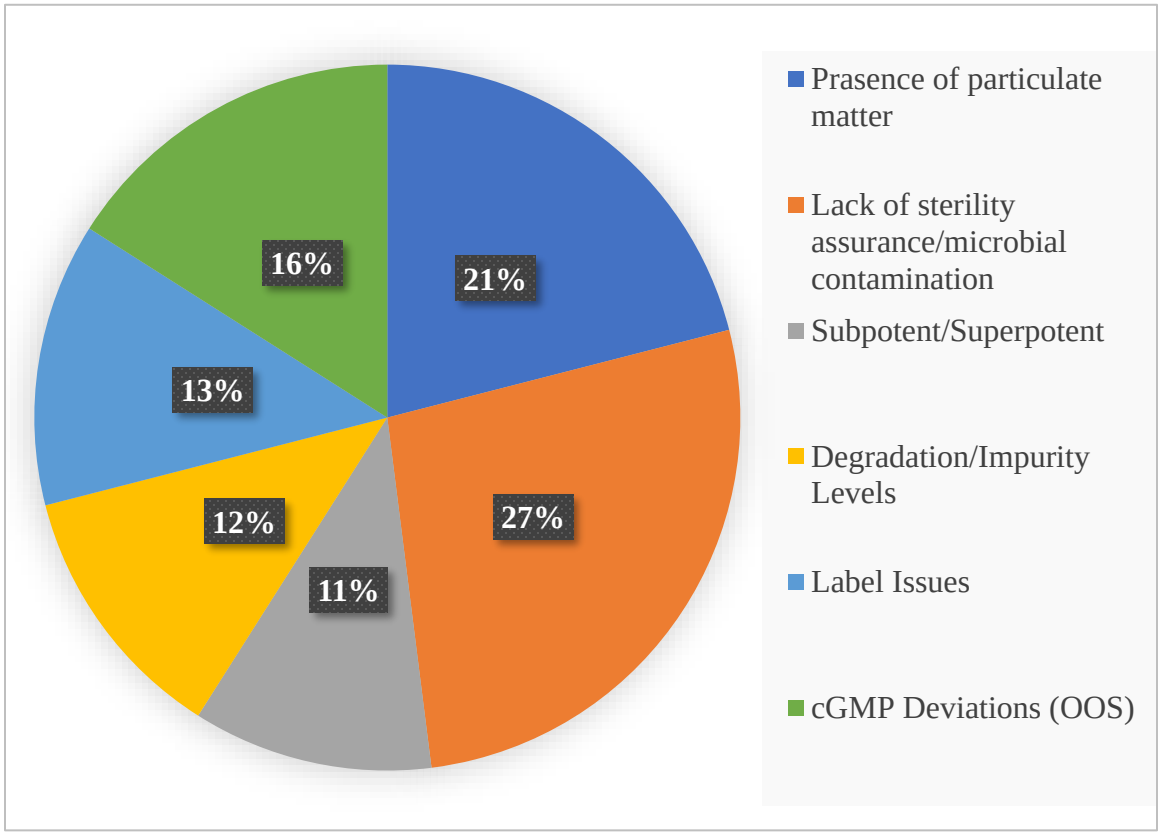


Figure 8: Trend of recalls of sterile drug products

Sandle investigated WLs in the context of cleanroom regulatory trends. According to the author, cleanrooms remain a major focus of regulatory inspections and assessing regulatory trends of noncompliance would be good practice to be adopted by the manufacturers.[68] In Europe, where only high-level summaries are available (due to privacy restrictions), this task however, becomes difficult. In addition, a high number of WLs issued, complicates evaluating the US FDA's findings. To assist in this process, this article reviewed recent US FDA WLs and highlighted major trends and nonconformities related to cleanroom design, testing, and operation.

Major issues related to WLs as observed from the review of literature are discussed below as case studies:

Media fill:

The US FDA inspectors identified several deficiencies during the review media-fill batch records during the inspections of Celltrion, Inc. Incheon-Korea sterile facility from 22 May to 2 June 2017.[69] The firm was found to have rejected integral vials without providing any justifications. The firm as per guidelines should have maintained records of the operators who examined media-filled vials. This negligence highlights the need for mandatory requirement of operator training for media fill inspection and the need for proper record keeping of rejections.

Leakage in Containers:

While inspecting the sterile facility of Bershtel Enterprises LLC Duarte-US from 15 October to 1 November 2018, US FDA inspection team found leaking containers and bottle defects and noted that the company had adjusted the filling equipment to address the defects.[70] However, the company still released these defective lots of products in the market. Subsequently, customers reported complaints about leaking containers. The FDA inspectors also observed that the company reused sterilizing filters up to 22 times without proper validation. These observations indicate a need for better understanding regarding reuse of the components, such as filters, with adequate validation and overview of product quality.

Laminar Air Flow:

During an inspection of Wintac Ltd. Nelamangala, Bangalore-India sterile facility from 10 to 19 February 2020, it was observed that the filling line in aseptic area lacked proper unidirectional airflow. [71] Smoke studies also did not indicate that the lines are designed to protect against microbial contamination or provide high assurance of product sterility.

EM Program:

During an inspection of Sun Pharmaceutical Industries Ltd., Baroda-India sterile product facility from 26 April to May 2022, inspector was observed to be lacking adequate EM

programs.[72] The firm did not follow proper procedures for collecting EM samples from all designated locations. The batch production records needed to include the reconciliation of the samples collected during the batch processing.

According to the USFDA Enforcement Reports published by Luis Jimenez (2019), Gram-negative bacteria were found to be the most common microorganisms in non-sterile-drugs in the United States. [73] Unidentified microbial contamination accounted for a significant number of drug recalls, indicating poor microbiological practices. According to the same report, microbial contamination of non-sterile and sterile drugs was extensively detailed. Unidentified microbial contamination accounted for a significant percentage of non-sterile (77%) and sterile (87%) drug recalls, indicating poor microbiological practices. Yeasts and molds were responsible for 52 recalls of sterile and non-sterile drugs, but only in 12% provided cases, the information at the genus or species level could be obtained.

Out-of-specification results were reported to be the most frequently reported violations in non-sterile recalls (34 recalls). [74] Lack of sterility assurance led to the recall of the majority of sterile drugs (1056 recalls). Undetermined cGMP issues (184 recalls) were the main reason for poor sterility assurance, followed by pharmaceuticals with inadequate cGMP procedures (121 recalls).

A review conducted by Jain et al., reported details of US FDA WLs issued to 85 manufacturing sites between January 2014 and December 2016.[75] Of these sites, 26 received import warnings, prohibiting affected products in the US market. Compromise in system quality, data integrity issues, poor laboratory and production control were reported as the main causes. The authors recommended that pharmaceutical manufacturers should regularly review such WLs, adopt a proactive-approach, and implement precautionary measures within their organizations to prevent quality issues. The review emphasized the need for improvement in adherence and compliance with quality-systems, including surveillance-systems, CAPA systems, and SOPs.

A report by Ananth et al., focusing on US FDA WLs issued to pharmaceutical companies in 2017 indicated that China and India were found to have received the highest number of WLs, followed by South Korea, Canada, and Japan. China and India accounted for approximately 80% of import warnings wherein about 20% products were reported to be sterile. The study observed an increasing trend of WLs issued for sterile pharmaceuticals, while the opposite was reported to be true for medical devices and biologics. [76]

Dalmaso et al., highlighted the US FDA's more aggressiveness response to companies with insufficient control over manufacturing, evident from the rise in observations and WLs.[77] EM program issues were identified as one of the top 15 reasons for issuing 483 observations. The study emphasized the importance of recognizing the reasons behind issuance of Forms 483 so that such mistakes could be avoided in future. It predicted a continued increase in 483 observations, particularly affecting quality control and EM, unless a robust monitoring strategy is implemented that aligns with industry standards and comprehensively addresses the expectations of US FDA.

Wang et al., reviewed the trend analysis of WLs issued for non-cGMP-compliant medicinal products by studying 997 WLs issued between 2007 and 2014. [78] An increasing trend was observed from 2009 to 2011. The peak occurred in 2011, with 159 WLs issued by the USFDA. The majority of letters (68.7%) were reported to be issued for medical devices, followed by finished drugs (22.4 %).

Deshpande et al., conducted a study on CAPA as a reason for violations of cGMP.[79] It was reported that during the period from 2016 to 2018, a total of 100 WLs were found relevant to cGMP violations. Some pharmaceutical companies were reported to distribute contaminated products that resulted due to errors in the sterilization process, improper storage practices, or contamination during packaging.

Another study observed that compared to the US pharmaceutical industry, the Indian pharmaceutical industry is more likely to experience nonconformities or irregularities in the controlled manufacturing of sterile drugs, design and construction elements of

buildings and equipment, and batch production and control records.[6] Local companies in both countries reportedly did not pay enough attention to test irregularities, errors, results out of specification, which are the main issues of the US FDA WLs.

In a study conducted by Moldenhauer on WLs issued for both aseptic and non-sterile products from 2000 to mid-2010, it was found that the number of WLs issued to pharmaceutical industries regarding the use of aseptic techniques has been increasing.[80] The study provided valuable information to help other companies avoid similar issues. Several categories of observations were identified as significant for aseptically processed medicinal products.

Among the top 1042 categories of observations, common issues included quality control department responsibilities, equipment cleaning and maintenance, procedures and deviations, general requirements (laboratory control), release for testing and sale, batch production and control records, and review of production records. The study highlighted various types of observations made during inspections. These included:

1. Lack of design of material flow throughout the building to prevent contamination.
2. Lack of separate or defined areas to prevent contamination or mixups
3. Inadequate air supply with HEPA filters
4. Insufficient air sampling at critical sites
5. Lack of proper control systems for contamination prevention, including the absence of smooth, hard surfaces on floors, walls, and ceilings for easy cleaning.
6. Inadequate system for cleaning and disinfecting rooms and equipment
7. Failure to conduct studies demonstrating the adequacy and effectiveness of the cleaning and disinfection processes employed
8. Lack of airflow pattern studies in areas with connections
9. Inadequate containment control and monitoring programs
10. Absence of appropriate written procedures for preventing microbiological contamination and failure to follow established procedures

2.9.Key Findings:

From the review of the literature, it can be concluded that in recent years there has been a substantial increase in the number of WLs related to sterile products. A paradigm shift in quality culture is needed to reduce WLs related to sterile products. Companies must focus on aseptic technique and microbial contamination to avoid such actions. Interactions between inspecting team and industry personnel during inspections should be completely transparent. Record keeping must be further improved. Observed violations of the sterility assurance could undermine the regulatory confidence of the US FDA and lead to a reduction in the potential operations of the pharmaceutical industry in the US market.

In a recent presentation to the US FDA Office of Compliance, the regulators highlighted some key problem areas and trends in WL observations, which included: [81]

- Sterility assurance
    - Lack of sterility assurance /absence of validated process
    - Failure of aseptic technique
    - Failure of environmental monitoring
    - Equipment design and qualification
- Basic cGMP
    - Batch release without ensuring sterility
    - Cleaning and maintenance of equipment
    - Failure of basic hygiene in the aseptic area
    - Risks of cross-contamination during product change

As can be seen from the list above, “lack of sterility assurance” is one of the issues identified by the US FDA, which was described almost 15 years ago as a critical initiative to improve the regulation of drug manufacturing and product quality.

However, the gaps that have been leading to the issuance of WLs and import warnings appear to be oversights, a lack of thorough understanding of the US FDA's expectations, and at times due to business prioritizing compliance.

Chapter 3 Rationale of the study

Review of existing literature on WLs to pharmaceutical industries for cGMP violations pertaining to sterile products reveals the following concerns:

- In recent years, there has been a significant increase in the number of WLs related to ‘sterility assurance’ of drug products
- There is a need for a paradigm shift in quality culture and transparent dealing with regulators while interacting during the inspections. Manufacturers need to exercise more control on sterilization practices as well as microbiological contamination
- Any observation about breach of sterility assurance shakes the confidence and trust of regulator and may lead to compromise in the manufacturer’s credibility as well as business for the US market

Though the gaps that lead to issuance of WLs and import alerts appear to be oversights, lack of thorough understanding of US FDA expectations and at times, the phenomenon of business taking priority over compliance cannot be ruled out. There is no report available in literature where the US FDA WLs to pharmaceutical industries for cGMP violations pertaining to sterile products have been systematically analyzed to decipher the causes and measures for prevention thereof. Therefore, no structured guidance has ever been provided to the pharmaceutical industry to take steps in order to avoid the issuance of such letters.

3.1. Aim and Objectives

The objectives of research are:

- To analyse the US FDA WLs issued to pharmaceutical industries for cGMP violations pertaining to sterile products
- To identify the cause and effect of increased number of WLs issued by the US FDA year after year, in spite of clarity in the guidance issued by the agency for aseptic processing of the sterile products
- To summarize the recurring observations which will help as guidelines for all the concerned organizations to avoid similar non-compliances
- To evaluate the economic impact of the issuance of WLs on the concerned organization
- To prepare an advisory document to be shared with pharmaceutical companies involved in manufacture of sterile products

The aim of research is:

- The research in this project is aimed at analysis of US FDA WLs to pharmaceutical industries for cGMP violations pertaining to sterile products and preparation of guidance document therefrom

Chapter 4. Research Methodology

The research would be carried out in the following stages:

Step 1: Ground work

- To gather information about sterile products, sterilizations methods, microbiological controls required during manufacturing of sterile products
- To gather information about WLs and causes of their issuance, inspection types, US FDA regulations related to sterile products and cGMP requirements

Step 2: Review of Literature

- The aim of the literature search is to collect available information on related sterile product and warning letters
- The literature search is done on the subjects relevant to sterile product, sterilization methods, aseptic techniques, US FDA inspection systems, types of inspections/audits, impact of cGMP non-compliance
- The literature review is done to understand the reported studies on WLs relevant to sterile products and build our study on the inferences therefrom

Step 3: Research phase

- The study involved the analysis of US FDA WLs for the last 14 years (January 1, 2010 to till date) issued pertaining to the sterile products from the Global Industry
- The US FDA's WLs records are reviewed from the US FDA's website[82]
- The following link is used for the purpose: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
- In the first part, using the excel spread sheet, the subject of each WL was reviewed manually. PDF files of the concerned WLs were then accessed and reviewed for violations of cGMP regulations. Only the content of warning letters concerning sterile products was analysed

Step 4: Compilation

- 120 warning letters associated to sterile products issued to global pharmaceutical industries have been studied
- After reviewing all these letters, causes were classified in the categories based on nature of observations.
- Statistical and descriptive analyses are performed to identify the nine top categories for warning letters. Further, review and Pareto analysis is conducted to identify the causes of the observations under these top nine categories.
    1. Design of aseptic processing line, buildings and facilities
    2. Aseptic process and equipment validation
    3. Media fill
    4. Personnel training, qualification, and monitoring
    5. Environmental monitoring
    6. Microbiological laboratory controls
    7. Sterilization of equipment, containers, and closure.
    8. Components and container/closures
    9. Endotoxin controls
- WLs were reviewed in three steps; in the first step WLs from the Indian industry were studied along with economic impacts (as case study), in the second step WLs from the US and in the third step, WLs from the rest of the countries (including European countries) were studied

Step 5: Summary and conclusion

- Conclusion of research work through summarisation of the study in accordance with predetermined objectives was drawn
- A guidance document has been prepared for the pharmaceutical industries involved in manufacture of sterile products to avoid any issues of non-compliance leading to WLs

Chapter 5. Results and Discussion

5.1: Warning Letters Statistics

Warning letters issued by US FDA for the period of last 14 years (1 January 2010 to 30 September 2024) were analysed. According to the US FDA Compliance Dashboard database published on 30 September 2024, total 151839 WLs have been issued to all industries worldwide, including those for drugs, biologics, devices, tobacco, and veterinary products, as shown in the Figure 9 below.

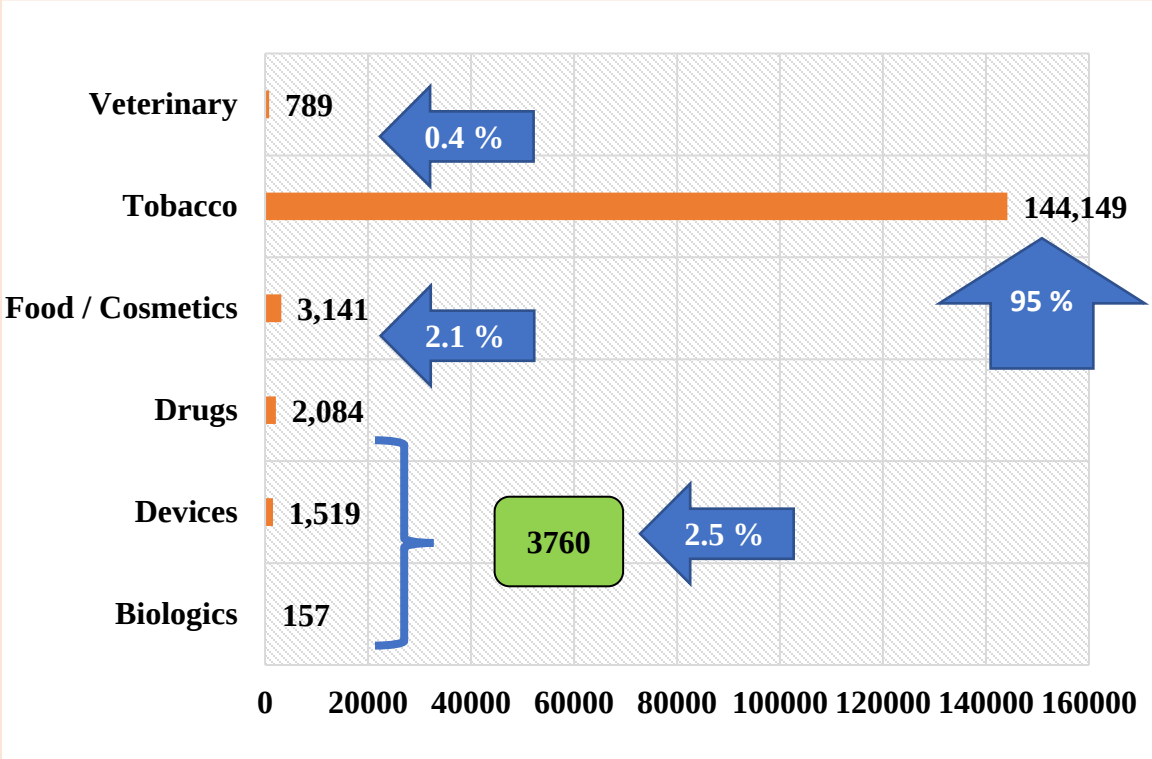
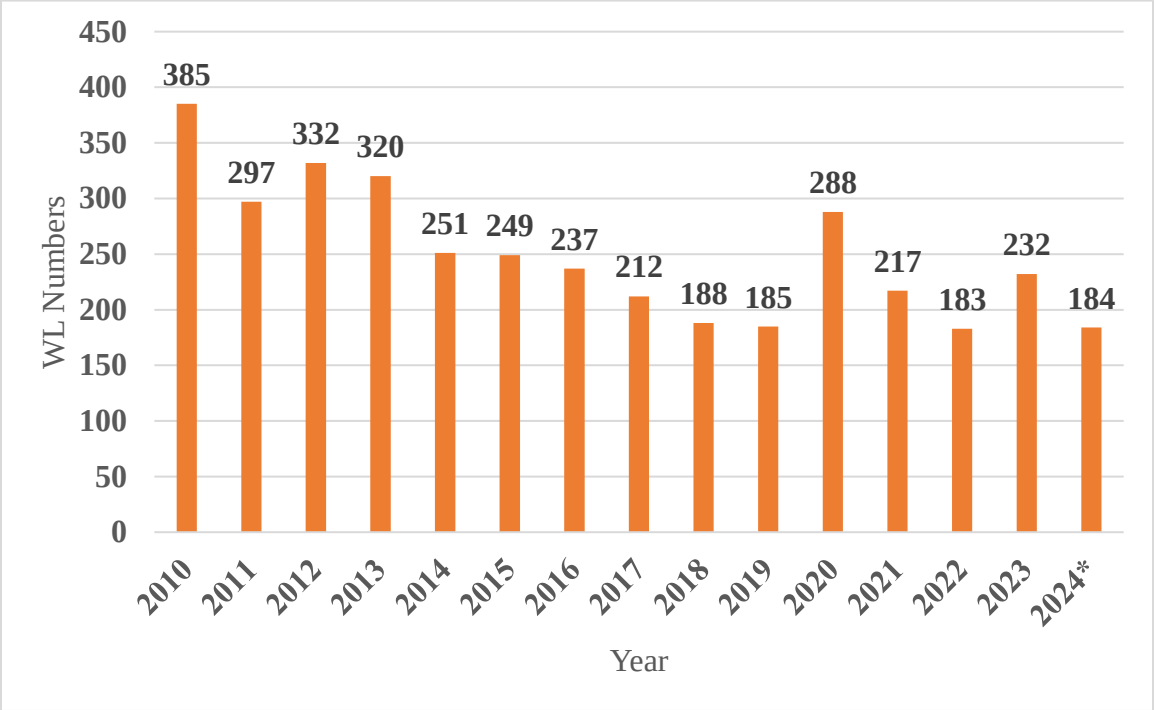


Figure 9 : USFDA WLs issued to global industry (*from 1 January 2010 to 30 September 2024)

Out of these, 94% of WLs are from category of Tobacco whereas 6% WLs are from the remaining categories i.e. veterinary, drugs, devices and biologics.

As the aim of the project was to evaluate US FDA WLs issued to pharmaceutical industries for cGMP violations pertaining to the sterile products, the WLs related to biologics,

devices, and drugs were selected, which turned out to be 3760 in number. These 3760 WLs were found to be issued worldwide to global industries for all types of sterile dosage forms. These were sorted out year-wise and are presented in the Figure 10 given below.

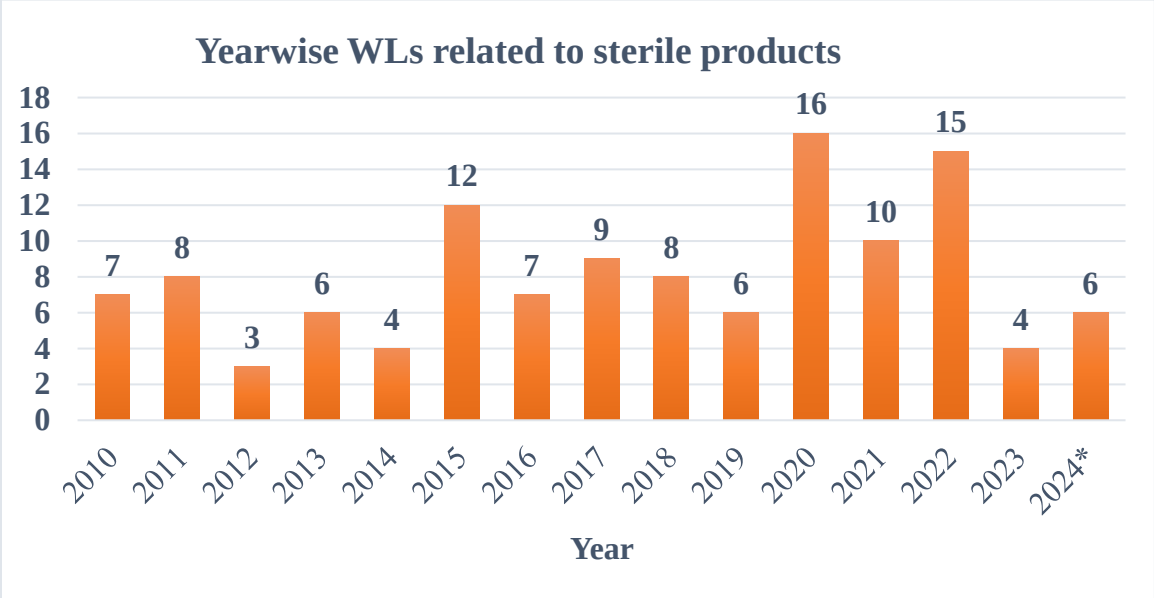


*As on 30 September 2024.

Figure 10 : US FDA WLs issued to the global pharmaceutical industry

A trend of almost perpetual decrease in WLs was observed for the decade from 2010 to 2019, which can be attributed to an enhanced compliance by the manufacturing facilities to the regulatory requirements of USFDA.[63] Thereafter in 2020, the increased number of WLs was observed which can be attributed to the sudden increase in the worldwide demand and resultant increase in manufacturing of vaccines and other pharmaceuticals to combat the COVID-19 pandemic.[83] It is pertinent to add here that during this period, the manufacturing of vaccines and other drugs was carried out in a rush in a record period of time.[84]

Further, the WLs associated with sterile products were sorted out, which turned out to be 120 in number and are presented year wise in the Figure 11 give below:



*As on 30 September 2024.

Figure 11: Year wise WLs issued to the global pharmaceutical industry for sterile products

Unlike the total number of WLs, no discernible trend could be observed in the WLs issued for sterile products before 2020. However, in the year 2020, similar to the peak in number of WLs issuance to entire pharmaceutical industry, a sudden increase was observed in this case too, which could again be attributed to the rise in manufacturing of sterile products to meet their increased demand due to COVID-19. [85,86]

To understand the trend of year wise total WLs issued ys. WLs to sterile product manufacturers is presented in table 2

Table 2: Year wise total WLs issued ys. WLs to sterile product manufacturers

[Fiscal Year]	**Year Wise WLs to global pharmaceutical industries**	**Year wise WLs related to sterile products-Worldwide**	**% of WLs related to sterile products-Worldwide**
2010	385	7	1.8
2011	297	8	2.7
2012	332	3	0.9
2013	320	6	1.9
2014	251	4	1.6
Average for year from 2010 to 2014			**1.78**
2015	249	12	4.8
2016	237	7	3.0
2017	212	9	4.2
2018	188	8	4.3
2019	185	6	3.2
Average for year from 2015 to 2019			**3.9**
2020	288	16	5.6
2021	217	10	4.6
2022	183	15	**8.2**
2023	205	4	2.0
2024*	184	6	3.9
Average for year from 2020 to 2024*			**5.1**
Total	3760	120	**Overall average 3.2**

*As on 30 September 2024.

From above table, it is clear that in FY 2012, the lowest percentage i.e. 0.9 % WLs were issued to industries related to sterile products whereas the highest i.e. 8.2 % were issued in FY 2020. The data also indicate an increase in percentage of WLs FY 2015 onwards. For the years from 2010 to 2014, the average percentage of WLs related to sterile products

was 1.78 % while for next five years i.e. from 2015 to 2019 it rose to 3.9 %. In last four years, however, the figure further increased to 5.1 %. This remarkable increase in percentage of WLs may be attributed to the increase in number of facilities involved in manufacture of vaccines and other sterile injectables whose demand rose unprecedentedly because of COVID-19 pandemic. Moreover, the resumption of onsite inspections by US FDA after the pandemic and prioritization of inspections of high-risk facilities of sterile products manufacturing might have resulted in the issuance of higher number of Forms 483 and WLs subsequently.[87,88]

WLs analysis over the past 14 years and 9 months shows that these 120 WLs have been issued to sterile product manufacturers worldwide, indicating that cGMP violations is not limited to a particular region but it is prevalent in almost all countries wherever US FDA approved facilities exist.

US FDA approved sterile facilities were sorted countrywise and are presented in the Figure 12 given below:

Figure 12: Country-wise sterile facilities and total number of WLs issued for sterile products

When compared with the data of the number of US FDA sterile facilities located in various countries, the ratio of WLs issued by US FDA is given in the below table 3.

Table 3: Ratio of no. of sterile facilities available vs. No. of WLs received since 2010

S.No.	Region	No. of sterile facilities available	No. of WLs received since 2010	% ratio
1.	US	179	43	25%
2.	India	63	38	60%
3.	Rest of World	61	38	62%
Total		303	120	38%

Worldwide, there are 303 sterile facilities registered with US FDA as on 30 September 2024. US have the highest number of these facilities i.e. 179, India being the second with 63 sterile facilities. US industries have received 43 WLs whereas Indian industries have received 38 WLs related to sterile products despite having a much lower number of such facilities. The region wise distribution of WLs pertaining to sterile products is shown in the Figure 13 below.

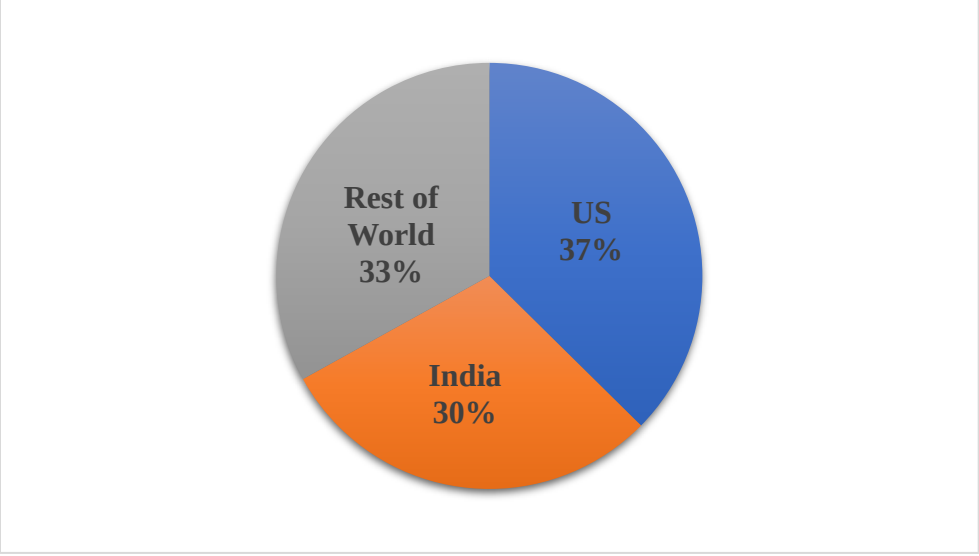


Figure 13: WLs US vs. India vs. rest of world, associated with sterile products

Much higher ratio of WLs issued for sterile product facilities outside US can be attributed to more stringent practices being followed by the US pharmaceutical industry as compared to that by the industries located in the rest of the world, including India. This in turn, may be due to better awareness regarding the FDA protocols, higher overall quality consciousness and more trained workforce in the US pharmaceutical industry.

The 120 WLs are further sorted for devices, biologicals and drug products and are presented in the Figure 14 given below.

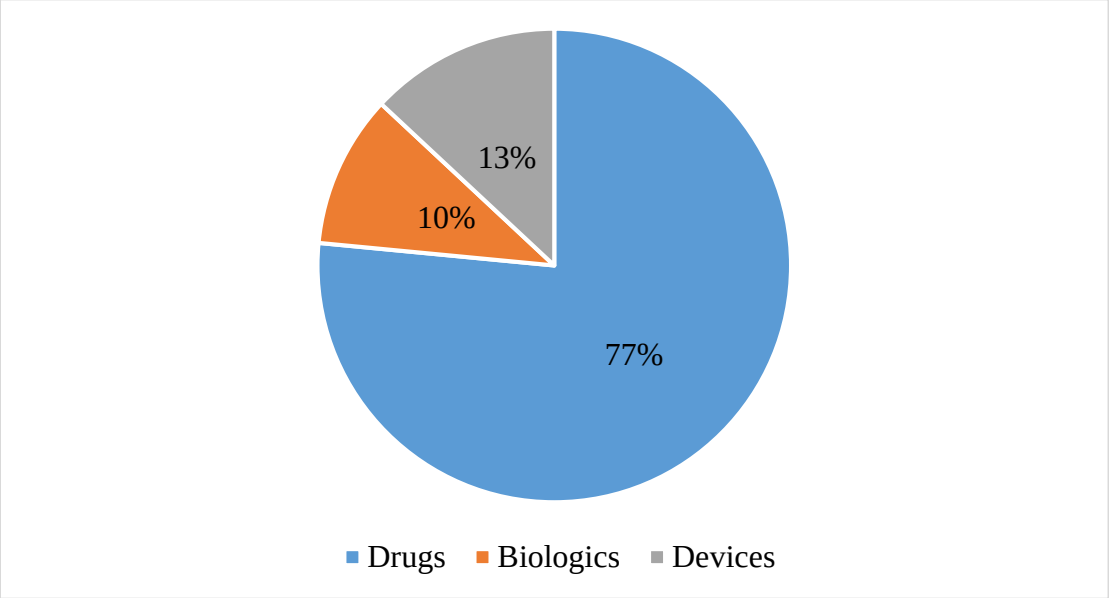


Figure 14: WLs issued for devices, biologics and drugs

The percentage of WLs to issued to industries engaged in manufacture of drug products, biologics and sterile devices seems to be consistent with the number of industries engaged in their manufacture.[89]

Companies such as Emcure, Pfizer, Baxter, Wockhardt, Dr.Reddy's, Mylan from India, and KC Pharma, Invitrx and Akorn from US have received WLs more than once in the period of study. Repeated issuance of WLs of similar or different nature indicates an

inadequacy on the part of concerned industry in rectifying the lacuna pointed out by the regulatory agency. The details of such incidences are shown in the below table 4.

Table 4: Country-wise issuance of WLs for sterile products facilities

S. No	Country Name	No. of Sterile Facilities	No. of WLs related to Sterile Product	Ratio of WLs received vs. Sterile facilities located	Repeated issuance of WLs
1.	Australia	5	2	1:2.5	No
2.	Bangladesh	2	0	0:2	No
3.	Belgium	3	0	0:3	No
4.	Brazil	3	3	1:1	No
5.	Brunei Darussalam	3	0	0:3	No
6.	Canada	7	7	1:1	No
7.	China	7	7	1:1	No
8.	Costa Rica	3	0	0:3	No
9.	Denmark	3	0	0:3	No
10.	France	1	1	1:1	No
11.	Germany	2	2	1:1	No
12.	Hungary	1	1	1:1	No
13.	India	63	38	1:1.85	6 (Emcure, Hospira (Pfizer), Wockhardt, Baxter, Dr.Reddys, Mylan)
14.	Indonesia	3	0	0:3	No
15.	Italy	2	2	1:1	No
16.	Japan	4	4	1:1	No
17.	Malaysia	2	0	0:2	No

S. No	Country Name	No. of Sterile Facilities	No. of WLs related to Sterile Product	Ratio of WLs received vs. Sterile facilities located	Repeated issuance of WLs
18.	Mexico	2	0	0:2	No
19.	New Zealand	1	1	1:1	No
20.	Jordan	1	1	1:1	No
21.	Singapore	1	1	1:1	No
22.	Switzerland	1	1	1:1	No
23.	United Arab Emirates (UAE)	1	1	1:1	No
24.	United Kingdom (UK)	2	2	1:1	No
25.	United States of America (USA)	179	44	1:4.06	3 (KC Pharma, Invitrx, Acorn Inc.)
26.	Venezuela	1	1	1:1	No
Total Numbers		303	120	1:2.63	--

The data indicate that the ratio of WLs issuance to pharmaceutical industries engaged in sterile product manufacturing is 1:1 for fifteen countries, being considerably poorer than that of India, which stands at a much lower ratio of 1:1.85. For the rest of the countries, including US, the ratio is more desirable, with eight countries boasting of no WL received. Moreover, apart from sterile facilities registered in India and US, such facility in no other country has received repeated WLs. Between India and US also, despite having almost one-third the number of such facilities as compared to US, double the number of Indian industries have received repeated WLs. This analysis indicates that the

Indian industries need to take up this issue with utmost seriousness in order to continue to sustain the US FDA approvals.

5.2: Analysis of Warning letters

The analysis of WLs is presented in three parts. In the first part, the WLs issued to the Indian industry and their economic impact is presented in the second part, the WLs issued to the US are deliberated while in the third part, the WLs issued to all other countries are dealt with.

5.2.1 WLs from Indian pharmaceutical industries

The findings of the warning letters associated to sterile drug products for the period 2010-2024 (up to 30 September 2024) are summarised in below table 5.

Table 5: Summary of WLs issued by US FDA to Indian pharmaceutical industries

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
1.	29/08/2024	Zydus Lifesciences Ltd. S.G. Highway Nr. Vashnodevi Circle Ahmedabad	Firm failed to investigate and determine the root cause of glass particulate contamination in multiple batches of Cyanocobalamin Injection, during the start-up and filling activity, investigators noticed numerous instances of poor aseptic procedures.[90]
2.	20/08/2024	Eugia Pharma Specialities Ltd., Hyderabad Knowledge City, Raidurg Panmaktha Hyderabad	The company failed to ensure that the data in the records for the production and process simulations (media fills) were accurate, failed to assure that the records for the cleaning, disinfection, and sterilisation of equipment were accurate and complete.[91]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
3.	18/06/2024	Sun Pharmaceutical Industries Ltd. Sun House, Goregaon East, Mumbai	Failure to adequately clean and maintain equipment used for drug product manufacturing. This is the repeat observations. Earlier, on 29 March 2019 company received a citation for not properly maintaining and cleaning its manufacturing machinery. On April 13, 2017, the company received a citation for failing to adequately investigate laboratory incidents including the recurrence of unidentified extraneous peaks.[92]
4.	28/03/2024	Kilitch Healthcare India Ltd., R – 904-905 TTC Industrial Road, Navi Mumbai	Insanitary conditions, poor practices and behaviours observed during the manufacturing of sterile drug products. Media fill does not simulate the actual process. Inaccurate laboratory records data.[93]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
5.	20/10/2023	Global Pharma Healthcare Private Ltd.,A-9 SIDCO, Thiruporur, Tamil Nadu	Failure to follow SOPs to prevent unintentional introduction of microorganisms and insufficient evidence to demonstrate the suitability of completely sterile products for sterile tear production.[94]
6.	28/07/2023	Intas Pharmaceuticals Ltd., Plot No. 255, Thaltej, Ahmedabad, Gujarat	Lack of complete and accurate laboratory records data to support the analysis performed.[95]
7.	15/12/2022	Sun Pharmaceutical Industries Ltd., Dist. Panchmahal, Halol, Gujarat	Failure in establishment and adherence to documented procedures for prevention of unintentional introduction of microorganisms. Failure of media fills to accurately simulate commercial operations.[96]
8.	10/09/2020	Shilpa Medicare Ltd., Plot No. S-20 to S-26, TSIIC, Polepally, Mahabubnagar, Telangana	Failure to follow SOPs describing the handling of all market complaints regarding distributed products, including review by the quality control department that may not comply with instructions for improper sterilization and compliance with pharmaceutical products.[97]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
9.	24/09/2020	Panacea Biotec Ltd., Nalagarh, Baddi, District Solan, Himachal Pradesh	Failure in establishment and adherence to adequate control of differential pressures in aseptic processing facility.[98]
10.	13/08/2020	Wintac Ltd., 54/1 Bodhihal, Nelamangala, Bangalore, Karnataka	Failure in establishment and adherence to documented procedures for prevention of unintentional introduction of microorganisms. Lack of simulation of interventions in airflow visualization testing (smoke studies).[71]
11.	25/03/2020	Pfizer Healthcare India Private Ltd., Parawada, Visakhapatnam, Andhra Pradesh	Inadequate investigations of failures of sterility testing. Higher bioburden counts in EM performed during the sterility test.[99]
12.	25/02/2020	Cipla Ltd., Verna, Goa	Inadequate cleaning procedure of the equipment resulting in cross contamination of drug products from the previous product.

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
			Inadequate investigations of HEPA filter leakages, compromising the aseptic conditions of sterile processing line and product quality.[100]
13.	25/02/2020	Cadila Healthcare Ltd., 419 & 420 8a, Moraiya, Ahmedabad, Gujarat	Poor aseptic behaviour during machine setting of filling activity. Significant equipment cleaning deficiencies resulting in cross-contamination between drug products.[101]
14.	08/02/2019	Emcure Pharmaceuticals Ltd., Phase II, MIDC, Hinjwadi, Pune. Maharashtra	Inadequate investigation of the sterility failures during routine batch release testing. Potential manufacturing failure modes not assessed adequately.[102]
15.	03/04/2019	Hospira Healthcare India Pvt. Ltd., Kancheepuram, Tamil Nadu	Inaccurate reporting of test results by Microbiology laboratory.[103]
16.	05/07/2018	Baxter Ltd., Ellis bridge, Ahmedabad, Gujarat	Inappropriate water drainage, including warped ceiling panels, puddles of water, and water stains. Ingress of air from the building's plenum into post-sterilization areas. [104]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
17.	24/04/2018	Goran Pharma Private Ltd., GDIC, Bhavnagar Road, Sihor, Gujarat	Inappropriate facility design leading to development of biofilms on piping and dead legs. No laboratory control, no proper storage, no growth testing done, no quality control.[105]
18.	18/12/2017	Fresenius Kabi Oncology Ltd., Baddi, Gurumajra, Himachal Pradesh	Inadequate investigation of sterility failure of injectable products. Microbiological growth in the media canisters.[106]
19.	27/03/2017	Indoco Remedies Ltd., Verna Industrial Estate Area, Verna, Goa	Unreliable process of finished product inspection compromising the quality, integrity, and sterility of solution. Failure to address the root causes of recurring container-closure integrity defect.[107]
20.	03/10/2017	USV Private Ltd., OIDC, Mahatma Gandhi Udyog Nagar, Dabhel, Daman	Absence of checkpoints. Insufficient sample collection methods to prevent unintentional introduction of microorganisms into sterile products.[108]
21.	23/12/2016	Wockhardt Ltd., Plot No. 138 G.I.D.C. Estate District Bharuch, Ankleshwar, Gujarat	Inappropriate study design for airflow analysis (smoke study) of sterile connections in laminar airflow equipment that has negative impact on the success of the product under these conditions.[109]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
22.	03/03/2016	Emcure Pharmaceuticals Ltd., Phase II, MIDC, Hinjwadi, Pune, Maharashtra	Poor aseptic processing techniques followed during the manufacture of sterile products.[110]
23.	22/10/2015	Sandoz Private Ltd., Plot Nos. D31 & D32, MIDC, Turbhe, Navi Mumbai, Maharashtra	Insufficient airflow studies (smoke studies) in sterile filling lines. The scientific basis for EM of sample locations in aseptic filling production areas is insufficient.[111]
24.	06/08/2015	Agila Ltd., Bannerghatta Road, Bangalore, Karnataka	Lack of assurance that the production facility is being maintained in a state of control suitable for aseptic processing.[112]
25.	06/08/2015	Mylan Laboratories Ltd., Industrial Area, Anekal, Bangalore, Karnataka	Poor practices followed during aseptic processing operations. EM data showed excursions in aseptic area.[112]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
26.	22/10/2015	Sandoz Private Ltd., MIDC, Navi Mumbai, Maharashtra	Insufficient airflow studies (smoke studies) in sterile filling lines. The scientific basis for EM of sample locations in aseptic filling production areas is insufficient.[113]
27.	05/11/2015	Dr. Reddy's Laboratories Ltd., Unit-VII, Visakhapatnam, Andhra Pradesh	Inadequate investigations of media-fill failures, records do not include reasons for rejection of filled vials.[114]
28.	05/11/2015	Dr. Reddy's Laboratories Ltd., CTO Unit V, Tripuraram, Mandal, Miryalguda Taluk, Nalgonda, Telangana	Inappropriate practices followed; simulation of critical manual interventions not done during media fills. Sample collection methods are not sufficient to prevent unintentional introduction of microorganisms of sterile pharmaceutical products.[114]
29.	05/11/2015	Dr. Reddy's Laboratories Ltd., CTO Unit VI, Srikakulam, Andhra Pradesh	Poor aseptic practices during the filling operation.[114]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
30.	17/12/2015	Sun Pharmaceutical Industries Ltd., Halol, Gujarat	Lack of study design, significant airflow turbulence in the laminar airflow (LAF) unit. Active (dynamic) airflow visualization testing not performed.[115]
31.	28/05/2013	Hospira Healthcare India Pvt., Ltd., Irungattukottai, Sriperumburdur, Tamil Nadu	Inadequate study design; inappropriate handling of aseptic manufacturing interventions. [116]
32.	09/08/2013	Promed Exports Private Ltd., Khera Nihla Village, Solan, Himachal Pradesh	Inadequate monitoring of aseptic processing environment. Inadequate EM program for ensuring suitability of environment for aseptic processing. [117]
33.	18/07/2013	Wockhardt Ltd., Chikalthana, Aurangabad, Maharashtra	Incomplete documentation on key GMP activities, including handling of sterile and non-sterile raw materials, use and transfer of media filled bottles[118]
34.	23/02/2012	Wintac Ltd., Nelamangala, Bangalore, Karnataka	Inadequate study design; failure of airflow visualization testing to prove the air flows in only one direction in critical areas. Poor aseptic practices[119]

S.No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
35.	20/05/2011	Aurobindo Pharma Ltd., Quthubullapur (M), RR, Hyderabad, Telangana	Data integrity issues observed during microbial plates count related to EM and personnel samples.[120]
36.	21/06/2011	Cadila Healthcare Ltd., Moraiya, Sanand, Ahmedabad, Gujarat	Inadequate EM and lack of SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[121]
37.	24/08/2010	Stericon Pharma Pvt. Ltd., Bommasandra Indl. Area Bangalore, Karnataka	Deficiencies in aseptic procedures and practices, including failure to perform air testing during filling operation. [122]
38.	01/11/2010	Claris Lifesciences Ltd., Chacharwadi -Vasana, Ahmedabad, Gujarat	Lack of evaluation of complaints for contamination of injectable product.[123]

US FDA observations in WLs issued to Indian pharmaceutical industries appear to be mainly related to the lack of sterility assurance; media fill failures, and inadequate environmental monitoring. Companies such as Wockhardt, Hospira, Emcure, Claris and Wintac have received repeat observations by US FDA, and therefore, have received WLs twice. The highest numbers of issues were found to be related to poor aseptic practices.

Key issues and trends in the issued 38 WLs to Indian pharmaceutical industries include:

1. Improper compounding and lack of sterility [14]
2. Aseptic technique failures [9]
3. EM failures [6]
4. Design and qualification of facilities [2]
5. Release testing [2]
6. Cleaning, maintenance of equipment [2]
7. Basic sanitation failures [2]
8. Cross-contamination risks [1]

The percentage of issues leading to issuance of WLs are summarized in Figure 15

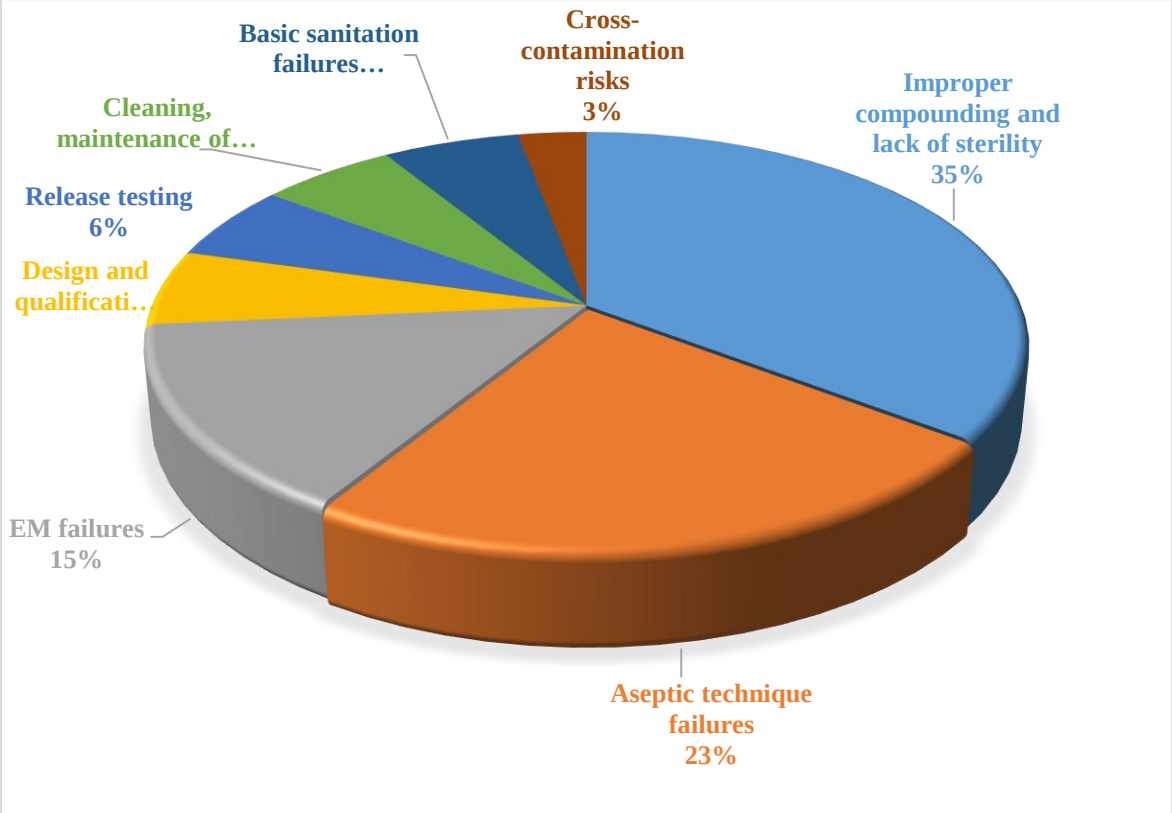


Figure 15: Summary of WLs issued to Indian pharmaceutical industries pertaining to sterile products

The above figure indicates that the highest incidences of WLs issuance in Indian pharmaceuticals industry i.e. 40%, accrue due to absence of sterility assurance while 12% each are described to failure of aseptic technique and failure of EM.

The table 6 given below illustrates the state wise WLs issued to Indian Pharmaceutical industries pertaining to sterile products:

Table 6: WLs issued to Indian pharmaceutical industry (state wise summary)

S.No.	**Sate**	**No. of sterile facilities available**	**No. of WLs received since 2010**	**Ratio of WLs received vs. Sterile facilities located**
1.	Telangana	17	4	1:4.25
2.	Gujarat	10	10	1: 1
3.	Maharashtra	8	7	1:1.4
4.	Himachal Pradesh	7	3	1: 2.33
5.	Andhra Pradesh	5	2	1: 2.5
6.	Karnataka	5	5	1:1
7.	Tamil Nadu	4	4	1:1
8.	Goa	4	2	1:2
9.	Daman	1	1	1:1
10.	Puducherry	1	0	0:1
11.	Panjab	1	0	0:1
Total		63	38	1:1.66

According to USFDA database as on 30 September 2024, the highest number of sterile facilities are located in Telangana (17) but the ratio of WLs received per facility is the lowest (1:4.25) there, indicating a better level of awareness and adherence to cGMP guidelines by the pharmaceutical industrial units located in Telangana. The ratio in Gujarat and Maharashtra is 1:1 and 1: 1.4 respectively while in Karnataka, Tamil Nadu and Daman a 1:1 ratio has been observed indicating thereby that 100% industries located therein have received WLs. Puducherry and Punjab are the only two states where one facility is located but no WLs have been issued.

5.2.2. Impact of USFDA WLs on economic growth of Indian pharmaceutical industries

Regulatory compliance has become a major challenge for the Indian pharmaceutical industry seeking US FDA approval.[124] To continue to enjoy a good share of US FDA approvals, they need to invest in hiring qualified and trained personal and upgrade their facilities to meet the cGMP standards. This also results in halting of the production process once the issue is identified. The halt remains until the problem is corrected, thus ensuring quality management. Not only has non-compliance proven to be costly, it may also lead to loss of credentials due to potential patient safety issues, and could even jeopardize the future of an entire business unit, ultimately affecting country's exports. This in turn affects the availability of the cost-effective drugs in the national as well as international market as the products manufactured in India are generally priced lower as compared to those manufactured in their western counter parts.[125] This section reports the economic impact of WLs from US FDA to Indian pharmaceutical sector engaged in exporting the drug products to US.

India's pharmaceutical exports increased more than 18% in FY20, the highest level in the last seven years. This is in contrast to the world market, which had a turnover of $1,265.2 billion in calendar year 2020 [126] and grew only 1%. The contribution of various sectors of pharmaceutical industries that make up the global market is shown in the table 7 given below.[127]

Table 7: Indian pharmaceutical market scenario

Group	**$ bn**
Developed Market	959.5
Pharma Emerging	290.8
Rest of word	15
Global market	1265.3

The global market is expected to reach US$1.6 trillion by 2025, growing at a compound annual growth rate (CAGR) of 3-4% over the next five years, adding approximately US$350 billion in value.[127]

According to the India Brand Equity Foundation (IBEF) Pharma Report 2023, the Indian pharmaceutical industry is well known for manufacturing and supplying generic drugs and vaccines at low cost. The Indian pharmaceutical industry is currently at the third rank in production of generic drugs. Indian products are exported to more than 200 countries around the world, and the US is a major market. The value of India's pharmaceutical exports stood at $15.78 billion between April and October 2023. The Indian vaccine industry produced the vaccine against Covid-19 in the shortest time possible and provided 115 million doses of vaccine to more than 97 countries.[128] India holds a 5.71% market share in pharmaceuticals worldwide. With a share of 72.54%, formulations and biologics constituted the biggest portion of India's exports, followed by bulk drugs and drug intermediaries. India's pharmaceutical industry reached $49 billion (domestic and export) in 2019-20.[129] In 2019-20, pharmaceutical exports were valued at US$24.47 billion, which include both APIs as well as finished products. Pharmaceutical exports continued to increase in 2021-22 despite a decline in the global economy. In 22-23, the Indian pharmaceutical market grew by approximately 5%, reaching US$ 49.78 billion. The Indian pharmaceutical industry grew at a compound annual growth rate (CAGR) of 6-8% from FY18 to FY23, driven by export growth of 8% and a large domestic market growth of 6%. Major segments of the Indian pharmaceutical industry include generic drugs, OTCs and generic drugs/APIs, vaccines, contract research and development, biosimilars and biologics.[130]

India exported medicines to 210 countries during FY23. About 60% of India's exports go to highly regulated markets such as North America and Europe. The USA is largest importer of Indian pharmaceuticals. Out of the world's 25 largest generic pharmaceutical companies, nine including Sun, Aurobindo, Cipla, Dr.Reddy's, Lupin, Intas, Zydus Cadila, Glenmark and Alkem are located in India.[131] Under these conditions, issuance of WLs to

an industry engaged in production of life saving drugs lead to a public health threat in manufacturing disruptions are imposed.[132]

In case of existing or anticipated shortages, FDA resorts to measures like working closely with the concerned manufacturers identifying potential alternative resources even exercising regulatory enforcements depends on the seriousness of the violation.[133] This however may not be possible in case of serious violations especially in the case of injectable formulations. In a typical example, Shilpa Medicare unit in Telangana faced ban in US for a majority of its product owning to multiple violations. As a result, the FDA's drug shortages list included their injectable Azacitidine.

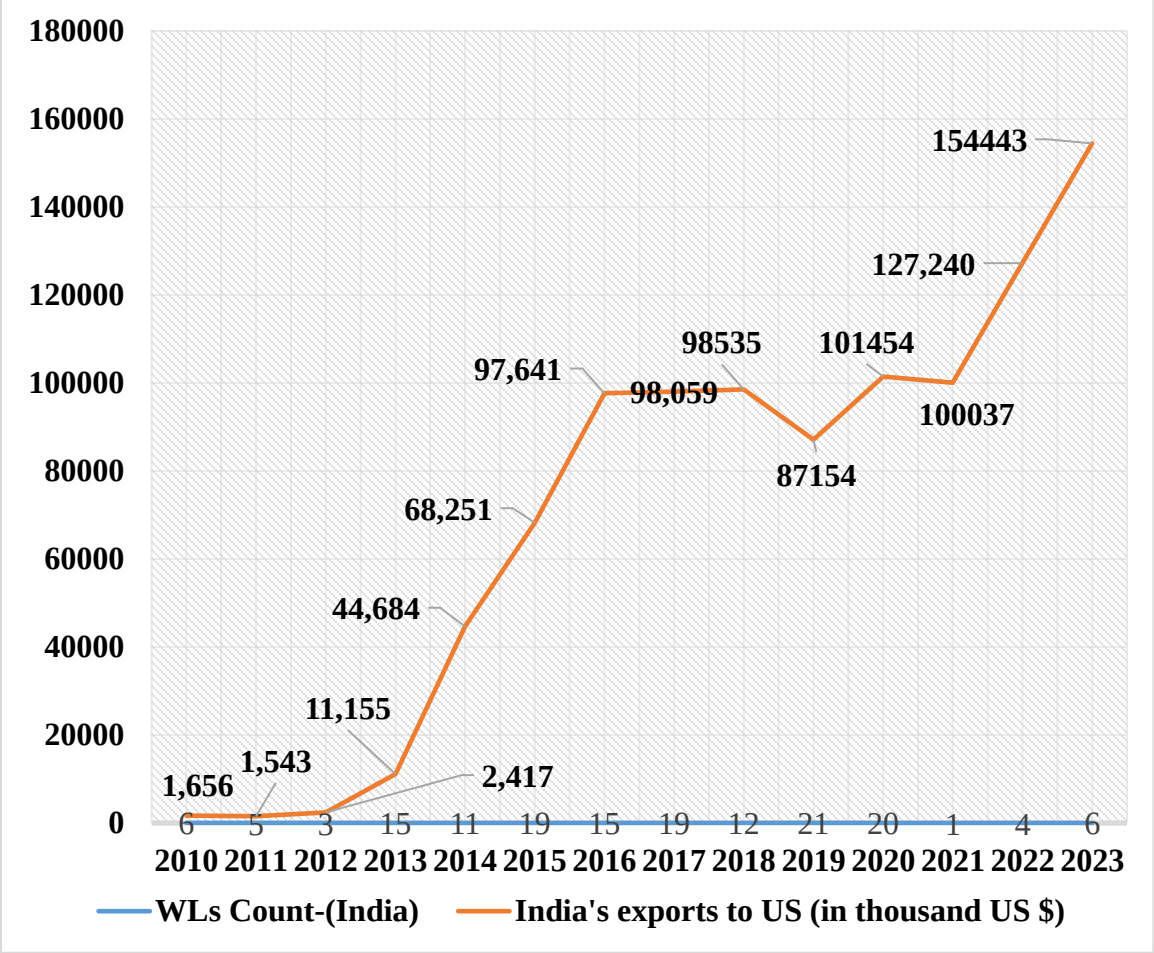
According to Pharmaceutical Export Promotion Council India's 19th report for FY 2022-23, the Global generic market holds 28.2 % of total pharmaceuticals market share and has touched a turnover of $ 401.24 billion in 2022. The Indian pharmaceutical industry produced $40.85 billion worth of generics in the period 2019-2020, of which $18.85 billion were exported.[134]

For any individual companies, the cost of a critical non-compliance is very high and it increases with every step of being undetected or neglected. A robust quality system, though costly in terms of physical facilities and trained personals presents the non-compliance from happening and this pays for itself. It however the issue is detected which it is within the system the cost increases as the issue needs to be addressed and measures to be taken to prevent its repetition in future.[135] Taking a step further, if the issue is detected after its releasing, the cost further increases due to recalls and may lead to closures of unit also.

Exports of pharmaceutical products from India to US, for the period of 2010-22 were evaluated and an effort was made to understand the effect of WLs on the export share to US. The data is presented in the table 8 and shown in Figure 16 .

Table 8: Exports of pharmaceutical products from Indian region

Fiscal Year	WLs Count (India)	India's exports to USA (in thousand US $)
2010	6	1,656
2011	5	1,543
2012	3	2,417
2013	15	11,155
2014	11	44,684
2015	19	68,251
2016	15	97,641
2017	19	98,059
2018	12	98535
2019	21	87154
2020	20	101454
2021	1	100037
2022	4	127240
2023	6	154443
Total	157	839,826



(Unit: US Dollar thousand)

Figure 16 : Exports of pharmaceutical products from Indian region

From the above data, it can be concluded that although the individual companies show an economic slump, the overall effect on the export is not so drastic. There are 151 WLs cases for India for the period of 2010-2023 (as on 30 September 2024), which is quite significant a number, but overall drug export was impacted only during the period from 2016 to 2020. It, however, picked up again during the COVID-19 pandemic and continues to grow in the post-pandemic period also. Indian pharmaceutical industry, though seems to be resilient to such issues a number of factors must be considered. This may be attributed to the fact that uninterrupted drug export was continued from the pharmaceutical companies other than those to which the WLs were issued, thereby rather increasing national income, especially

during and after the COVID-19 pandemic. On the other hand, had these actions not been taken due to stronger quality management, the Indian pharmaceutical industries might have been superior positions of export market.

5.2.3. WLs to US pharmaceutical industries

The details of warning letters pertaining to sterile products manufactured in US pharmaceutical industries are summarized in the table 9 given below:

Table 9: Summary of US FDA WLs issued to US pharmaceutical industry

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
1.	13/02/2024	Delsam Pharma LLC., Gun Hill Road, Bronx, New York	Failure to have adequate procedures to ensure that ophthalmic drug products met quality attributes and were free of microbial contamination. Inadequate supplier qualification procedures to ensure the drug products received from CMO were manufactured in compliance with cGMP.[136]
2.	03/08/2023	K.C. Pharmaceuticals Inc., 3215, Producer Way, Pomona	Inadequate study design for aseptic area qualification; airflow visualization testing in filling lines were not performed under conditions that adequately simulate actual process.[137]
3.	28/04/2023	Pharmedica USA LLC., 4734 E, Mossman Rd, Phoenix	Inadequate SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[138]
4.	24/03/2023	Sure Biochem Laboratories LLC., Atlantic Ave, Camden	Inadequate laboratory controls and lack of appropriate standards and testing procedures.[139]
5.	13/12/2022	Optum Infusion Services, 308, Chandler, Arizona	Inadequate product evaluation and inappropriate corrective action taken to avoid unintentional introduction of microorganisms.[140]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
6.	09/11/2022	Invitrx Therapeutics Inc., 20503, Crescent Bay Drive, Lake Forest	Inadequate EM procedures for aseptic processing area where products are manufactured. Failure to validate the aseptic processes.[141]
7.	21/10/2022	Nephron Pharmaceuticals Corporation, 12th Street Extension, West Columbia	Lack of sterility assurance, insanitary conditions.[142]
8.	27/09/2022	Sterling Pharmaceutical Services LLC., 109 South Second Street, Dupo	Inadequate investigation of the excursions observed above action limits during the environmental monitoring. Failure to establish appropriate procedures to monitor the environment in the aseptic work area.[143]
9.	23/08/2022	BioLab Sciences Inc., Broadway Rd #102, Mesa Scottsdale	Failure to establish SOPs designed to preclude microbial contamination. Aseptic processing areas deficiently designed.[144]
10.	19/08/2022	Green Wave Analytical LLC.,10366 Roselle St., Suite C, San Diego	Failure to establish a system for EM activity in the sterile area.[145]
11.	10/08/2022	Cangene BioPharma LLC., Professional Drive Suite,	Failure to establish and comply with SOPs for cleaning and maintenance of equipment.[146]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
		Gaithersburg	
12.	26/08/2021	Infusion Options Inc., 4510, 16th Avenue, FL, 2 Brooklyn	Inappropriate storage of drugs requiring temperature-controlled conditions. The medicine is stored in the absence of temperature control.[147]
13.	06/08/2021	Maitland Labs of Central Florida, 7972 Forest City Road,Orlando	Failure to test for sterility of each batch of drug product released in market.[148]
14.	15/04/2021	Joe Wise Pharmacy Inc., 6179, S. Balsam Way, Ste 150 Littleton	Poor practices in aseptic process; deficiencies in practices for producing sterile drug products.[149]
15.	26/08/2021	Infusion Options Inc., 4510, 16th Avenue, FL 2, Brooklyn	Poor practices in aseptic area.[150]
16.	09/10/2020	Surgery Pharmacy Services Inc., 3908 Tennessee Avenue, Suite F Chattanooga	Poor practices during aseptic processing. Improper work surfaces in Classified area.[151]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
17.	17/09/2020	Randol Mill Pharmacy, Fielder Rd, STE 110, Arlington	Poor practices during aseptic processing. Failure to conduct adequate airflow visualization testing under active conditions to prove the air flows in only one direction in the sterile area.[152]
18.	06/10/2020	West Coast Nuclear Pharmacy, 3906, Cragmont Dr, Tampa	Presence of microbial contamination in the aseptic area during aseptic production. Poor practices during aseptic processing.[153]
19.	12/06/2020	Nanobots Healthcare LLC.,South Loop West, Suite 555, Houston, Texas	Failure to conduct adequate airflow visualization testing under active conditions to prove the air flows in only one direction in the sterile area.[154]
20.	03/06/2020	Auro Pharmacies Inc., 520 W, La Habra	Failure to perform adequate airflow visualization testing under active conditions to prove the air flows in only one direction within the aseptic area.[155]
21.	12/03/2020	Altaire Pharmaceuticals Inc. P.O. BOX 849, Aquebogue, New York	Failure to follow SOPs for monitoring the environment in the sterile area. Failure to ensure that production personnel wear appropriate clothing to protect sterile products from contamination.[156]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
22.	11/03/2020	Pharmcore Inc., 2666, SW ,36th St Fort, Lauderdale	Inappropriate facility design; failure to conduct adequate airflow visualization testing under active conditions to prove the air flows in only one direction in the sterile area.[157]
23.	11/02/2019	Bella Pharmaceuticals Inc., 4301, Regency Dr. Glenview	Inadequate media fill simulations to validate aseptic filling operations. Lack of assurance that firm can aseptically produce drug products within facility.[158]
24.	04/02/2019	Akorn Inc., West Field Court, Suite 300,Lake Forest	Inadequate SOPs intended to preclude unintentional introduction of microorganisms for sterile medical products, including identification of all sterilization and sterilization methods. Poor practices in aseptic processing.[159]
25.	20/03/2019	Infusion Partners LLC.,1600, Broadway, Suite 700, Denver	Inadequate design of the aseptic area. Poor practices during aseptic processing. [160]
26.	03/01/2019	Akorn Inc., West Field Court, Suite 300, Lake Forest	Failure to comply with specifications intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products, including sterilization validations.[161]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
27.	24/09/2018	Auro Pharmacies Inc., 520 W, La Habra	Lack of evidence for product sterility test to show that all batches of products are sterile according to the specifications.[162]
28.	10/09/2018	Atlas Pharmaceuticals LLC., 711 E, Carefree Hwy #207, Phoenix	Failure to perform airflow visualization testing under active conditions to prove the air flows in only one direction in the sterile area. [163]
29.	13/12/2018	Samson Pharmaceuticals Inc., 5635 Smithway St, Commerce	Failure to perform aseptic processing operations within specifically defined areas, failure to follow the acceptable system for monitoring environmental conditions in aseptic processing areas.[164]
30.	14/02/2017	Hospira Inc., 235, East 42nd St., New York	Failure to comply with SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[165]
31.	12/05/2017	B. Braun Medical Inc., McGaw Avenue, Irvine	Failure to perform the leak test. Absence of SOPs for conducting leak tests of container-closures.[166]
32.	07/09/2017	Pharmakon Compounding Pharmacy Inc., Noblesville	Inappropriate aseptic processing of sterile drug products. The certification for the sterile isolator showed that airflow as

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
			observed in the airflow visualization testing was turbulent in both isolators.[167]
33.	19/10/2016	Meditech Laboratories Inc., 3200, Polaris Ave, Las Vegas	Deficiency regarding air supply filtered through HEPA filters under positive pressure.[168]
34.	08/05/2017	Alexander Infusion LLC., 75, Nassau Terminal Road, New Hyde Park, New York	Non-compliance with SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[169]
35.	13/10/2016	Eagle Pharmacy Inc. 2200, River chase Centre, Suite 675, Hoover, Alabama	Poor practices in aseptic area.[170]
36.	23/12/2016	Horizon Pharmaceuticals Inc., 7788, Central Industrial, Dr. Riviera Beach, Florida	Failure to comply with procedures intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products. Cleaning facilities are not good.[171]
37.	21/05/2015	Pharmakon Pharmaceuticals, 14450, Getz Road, Noblesville	Failure to comply with SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[172]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
38.	02/11/2015	WalkMed Infusion LLC, 6555 S, Kenton St, Suite 304, Centennial	Poor aseptic processing techniques during the manufacture of sterile product. [173]
39.	09/12/2014	Delta Pharma Inc., 114 W. Mulberry Street, Ripley, Mississippi	Failure to comply with SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[174]
40.	31/05/2013	Baxter Healthcare Corporation,, One Baxter Parkway, Deerfield, Illinois	Failure to ensure integrity of container closure system that provides protection against sterility failure during shipment.[175]
41.	22/02/2012	APP Pharmaceuticals LLC, 1501, East Woodfield Road, Suite 300E, Schaumberg, Illinois	Presence of insects found in a sterile container was not recorded. The company did not submit a field alert report (FAR) for Heparin Sodium Injection when it confirmed the presence of small particles in the sample after receiving a complaint.[176]
42.	17/03/2011	Dakota Laboratories LLC St. Louis, Missouri	Failure to monitor the EM of data collected during the sterilization process and failure to meet specified limits.[177]

S. No.	Action Taken Date (WL issued date)	Firm Name	Crux of warning letters
43.	31/08/2011	Luitpold Pharmaceuticals Inc., One Luitpold Drive Shirley, New York	Failure to resolve the particulate contamination issue in sterile products.[178]
44.	21/09/2010	Gilead Sciences Inc., Cliffside Drive, San Dimas	Non-availability of dedicated areas and controls to prevent cross contamination and mix up during sterile operations.[179]
45.	30/09/2010	Bristol-Myers Squibb Company, 345, Park Avenue, New York	Failure to design and perform appropriate sterile procedures (e.g. media fill) under the same controls used for routine production.[180]
46.	21/05/2010	K.C. Pharmaceuticals Inc., Producer Way, Pomona	Inadequate EM, failure to conduct a thorough investigation regarding the media fill failures.[181]

From the above table it is apparent that several WLs have been issued to US pharmaceutical companies that have been found to have deficiencies in their quality system and aseptic practices. Some companies that received repeated WLs include KC Pharma, Invitrx, Acorn Inc that have been severely criticised by USFDA. The inefficient quality system and deficient written procedures intended to preclude unintentional introduction of microorganisms for sterile products are claimed to be sterile with regard to cGMP, in particular the lack of an efficient quality monitoring system have also been a subject of criticism by US FDA.

5.2.4. WLs from rest of world's pharmaceutical industries

The details of warning letters pertaining to sterile products manufactured in pharmaceutical industries located in rest of countries (other than US and India) are summarized in the table 10 given below:

Table 10: Summary of US FDA WLs issued to rest of countries (except India and US) pharmaceutical Industry

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
1.	14/02/2024	Jordan	Amman Pharmaceutical Industries, Building 108, Street A3, Amman	Insufficient aseptic areas to prevent contamination and mixing of sterile workplaces. High-risk manual interventions during batch manufacture observed. Failure to sterilize equipment that come in direct contact with sterile products. Laboratory records lacked complete and trustworthy data (data integrity issues).[182]
2.	15/03/2023	Japan	Olympus Medical Systems Corp., Tokyo	Sterility was compromised because of the modification made to the sealing process.[183]
3.	07/01/2022	China	Wickimed Medical Equipment Manufacturing Co., Ltd., LiLin Town,	Failure to establish, maintain proper procedures for handling complaints; for medical devices, the design of the control system is not sufficient. Failure to

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
			Huizhou Shi Guangdong Sheng	indicate the conformance of product with acceptance criteria.[184]
4.	06/01/2022	China	Unimicro Medical Systems-Shenzhen Co., Ltd., 201, Bldg 38 101 Heshui Kou	Lack of evidence regarding medical device manufacturing, EtO sterilization and storage according to labelling conditions.[185]
5.	23/11/2021	China	Hubei Kangzheng Pharmaceutical Co., Ltd., 88, Hexi Jinquan Road, Anlu City, Hubei Sheng	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[186]
6.	16/11/2021	China	Global Medical Production Co. Ltd., Zhejiang Sheng	Failure to create a maintenance schedule for air handling units with HEPA and water filters.[187]
7.	09/06/2020	Japan	Takeda Pharmaceutical, Chuo-ku, Tokyo	Restart of aseptic area after a power outage resulting in adverse impact on cleanroom conditions.[188]
8.	23/05/2018	Japan	Toyobo Co. Ltd., Otsu, Shiga	Inadequate investigation of significant particulate defects in firm’s sterile drug product, including

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
				recurring incidents of extrinsic particle contamination.[189]
9.	04/9/2018	Canada	Lernapharm (Loris) Inc., 2323 Halpern St., Saint-Laurent, Montreal	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[190]
10.	27/06/2018	China	Zhuhai United Laboratories Co., Ltd., No. 2428 Anji Road, Sanzao Town, Zhuhai, Guagdong	Missing data regarding sterile operation and inability to control electronic data in Class A area.[191]
11.	31/05/2018	Taiwan	Taiwan Biotech Co., Ltd., 22, Chieh-Shou Road Taoyuan District, Taoyuan City, Taiwan	Failure to establish SOPs to monitor the environment in aseptic work area.[192]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
12.	23/05/2018	Australia	IDT Australia Ltd., 45, Wadhurst Dr. Boronia	Failure to comply with adequate laboratory controls, including change procedure followed for quality control.[193]
13.	01/11/2017	China	Guangzhou Baiyunshan Pharmaceutical Co., Ltd., No. 52, Guangzhou, Guangdong	Failure to clean, maintain, disinfect and/or sterilize equipment and materials in a timely manner.[194]
14.	07/09/2017	China	Wuxi Medical Instrument Factory, Wuxi City, Jiangsu	Failure to adequately validate the process used to manufacture sterile products.[195]
15.	08/04/2017	Brazil	MB Industria Cirurgica Ltd., Rodovia, BR 101 - Norte Km 56,7 - Paratibe, Paulista	Failure to follow the proper packaging procedures to guarantee that the product remains sterile after sterilization.[196]
16.	17/03/2017	Singapore	Opto-Pharm Pte Ltd., 13 Tuas Ave 12	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[197]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
17.	17/01/2017	United Kingdom	Porton Biopharma Ltd., Manor Farm Rd, SP4 0JG Salisbury	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[198]
18.	12/08/2016	Brazil	Antibioticos do Brasil, RodProfessor Zeferino Vaz, Sao Paulo	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[199]
19.	13/10/2016	Hungary	Teva Pharmaceutical Works Pvt. Ltd., Mihalyut, Godollo	Inadequate investigation of media fill contamination in aseptic manufacturing lines.[200]
20.	30/06/2016	United Kingdom	SmithKline Beecham Ltd., 980, Great West Road, Brentford	Failure to follow SOPs to prevent contamination from penicillin production facilities to unsustainable sites.[201]
21.	20/05/2016	Italy	Corden Pharma S.p.A, Sermoncta, Latina	Failure to have adequate facilities to enable cleaning, maintenance, and proper operation.[202]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
22.	22/06/2015	Canada	Attix Pharmaceuticals, 425, University Ave Suite, 800, Toronto	Failure to use separate facilities, or equipment like hoods and air handling units (AHU), to handle penicillins, non-penicillin beta-lactams, and non-beta-lactam APIs.[203]
23.	31/03/2015	Italy	Hospira S.p.A, 275 N, Field Drive, Lake Forest	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[204]
24.	27/02/2015	New Zealand	Molteno Ophthalmic Ltd., 152, Frederick Street, Dunedin	Lack of sterility assurance of the Molteno 3 glaucoma implant.[205]
25.	21/10/2014	Jordan	Hikma Pharmaceuticals Ltd., 21, Saleem Bin Hareth, Street Industrial Area, Amman	Failure to conduct thorough investigations of firm's EM excursions in Class 100 areas.[206]
26.	26/09/2014	Australia	Hospira Australia Pty Ltd.,Lexia Place, Mulgrave	Failure to establish SOPs to monitor the environment in the aseptic work area.[207]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
27.	12/06/2014	Canada	ID Biomedical Corporation, Quebec City	Absence of SOPs to protect sterile medical products from microbial contamination.[208]
28.	11/04/2014	Germany	Sanum-Kehlbeck GmbH & Co. KG, Hasseler Steinweg	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[209]
29.	21/02/2013	Canada	Apotex, Inc., 150 Signet Drive, Toronto	Failure to do airflow study in the filling line used to produce sterile products.[210]
30.	20/02/2013	Canada	Jubilant Hollister Stier Canada, Kirkland, Québec	Inadequate CAPA, firm committed to modifying the visual inspection procedure which was not implemented. Failure to adequately address the quality of the product released in the market.[211]
31.	12/07/2012	France	Sanofi Pasteur, World Wide Headquarters, Paris	Failure to implement and follow SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[212]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
32.	12/07/2012	Canada	Sanofi Pasteur, World Wide, Ontario	Failure of sterility testing for BCG Live vaccine.[212]
33.	23/02/2012	United Arab Emirates	Gulf Pharmaceutical Industries, Digdaga - Ras al Khaimah, Julphar	Failure to implement and follow appropriate SOPs intended to preclude unintentional introduction of microorganisms for sterile pharmaceutical products.[213]
34.	18/11/2011	Switzerland	Novartis International AG, Novartis Campus CH-4056, Basel	Aseptic process simulation is inadequate to determine whether aseptic techniques are being maintained, resulting in inconsistent and inaccurate data collection.[214]
35.	26/07/2011	Brazil	B. Braun Melsungen AG, Sau Goncalo	Failure to establish, maintain and implement the medical record (MDR) process.[215]
36.	09/02/2011	Germany	Sanofi Aventis Deutschland GmbH, Industriepark Hochst	Non-availability of control area required to prevent contamination or mixing during sterile procedures.[216]

S.No.	Action Taken Date (WL issued date)	Country/ Area	Firm Name	Crux of warning letters
37.	12/05/2010	Venezuela	Laboratorios L.O. Oftalmi Calle 6, Zona Industrial de La Urbina, Caracas	Inadequacy of SOPs to prevent unintentional introduction of microorganisms in sterile pharmaceutical products.[217]
38.	29/03/2010	Canada	Apotex Inc., 150, Signet Drive Toronto, Ontario	Failure to follow cleaning and maintenance SOPs to prevent contamination of sterile product.[218]

Key issues and trends in issued WLs identified by the above analysis include:

Sterility assurance

- Poor practices and lack of sterility assurance
- Failure of aseptic technique
- Failure of EM
- Inadequate design of facilities

Basic cGMP

- Cleaning and equipment maintenance
- Basic sanitation failures

Pareto analysis

Pareto analysis of WLs (Figure 17) shows that 80% of the observation group is due to poor aseptic behaviour, poor microbiology performance and lack of sterility assurance.

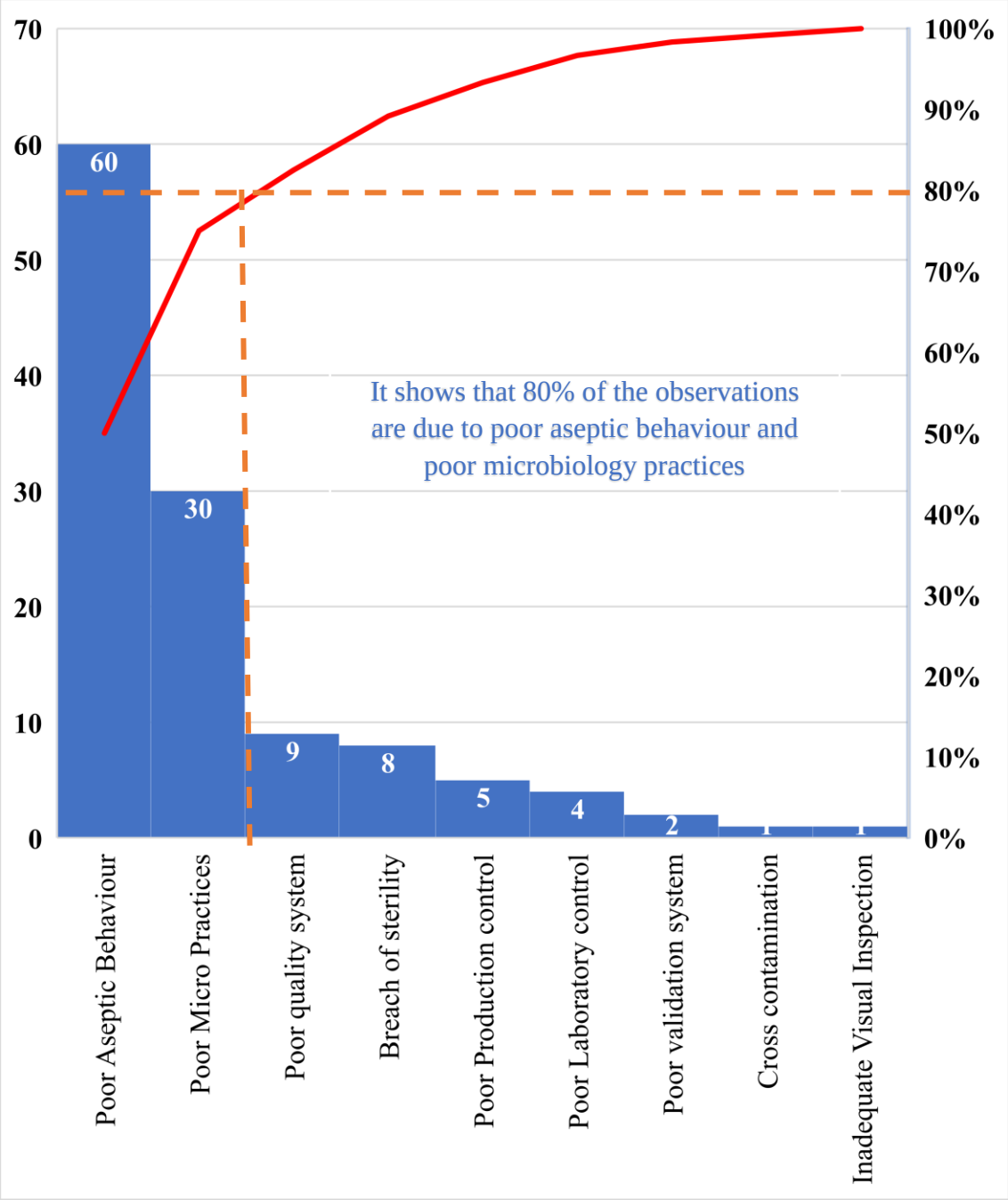


Figure 17: Pareto Analysis - WLs observations (01 January 2010 to 30 September 2024)

Based on the above studied WLs, the summary of violations of 21 CFR parts are detailed in table 11 given below. This indicates the trend of violations and most frequent observations.

Table 11: Summary of violations of 21 CFR parts.

21 CFR 211		**Percentage of deficiencies (%)**		
Section	**Section Name**	**India**	**US**	**Rest of Countries**
21 CFR 211.22	Responsibilities of Quality Control Unit	1.23	1.23	1.23
21 CFR 211.25	Personnel Qualifications	0.93	--	0.31
21 CFR 211.42	Design and Construction Features	3.70	6.48	2.78
21 CFR 211.56	Sanitation	--	--	0.31
21 CFR 211.63	Equipment Design, Size, and Location	0.62	0.93	0.31
21 CFR 211.67	Equipment Cleaning and Maintenance	1.23	2.16	1.85
21 CFR 211.68	Automatic, Mechanical, and Electronic Equipment General Requirements	1.85	0.62	0.62
21 CFR 211.80	Control of Components and Drug Product Containers and Closures	--	--	0.31
21 CFR 211.84	Components, Drug Product Containers, and Closures	0.62	1.54	0.31
21 CFR 211.94	Drug product containers and closures	--	0.31	--
21 CFR 211.100	Written Procedures; Deviations	--	--	0.62

21 CFR 211		Percentage of deficiencies (%)		
Section	**Section Name**	**India**	**US**	**Rest of Countries**
21 CFR 211.110	Sampling and Testing of In-Process Materials and Drug Products	--	--	0.31
21 CFR 211.111	Time limitations on production	--	0.31	--
21 CFR 211.113	Control of Microbiological Contamination	6.17	10.80	7.41
21 CFR 211.125	Labeling issuance	0.93	--	0.31
21 CFR 211.137	Expiration dating	--	--	0.31
21 CFR 211.142	Warehousing procedures	--	0.31	--
21 CFR 211.160	General Requirements (Laboratory Control)	1.85	2.78	1.54
21 CFR 211.165	Testing and Release for Distribution	0.93	2.16	0.31
21 CFR 211.166	Stability testing	--	2.47	0.93
21 CFR 211.180	General Requirements (Records and Reports)	--	--	0.31
21 CFR 211.186	Master Production and Control Records	--	--	0.31
21 CFR 211.188	Batch Production and Control Records	1.54	--	--
21 CFR 211.192	Production Record Review	5.86	4.32	4.01
21 CFR 211.194	Laboratory Records	2.16	0.62	1.23
21 CFR 211.198	Complaint Files	0.62	0.31	--
21 CFR 211.100	Written procedures; deviations	0.93	2.16	1.85

21 CFR 211		Percentage of deficiencies (%)		
Section	**Section Name**	**India**	**US**	**Rest of Countries**
21 CFR 200.10	General Provisions: Contract facilities (including consulting laboratories) utilized as extramural facilities by pharmaceutical manufacturers	--	0.62	--
21 CFR 210.1	Status of current good manufacturing practice regulations	--	0.31	--
21 CFR 225.1	General Provisions: Current good manufacturing practice	--	0.62	0.31

From the above table, it is clear that the highest percentage of deficiencies i.e. 24.38% is related to 21 CFR 211.113 (Control of microbiological contamination) with highest occurrence i.e. 10.80% in US as compared to that in India (6.17%) or rest of countries (7.41%)**.** This can be attributed to lack of awareness of cGMP requirements, particularly those related to microbiological controls to produce sterile product.[219] The production records review (21 CFR 211.192) and facility design (21 CFR 211.42) is another concern found in sterile products facilities.

5.3. Guidance and recommendations

The US FDA released guidelines for industry over 20 years ago. The guidance was titled "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice September 2004". The scope of this guideline is limited; it does not address all aspects of sterile product, including product processed by TS processing. The guidelines mostly deal with cGMP issues related to finished products, but they do not go into detail beyond the upstream bulk processing. The expectations of regulators and the procedures currently followed for sterile product facility inspections are not covered by this guidance. To enhance understanding of the requirements for inspections of sterile product facilities, US FDA did not organized any training courses in specifically in India where largest sterile facilities are located. Furthermore, there are no reports of Indian firms taking up any effort to provide this kind of training. Thus, guidelines needs to be introduced in order to address the challenges that sterile manufacturers are experiencing right now. Based on review of WLs issued to sterile products, a brief guideline is prepared. The guideline provides essential recommendations for sterile product facility inspections and can be used as a manual for preventing cGMP violations pertaining to sterile products.

Below guideline addresses several important topics pertaining to sterile products, for which the US FDA often issues warning letters:

5.3.1. Responsibilities of quality control unit (21 CFR 211.25)

In the pharmaceutical industry, quality control (QC) plays a vital role since it ensures that the pharmaceutical products are safe, effective, and complies with the predetermined specifications before the products are distributed in market. QC role should involves:

i. Effective QC systems and SOPs should be established in order to prevent microbiological contamination during processing of sterile drug products
ii. The quality system should include an audit process to detect deficiencies in the sterilization process and to evaluate uncontrollable deviations from standard procedures
iii. SOPs should be available with defining role and responsibilities for analysing, approving and rejecting the incoming material as well as finished product

iv. Training records of each employee engaged in quality control activity should be up to date

v. Risk management process should be in place to reduce the risk of microbial, endotoxin and particulate matter contamination of medicinal products

vi. Documentation management system should consist change control, SOP, process flow chart, testing process for intermediate products, finished products, equipment and equipment layout drawings, calibration data, EM data

vii. QRM (Quality Review Management) system should be in place to review periodic quality documents

5.3.2. Personnel qualifications (21 CFR 211.22)

In a sterile area, personnel qualifications is crucial because it ensures that non-measurable factors like behaviour, hygiene, attitude, and sensitivity are taken into account. In microbiological labs and sterile injectable facilities, personnel qualification is applicable to the aseptic processing and sterility testing sections. The essential components listed below should be taken into account for personnel qualifications:

i. Employees involved in the operation and monitoring of sterile pharmaceutical products must have the necessary education, training and experience to perform their duties

ii. The largest source of microbial contamination in sterile processing areas of manufacturing operations is humans. Therefore, human intervention should be minimized to eliminate the source of contamination. Employees must follow the hygiene rules

iii. SOPs for aseptic processing should be prepared and implemented. The SOP should include a detailed description of the tasks that personnel must perform during aseptic procedures

iv. A training program should be developed and implemented for personnel involved in the production of sterile product

v. Employees should be trained for proper hand washing, changing and disposal procedures before entering and exiting a sterile workplace

5.3.3. Design and construction features (21 CFR 211.42)

21 CFR Part 211.42 on buildings and facilities mandates the proper design of production facilities. A facility qualification (FQ) ensures that an area, room, or building has the utilities and environmental conditions required for product manufacturing. Following are the prerequisites that must be met before producing a commercial product:

i. Buildings and facilities should be constructed appropriately and their ceilings should not leak. The wall should be smooth and dust should not accumulate on the wall/ceiling, and should be easy to clean
ii. A suitable and isolated area must be available to perform all necessary operations to prevent contamination or mixing during sterile product activity
iii. Temperature and humidity should be controlled to meet product storage needs.
iv. SOPs for cleaning and sterilization of products containers closures should be available
v. The pressure limits for critical areas (preparation, filling and sealing area) should be appropriate and established based on the worst case-criteria considering risk of contamination
vi. HEPA filter integrity must be maintained to prevent contamination
vii. Compressed gases used in sterile areas must be inert, clean, i.e. free of oil and condensation. Compressed air and nitrogen must be filtered through a pre-filter.
viii. In sterile areas, drainage is not recommended due to the risk of microbial growth

5.3.4. Sanitation (21 CFR 211.56)

Maintaining sanitation during the manufacturing of sterile products is important for preventing contamination of products. The objective of sterile manufacturing is to make sure that the finished products are free from contaminants, microorganisms, and particulates. Below critical parameters should follow with respect to sanitation in sterile area:

i. Employees engaged for sterile products processing should not apply cosmetics or use ornaments (such as rings, earrings, watches)

ii. Employees should be trained for proper hand washing and cleaning. Supervisors should regularly evaluate their performance to ensure they are following established SOPs
iii. Untoward man movement in critical areas should be restricted
iv. Appropriate, clean gowns should be worn in critical areas where sterile products are processed
v. Direct contact to the sterile materials is to be done with sterile instruments
vi. In the sterile area, man movement should be slowly and deliberately as rapid movement can generate unacceptable turbulence thereby be disturbing unidirectional airflow in the sterile area

5.3.5. Equipment design, size, and location (21 CFR 211.63)

Sterile facilities are designed to prevent microbial contamination during the manufacturing, packaging, and filling processes. The equipment design, size and location in sterile facilities is important for preventing contamination of products and materials. The following basic requirements that can be maintained while designing the equipment, including its location and size:

i. Equipment used for product processing should be non-reactive to the product and there should not be any incompatibility between drug and equipments
ii. Equipment and instruments used in the aseptic processing area should be qualified
iii. A calibration schedule including its frequency should be prepared and followed for analytical equipment in quality control as well as equipment used in the production process
iv. Qualifications and certification procedures for sterile workplaces and production equipment must be ensured
v. The training program should be available for handling/operating instruments and equipment
vi. Any untrained personnel, including vendor engineers shall be accompany by trained and qualified personal

5.3.6. Equipment cleaning and maintenance (21 CFR 211.67)

21 CFR 211.67 mandates that utensils and equipment in sterile facilities be frequently inspected, cleaned, and sterilized or sanitized. This procedure serves to avoid any contamination or malfunctions that can alter the drug product's quality. The general guidelines for equipment cleaning and maintenance in sterile facilities are listed below:

i. Equipment should be cleaned, stored and disinfected regularly to prevent product contamination
ii. Each equipment should be validated for the processes used for sterile drug process
iii. The equipment should be designed to be easy to clean, maintain and operate.
iv. The performance of equipment should be reviewed periodically to ensure these are working for its intended use
v. After sterilizing the equipment, the integrity should not be compromised during transportation from one room to another room for processing

5.3.7. Automatic, mechanical, and electronic equipment general requirements (21 CFR 211.68)

21 CFR 211.68 mandates that drug products can be manufactured, processed, packed, and held using automated, mechanical, or electronic equipment as long as it is regularly examined, calibrated, or checked in accordance with a defined procedure. It is also necessary to maintain written records of these inspections and calibration checks. The prerequisites must to comprise:

i. Sterilization equipment must be equipped with computer to ensure the recording of online process data.
ii. Computer system should have provisions to prevent unauthorized access.

5.3.8. Control of components and drug product containers and closures (21 CFR 211.80)

Regulation 21 CFR 211.80 requires that drug product components, closures, and containers be handled and kept in a way that reduces the risk of contamination. Contamination may occur through contact with unclean surfaces, exposure to external contaminants, and cross-contamination between products. Following specific recommendations are helpful in this particular circumstance:

i. SOPs describing
   the receipt, identification, storage, processing, testing, approval or rejection of containers and closures should be in place
ii. Containers, closures and other product contact component should be tested for microbiological testing before use, should be cleaned, washed and sterilized by validated process before use

5.3.9. Components, drug product containers, and closures (21 CFR 211.84/94)

21 CFR section 211.84 211.94 deals with testing and the approval or rejection of components, drug product containers, and closures. Containers and closures for drug products are covered under 21 CFR 211.94. Below outline a few requirements for drug product closures and containers:

i. Sterilized containers and closures should be protected from microbial or pyrogenic contamination by appropriate preventive measures
ii. The depyrogenation/sterilization process of container closures should be validated to achieve sterility assurance level

5.3.10. Written procedures; deviations (21 CFR 211.100)

Written procedures have become necessary in sterile facilities to ensure that sterile products are free from microbiological contamination. They also improve the quality of pharmaceutical items, which is necessary for maintaining their strength, identification, purity, and quality. The few essential suggestions in this regard are listed below:

i. Written manufacturing processes must be in place to ensure the identity, potency, quality and purity of the sterile product
ii. While various production and control process studies are carried out, documentation of the production process and control process should be followed and recorded when completed
iii. Any deviations in the process should be documented and justified
iv. Change management system should address atypical situations caused by the shutdown of air handling unit and other electronic equipment and assess the impact

5.3.11. Sampling and testing of in-process materials and drug products (21 CFR 211.110)

As part of regular manufacturing procedures, in-process testing verifies that the final product fulfils predetermined requirements for product quality. To evaluate the quality of the pharmaceutical product and regulate process parameters, samples are collected at different stages of the manufacturing process. Here is a crucial suggestion in this regard.

i. Quality and purity of the materials used in the process must be checked and approved or rejected by the quality control department
ii. During manufacturing of sterile product, the QC unit has to approve or reject products, which are under the process, regardless of whether it is at the beginning or end of critical stages. Testing is required to ensure the materials' identity, strength, quality, and purity. Rejected materials have to be stored in quarantine and kept out of manufacturing or processing

5.3.12. Time limitations on production (21 CFR 211.111)

Time limits play an important role in sterile facilities in order to minimize the growth of microbes in products. For example, extended filtration times in the pharmaceutical manufacturing process could allow products that promote microbiological growth. For this context, the following are the important recommendations:

i. While establishing the hold time for intermediate and bulk solution, critical quality attributes such as impurities, bioburden, endotoxins should be ensured

ii. Manufacturing of drugs solutions, filtration, and sterilization, as well as other manufacturing procedures, should be completed as soon as possible in order to produce sterile pharmaceutical products. The maximum period of time that can be allowed between filtration, storage, filling, and sealing should be established by evaluating the risks associated with each operation, as well as the manufacturing procedures, storage conditions

iii. While establishing the hold time for sterile product, critical quality attributes such as the endotoxins and bioburden must be assessed

5.3.13. Control of microbiological contamination (21 CFR 211.113)

Microbiological contamination is the most commonly violated aspect in sterile facilities. The US FDA recently sent WL to Kilitch Healthcare India Ltd. in March 2024 for cGMP violations, particularly for the company's failure to establish and follow standard processes in order to prevent microbiological contamination of sterile pharmaceutical products. The key recommendations in this perspective are listed below:

i. Sampling plans and testing procedures should be designed to produce sterile products, which maintains the sterility of the product throughout shelf life. Scientifically based specifications limits for microbiological tests should be in place

ii. Validation of sterility methods should include microbial testing to demonstrate reproducibility

iii. Sterile environment should be available for sterility testing of product.

iv. The EM location of critical areas should be defined in the SOP. The EM plan should include sampling of a variety of surfaces for microbial quality, including contact surfaces, floors, walls, and equipment, and should be tested regularly

v. Manufacturing process controls should be designed to minimize bioburden on unfiltered bulk and raw materials

vi. SOPs should be established to control unintentional introduction of microorganisms for sterile pharmaceutical products

vii. EM of non-viable particles should include worst-case area where there is most risk to exposed product, container and closures. Disinfectants used in critical areas should be in a sterile form to avoid contamination

viii. Any unexplained deviation or non-conformity to any of its specifications should be thoroughly investigated and documented

ix. Product process should be selected to have a low microbial load in the unfiltered bulk product. For example, for incoming raw materials, control limits for bioburden is to be required to avoid a sterility failure of the finished product.

x. Content of viable and non-viable particles should be monitored during environmental monitoring

xi. For sterile products, each operations involved in aseptic processing i.e. sterilization of equipment, components, packaging materials shall adequately validated

xii. An aseptic processing operation is also called as media fill should be performed to validate the process that involves all intervention covered in product processing including operator movement, number of operator, maintenance, stoppages, equipment adjustments, duration of product process

xiii. SOPs related to aseptic processing should be available

5.3.14. Labeling issuance (21 CFR 211.125)

Labeling ensures product identification and is an aspect of trademark. Labeling that includes particular content determined by regulatory agencies or labeling and packaging that functions in a specific manner. Some recommendations are included below.

i. Issuance of product labels must be strictly controlled

ii. The information listed on the product must be independently checked and conform to the information listed in the batch manufacturing record

5.3.15. Expiration dating (21 CFR 211.137)

Unopened sterile products must retain their quality throughout the duration of the declared expiration date. Drug applicants submit the stability results for supporting the suggested expiration date to the US FDA. The FDA determines that the applicant provides sufficient

data to back up the requested expiration date. Here are some recommendations for expiration dating:

i. Drug product including packaging, raw materials and other materials must have an expiration date
ii. For the reconstituted at the time of dispensing, label must contain information about the in-use period after reconstitution and the expiration date of the reconstituted drug

5.3.16. Warehousing procedures (21 CFR 211.142)

Proper storage of all the materials as well as finished product is essential to maintain their quality. The product should be stored according to prescribed storage conditions on the label. The following are suggestions regarding warehousing procedures:

i. SOP should be available for receiving, storage and issuance of all materials in warehouse
ii. Before release of materials, it should be quarantined and to be kept under restricted use
iii. Storage of drug products under appropriate conditions of temperature, humidity, and light to maintains its quality

5.3.17. General requirements laboratory control (21 CFR 211.160)

The US FDA issues WLs in case violations observed for the inadequate laboratory controls. Below are the recommendations to avoid the issuance of WLs:

i. The quality control unit should have the specifications of materials and finished drug products
ii. Sampling plans, procedure and standard testing procedures should be available in laboratory
iii. The SOPs should be available for laboratory personals with defined duties and responsibilities

5.3.18. Testing and release for distribution (21 CFR 211.165)

According to 21 CFR 211.165, QC must ascertain that each batch meets the final specifications prior to the release of a drug product in to the market. This includes each

active ingredient's identification and potency. The recommendations for avoiding the issuance of WLs are listed below:

i. The SOPs or standard testing procedure must be available for testing of batches before release into the market
ii. Prior to release drug product batch in the market, each batch shall be tested and ensured for satisfactory compliance to predefined specifications

5.3.19. Stability testing (21 CFR 211.166)

Inadequate stability studies that failed to provide a product's shelf life could result in a WL from the USFDA to the sterile facility. Below is a list of suggestions for preventing the issuing of WLs:

i. Written master stability plan should be available for each product to be placed on stability for determination of the shelf life/expiration dates
ii. Sufficient number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained
iii. Accelerated studies, photostability and thermal excursion studies shall be designed to determine the storage conditions of drug product

5.3.20. General requirements -records and reports (21 CFR 211.180)

General requirements for records and reporting are covered by 21 CFR 211.180. According to the regulations, industries must maintain the records that includes:

i. APQR i.e. annual product quality review system and process validations, trend report for critical quality attributes (CQA) should be available for each product
ii. Re-validation criteria should be defined in the process validation protocol and reports

5.3.21. General recommendations during the inspections of sterile facility

Here are a few important recommendations based on the findings from the study of the WLs and interaction with personnel involved in sterile facility inspections in a couple of Indian pharmaceutical Industries:

i. A brief introductory presentation can be made on the first day showing company history, compliance history, organization chart, number of employees, operating

hours, product list, major equipment and computer/software list, and facility layout. This will assist the investigator in familiarizing themselves with the facility prior to commencing the investigation

ii. Before meeting the US FDA inspection team, discuss the question with the site staff in the "backroom" and prepare answers for it. Ask for clarification if a question or request is unclear. Listen carefully to what is being asked and answer the question directly. Do not delay or refuse to provide requested documents/data as this may lead to further legal action by the agency

iii. To ensure the timely completion and evaluation of all relevant activities and documentation, it is essential to assign an inspection readiness team along with an inspection coordinator

iv. The inspection coordinator should regularly take updates regarding assistance of operational plans to facilitate seamless inspection preparations and promptly address any arising issues

v. It is not uncommon for US FDA inspectors to request documents, particularly before an inspection. Investigators may expect the firm to have all necessary documents prepared on the initial day of the inspection. Document readiness before the start of inspection must be ensured

vi. US FDA inspectors have quite different preferences when it comes to document retrieval; some require both physical copies and electronic files, while others prefer electronic files. These requirements should be understood and preparations done accordingly

vii. As per the US FDA's Investigations Operations Manual (IOM), [220] it is advised that investigators make reasonable attempts to communicate all observations to facility management on a daily basis. This is done in order to minimize unexpected findings, mistakes, and misunderstandings when issuing Form 483.

viii. The discussion related to Form 483 observations should cover any notes made on the form and will only be addressed with management during the closing meeting. The company can use this time to ask questions about the observations,

ask for clarification, and let the inspection team know what corrections have been, or will be, made during the inspection

ix. Ensure that the most senior employee in the facility is present during the final audit meeting. This shows that firms take the inspection outcomes seriously and are interested in learning more about the outcomes of the inspection so that deficiencies can be addressed

x. The US FDA typically allows 15 business days to respond to Form 483 comments. Form 483 observation should be communicated to a cross-functional (CFT) team immediately

xi. Responses to observations should be as detailed as possible. If there is more than one part to an observation, respond to each part

xii. Responses to Form 483 must include corrections to any incorrect statements in the form. If possible, explain how and why the current existing systems meet cGMP standards and therefore are not deficient. In the firm's response, provide the CAPA as well as a realistic timeline for completion of each CAPA action

5.3.22. Suggestions to the pharmaceutical manufacturers of the sterile products to avoid issuance of the warning letters due to the cGMP violations

Based on review of WLs issued to sterile products' manufacturers, above brief guideline document is prepared that provides essential recommendations and can be used as a manual for avoiding cGMP violations pertaining to sterile products. Along with the specific guidance for each issue, the following suggestions are recommended to the pharmaceutical manufacturers of the sterile products to avoid issuance of the warning letters due to the cGMP violations:

i. **Quality by Design (QbD) approach:** The focus needs to be shifted on comprehensive quality management rather than isolated, expedient compliance efforts. For this, the principles of QbD may be used to enhance the product and process quality. QbD involves thorough understanding of the processes involved. Objectives are defined before the actual start of process. Based on the real time risk assessment, implementation of QbD will help risk reduction. This in turn will help in avoiding the warning letters [221,222]

ii. **Automation:** Though regulatory authorities issue guidance documents on the topic of automation of processing as well as data management, the compliance continues to be poor.[223] Automation uses technology to perform repetitive tasks quickly and accurately, eliminating the risk of human error. Automation enables companies to minimize human errors by eliminating manual activities in aseptic area. The use of automation, however, is not very common because of the high cost involved in automation and a general notion that no automated system can substitute for human supervision.[224] Awareness trainings for decision makers on resource constraints, explaining the cost of non-compliance vs. that of the cost of compliance using case studies, need to be conducted. On the other hand, while these innovations enhance efficiency and reduce the risk of human error, they also require a workforce that is adept at using them optimally. The need for ongoing training and development in new technologies will instill skill and confidence in the workforce that still feels intimidated by the rapid pace of change[225]

iii. **Use of artificial intelligence (AI) and Machine learning (ML):** The integration of advanced technologies, such as artificial intelligence (AI) and Machine learning (ML), into aseptic manufacturing processes is set to transform the regulatory compliance of the industry. AI and ML can support in dossier compilation, data retrieval and processing, auditing as per latest regulatory requirements, and even quality control. AI can also assist in identification of critical quality attributes (CQA), critical material attributes (CMA), and critical process parameters (CPP) by extensive analysis of earlier production datasets and scientific literature[226]

iv. **Trained personnel**: Aseptic manufacturing is a critical process in the production of sterile products. As demand for sterile products continues to rise, so does the need for skilled professionals in aseptic manufacturing. However, there is a lack of adequately trained professionals who possess the necessary skills in aseptic techniques and sterile processing.[227] Most of the training programs offered frequently do not fully address the complexities of aseptic manufacturing, leading to a gap between industry needs and workforce capabilities. Recruitment, training and engagement of the right people for aseptic process operations will avoid the issuance of warning letters. The US FDA needs to work with industry to train people in the finer nuances of the process so as to avoid the issuance of WLs

v. **Formation of expert committee:** Establish an indigenous expert committee of sterile product facility pre-audit from the professionals of sterile product manufacturing firms who can share their expertise and experience with the industry. This committee may provide insight into the expectations of the US FDA for facility audits and how to overcome warning letter issuance[228]

5.3.23. The changes need to be done in cGMP to avoid the warning letters

As indicated by the addition of 'c' indicative of the word "current", before GMP, cGMP is constantly evolving and pharmaceutical companies are expected to stay updated with the latest changes to ensure compliance. Following are the changes that may be done in cGMP to avoid the warning letters:

i. The cGMP regulations require that training be conducted on cGMPs on a periodic basis. However, the cGMP guidelines are complex, and quite exhaustive. Training on cGMPs is not adequately imparted in terms of frequency as well as extent. Hence there is need of changes in cGMP to have continuous trainings on cGMP from the USFDA on the key areas such as facility design, aseptic practices, good documentation and laboratory practices. Furthermore, these trainings should include the lessons learned and remedial programs put in place by other company who had warning letters and are now compliant with the cGMP (as case studies)

ii. The study of USFDA warning letters pertaining to sterile products reveals that the top reasons for issuance of WLs include the poor environmental monitoring, lack of sterility assurance and poor aseptic practices. Hence, there is need of bring change in cGMP with respect to detailed process for environmental monitoring to introduce continuous microbiological environmental monitoring, thereby reducing interventions and future replacement of Grade A settle plates and non-remote active air sampling. The replacement of traditional monitoring with biofluorescent particle-counting systems provides an improvement in process understanding and product safety and reduces operator manipulations, assuring product quality and real-time process verification[229]

iii. Artificial intelligence (AI) has emerged as a powerful tool that harnesses anthropomorphic knowledge and provides expedited solutions to complex challenges. Remarkable advancements in AI technology and machine learning present a transformative opportunity in the drug discovery, formulation, and testing of pharmaceutical dosage forms.[230] Hence it is need to bring a change in cGMP to introduce continuous processing executed with the assistance of AI. Environmental

monitoring (EM) requires the introduction of the AI concept, which will allow automated data collection and interpretation of EM samples, generate precise, usable data for prompt decision-making, and enhance data integrity (DI) and also compliance through the use of auditable electronic records[231]

5.3.24. The reasons why pharmaceutical companies are not able to comply requirements of US FDA but easily comply with requirements of other countries including India

The GMP requirements of US FDA and other countries including India for manufacturing of sterile products are broadly similar except for environmental factors and water system. The guidelines from these countries are focused on high quality requirements for the manufacturing process for sterile products. USFDA focuses more on clean area classification, microbial monitoring, validation aspects and personnel training. In spite of similar GMP requirements, the reasons why pharmaceutical companies are not able to comply requirements of USFDA but easily comply with requirements of other countries including India Are mentioned below:

i. The US FDA GMP inspections are considered as more stringent and they take quick enforcement actions such as issuing warning letters, import alerts or initiating product recalls. US FDA inspections typically include extensive review of documentation and focus on holistic Corrective and Preventative Action (CAPA) and remediation plan against any deviations of the process whereas Indian and other countrys' GMP inspections are considered as relatively flexible and focused on end product quality

ii. Lack of up-to-date knowledge of the USFDA cGMP requirements seems to be another reason for higher non-compliance issues. Employees are generally not very well aware of the USFDA requirements that are relevant to their jobs. This may result in inadvertent non-compliance. On the other hand, Indian regulatory agency, Central Drugs Standard Control Organization (CDSCO) is situated in India and their experts are readily available for responding to queries raised from

the Indian manufacturers. No training programs from USFDA are conducted in India for imparting the awareness to the drug product manufacturers with respect to current expectations of GMP practices

Chapter 6. Summary and Conclusion

Pharmaceutical industry involved in the manufacture of sterile products across the globe has been receiving a number of WLs from the US FDA. This phenomenon has, however, increased in recent years, which is a major concern for the pharmaceutical industry worldwide. Because sterile products are administered directly into human blood, any compromise in the quality of such products poses a very high risk to the patients. In light of this, any WLs received in context to sterile products assume much higher significance. There are several available studies on WLs issued by the US FDA. However, there are no specific reports on WLs associated with sterile products.

Analysis of WLs over the past 14 years and 9 months i.e. from 2010 to 2024 (as on 30 September 2024) shows that 120 WLs have been issued to pharmaceutical industries for sterile products. Our study indicates that non-compliance is not specific to a country, region, or particular continent. However, the percentage manufacturers of US FDA approved sterile products that have been issued WLs is 38%. Highest number of US FDA approved sterile products manufacturers are located in US and India. The weakness of Indian pharmaceutical industries involved in sterile product manufacture is reflected by the fact that, despite having almost one-third the number of sterile facilities as compared to US, double the number of Indian industries have received repeated WLs. This analysis indicates that the Indian industries need to take up this issue with utmost seriousness in order to continue to sustain the FDA approvals. Regarding the economic impact of WLs from US FDA on Indian pharmaceutical sector engaged in exporting the drug products to US, it can be concluded that in spite of significant WLs cases in India for the period of 2010-2022, overall drug export is not much impacted, and therefore the economic growth of Indian pharmaceutical industry seems to be resilient to such actions. This could be attributed to the fact that the drug export was continued from the other pharmaceutical companies where the WLs were not issued and they continued an uninterrupted supply of the drugs to the US region, thereby rather increasing national income. However, had the firms against whom WLs were issued and subsequent action was taken, continued their

export, the situation of the Indian pharmaceutical industry would have been much stronger as it is today.

The study observed that a larger number of WLs were issued to drug product as compared to devices and biologics product. The major reasons for this were poor cGMP compliance related to sterile product. Content analysis of reviewed WLs issued to pharmaceutical manufacturers shows that US FDA closely monitor operations of quality control unit, validation of manufacturing process, and data record and integrity**Error! Bookmark not defined.**.

The major findings of WLs evaluations indicate that there are significant cases of cGMP violations resulting in sterility breach and other non-compliance issues with the sterile product market. Various cases demonstrate the current state of cGMP through risk assessment-based problem detection, classification of data by non-conformance type, and audit to determine the cause of the nonconformity. Frequent data breaches, human error, lack of training, and improper use and maintenance are reasons for deviations from many cGMP regulations. Thus, if cGMP labs are well managed in a strict control of EM, they would be able to improve quality and eliminate the risk of sterility failures.

Our study shows that the pharmaceutical companies must improve their quality systems and expand its knowledge of handling sterile products. Firms must work out to have greater control over aseptic practices, specifically to maintain product sterility and environmental monitoring. Any finding of a sterility violation will shake the confidence of the regulator and result in a shutdown of the US market.

Root causes of WLs in sterile facilities are shown in the fault tree diagram below Figure 18:

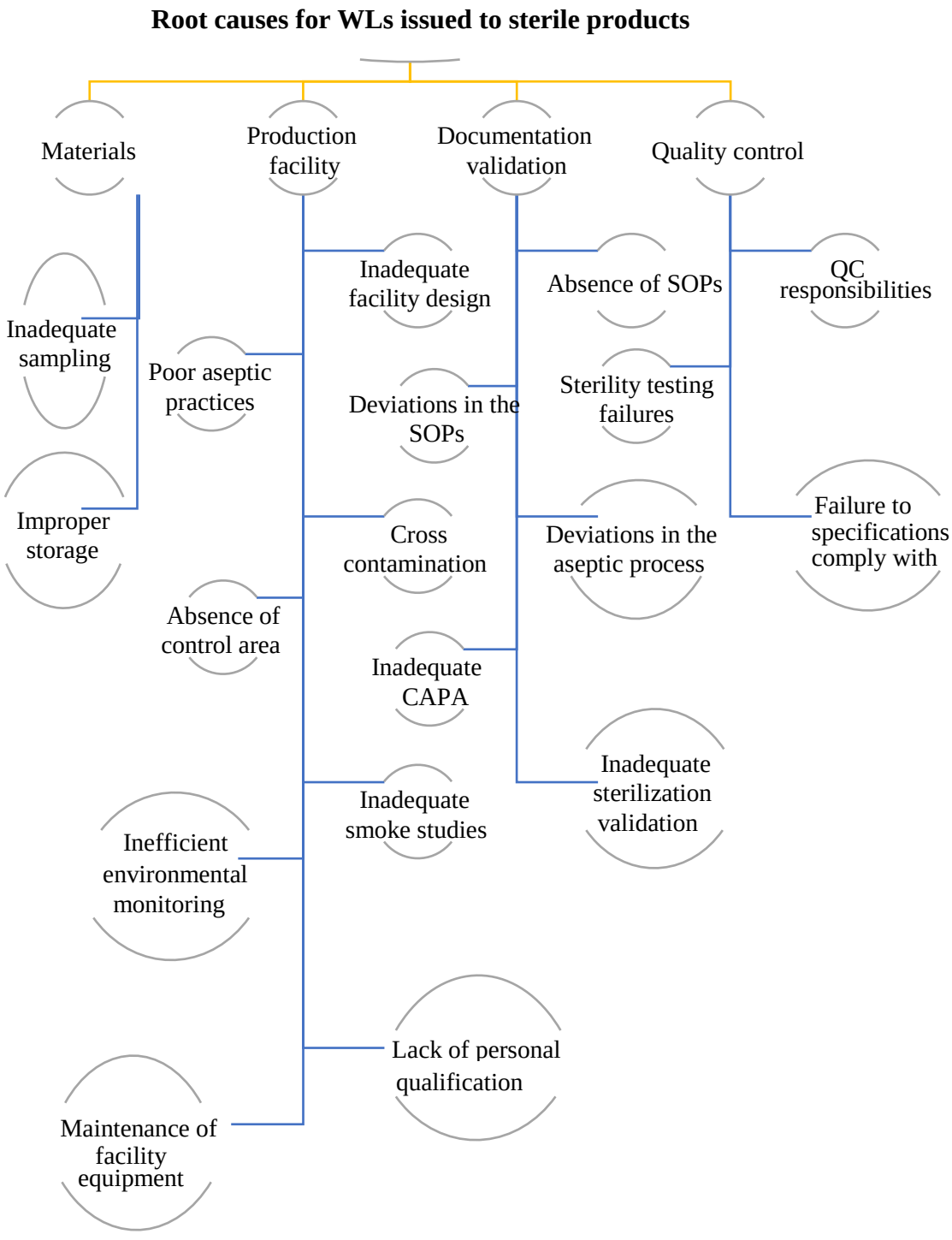


Figure 18: Fault tree diagram showing root causes of WLs for sterile product facilities

A paradigm shift in quality culture is needed to reduce WLs related to sterile products. Companies must further control aseptic technique and microbial contamination. Interactions during inspections should be completely transparent. Observed violations of the sterility assurance could undermine the regulatory confidence of the US FDA and lead to a reduction in the potential operations of the pharmaceutical industry in the US market. It is suggested that firms involved in the sterile product manufacturing that are not US FDA approved should also regularly review sterile product related WLs issued to other such manufacturers to understand and implement preventive measures to provide high quality products in the market.

Based on analysis of WLs issued to sterile products, specific guidelines are framed which may serve as an ongoing information of the most recent US FDA inspection and enforcement trends, specifically in the area of cGMP violations related to sterile products. Based on the WLs that are issued to manufacturers of sterile products, these guidelines may be revised after a period of every five years to keep them relevant and meaningful to the industry.

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Appendix I
Letter of Candidacy for Ph.D.

LOVELY PROFESSIONAL UNIVERSITY

Centre for

Research Degree Programmes

LPU/CRDP/PHD/EC/20210107/000529

Dated: 16 Sep 2020

Gambhire Hanumant Pandurang
Registration Number: 41900056
Programme Name: Doctor of Philosophy (Pharmaceutics)

Subject: Letter of Candidacy for Ph.D.

Dear Candidate,

We are very pleased to inform you that the Department Doctoral Board has approved your candidacy for the Ph.D. Programme on 16 Sep 2020 by accepting your research proposal entitled: "USFDA warning letters issued to pharmaceutical industries for cGMP violations pertaining to sterile products: Analysis and guidance"

As a Ph.D. candidate you are required to abide by the conditions, rules and regulations laid down for Ph.D. Programme of the University, and amendments, if any, made from time to time.

We wish you the very best!!

In case you have any query related to your programme, please contact Centre of Research Degree Programmes.

Head

Centre for Research Degree Programmes

Note:-This is a computer generated certificate and no signature is required. Please use the reference number generated on this certificate for future conversations.

Appendix II
List of Publications and Presentations

https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(4s) (December 2024); 11278 - 11289
Research Article

Guidance And Recommendations: Avoiding USFDA Warning Letters For cGMP Violation Pertaining To Sterile Products

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Abstract The US FDA released guidelines for industry over 20 years ago. The guidance was titled "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice September 2004". The scope of this guideline is limited; it does not address all aspects of sterile product, including product processed by TS processing. The guidelines mostly deal with cGMP issues related to finished products, but they do not go into detail beyond the upstream bulk processing. The expectations of regulators and the procedures currently followed for sterile product facility inspections are not covered by this guidance. To enhance understanding of the requirements for inspections of sterile product facilities, US FDA did not organized any training courses in specifically in India where largest sterile facilities are located. Furthermore, there are no reports of Indian firms taking up any effort to provide this kind of training. Thus, guidelines needs to be introduced in order to address the challenges that sterile manufacturers are experiencing right now. Based on review of WLs issued to sterile products, a brief guideline is prepared. The guideline provides essential recommendations for sterile product facility inspections and can be used as a manual for preventing cGMP violations pertaining to sterile products.
The guideline addresses several important topics pertaining to sterile products, for which the US FDA often issues warning letters:

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1. Introduction

Sterile products are intended for direct administration into the human body and are thus critical for human health. Due to high demand of sterile products including vaccines owing to recent pandemic of COVID-19, the focus on manufacture of sterile products has enhanced. Due to this, the regulatory

authority from the US, US Food and Drugs Administration (US FDA) has also increased its focus on quality of such products through strict compliance of cGMP requirements. US FDA issues warning letter upon any noncompliance observed during the inspection of sterile product facility resulting in imposition of import ban and recall of sterile products from market. The non-compliant firm incurs financial loss as well as loss in customer faith on their entire product range. Besides, the resulting shortage of sterile products results in unavailability the product to the public. For analysing the causes for such cases, warning letters were accessed from US FDA website and sorted for sterile products manufacturers. A total of 120 warning letters were found to be related to sterile products. A review of WLs over the past 14 years shows that the pharmaceutical industry needs to improve its quality systems and enhance its knowledge of handling sterile products. Firms must work towards the direction of exercising greater control over aseptic practices, specifically to maintain product sterility and environmental monitoring. Any finding of a sterility violation is expected to shake the confidence of the regulator and result in a shutdown of the export to US market. Based on analysis of WLs issued to sterile products, a comprehensive guideline document is drafted which may serve as a document to follow to avoid cGMP violations pertaining to sterile products.

3. Glossary

3.1 Air lock: A small room that is generally composed of interlocked doors, constructed to maintain air pressure control between adjoining rooms. The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area. The air balance for the biosafety facility should be established and maintained to ensure that airflow is from areas of least- to greater contamination.

3.2 Action level: Established criteria of microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

3.3 Air cleanliness level: A quality which indicates the condition of cleanliness of a monitored item, expressed as number of particles larger than 0.5 µm permitted per m3. It is classified in grades A, B, C, and D according to the required particulate number in the air.

3.4 Alert level: Established criteria of microbial or airborne particle level (and microbial species if necessary) giving early warning of potential drift from normal conditions.

3.5 Aseptic filling: A Part of aseptic processing where sterilized products are filled and/or packaged into sterile containers and closed under Grade A area.

3.6 Aseptic processing: A method of producing sterile products in which sterile bulk product or sterile raw materials are compounded and filled into sterile containers in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

3.7 Aseptic processing area (APA): Controlled environments, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate number to acceptable levels. APA is consisted of "critical (processing) area" and "direct support area."

3.8 Barrier: A physical partition to protect direct intervention of operating personnel in a controlled environment.

3.9 Bioburden: Population of viable microorganisms which may be present in non-sterile drugs or materials including intermediate products and raw materials.

3.10 Biological indicator (BI): Microbiological test system providing defined resistance to a specified sterilization process under defined conditions to be used as an indicator for the sterilization cycle efficacy.

3.11 Change control system: A formal system planned and designed to assess all changes that might affect the quality of pharmaceutical product to be intended to ensure the maintenance of process control

3.12 Chemical indicator (CI): Test system that reveals change in one or more process variables based on a chemical or physical change resulting from exposure to a sterilization process.

3.13 Clean area: An area maintained and controlled to prevent contamination of pharmaceutical products with microorganisms or foreign substances, in compliance with defined particle and microbiological cleanliness standards. For the purposes of this document, this term is synonymous with manufacturing area for aseptic products.

3.14 Colony forming unit (CFU): Visible growth of microorganisms arising from a single cell or multiple cells.

3.15 Critical area: A limited processing area where sterilized containers, raw materials, intermediate products or the surface of equipment that comes into contact with sterilized product is exposed to environment. This area is also known as the "critical processing area."

The level of environmental cleanliness of this area is commonly referred to as Grade A.

3.16 Critical processing: A process that can affect one or more critical quality attributes of a pharmaceutical product.

3.17 Culture conditions: Stated combination of conditions, including the type of medium and the period and temperature of incubation, used to promote microbiological growth.

3.18 Decontamination: A process that reduces or removes contaminating substances to a defined acceptance level using a reproducible method.

3.19 Design qualification (DQ): Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

3.20 Direct support area: A background area directly supporting the critical area. Sterilized products are not directly exposed to the environment in this area. This quality of the environment is commonly referred to as Grade B.

3.21 Disinfection: A process by which environmental or equipment bioburden is reduced to a safe level or eliminated.

3.22 D value: A value indicating the extinct rate of microorganism. The time or radiation dosage required to achieve inactivation of 90% of a population (one tenth of the survival rate) of the test microorganism under stated exposure conditions.

3.23 Endotoxin: Lipopolysaccharide constituting of outer membrane of Gram negative bacteria and may have pyrogenic reactions and other biological activities to humans.

3.24 Environmental monitoring program: A system to plan, organize and implement all the activities to achieve and maintain the required levels of air and surface cleanliness in the manufacturing areas. The intent is to manufacture aseptic pharmaceutical products in high quality level, by foreseeing deterioration of environments in manufacturing areas, preventing bad influence to the quality of products, and performing appropriate cleanliness control through a proper monitoring of the manufacturing environment.

3.25 Heating ventilation and air condition (HVAC) system: An air handling system including heating, ventilation, and air conditioning.

3.26 High efficiency particulate air (HEPA) filter: Air filters designed to retain particulates of larger than a certain size with defined efficiency. The filter retaines particles of ≥ 0.3 μm size with a minimum efficiency of 99.97%.

3.27 Indirect supporting area: An area where containers, raw materials, and unsterilized intermediate products are exposed to the environment and where materials and equipment used for aseptic processing are cleaned.

3.28 Installation qualification (IQ): Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.

3.29 Integrity test for containers: Test for confirming container's closure integrity as a part of stability testing for sterile products until the use.

3.30 Integrity test for filter: A non-destructive test which is used to predict the functional performance of a filter.

3.31 Isolator: A sealed and sterilized enclosure capable of preventing ingress of contaminants by means of total physical separation of enclosure to the surrounding exterior environment, An isolator's air supply is filtered using HEPA or ULPA grade filters.

3.32 Gas filter: Hydrophobic filters equipped in compressed air pipe lines for the porpose of removing microorganisms and particulates from gases.

3.33 Leak test: A test performed to verify that air leak from equipment/ devices and the container closure system that require to maintain sealing performance remains within the specified limits.

3.34 Material safety data sheet (MSDS): A specific document that shows important physical and chemical characteristics of a chemical or product to alert a user, transporter or other interested party to potential safety hazards that may be associated with the material. An MSDS is a legal requirement under "Pollutant Release and Transfer Register" for all aspects of commerce involving chemicals designated in the ordinance as Class I Designated Chemical Substances, Class II Designated Chemical Substances and products containing these substances.

3.35 Microorganism: General term for bacteria, fungi, protozoa and virus. Microorganism indicates only bacteria and fungi in this text.

3.36 Operational qualification (OQ): Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

3.37 Overkill sterilization: A process which is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1.0 minute, regardless of bioburden count in the product being sterilized or the resistance of the objective microorganisms to the sterilization.

3.38 Performance qualification (PQ): Documented verification that the equipment and ancillary systems, as when operating together, can perform effectively and reproducibly based on the approved process method and specifications.

3.39 Process parameter: Specified value for a process variable.

3.40 Process simulation test or media fills: One of the processing validations employed to evaluate the propriety of the aseptic processing of pharmaceutical products using sterile media instead of actual product.

3.41 Pure steam: Saturated steam that is generally produced using purified water or water of better quality and will then be condensed into such high grades of water that meet the criteria for water for injection under Pharmacopoeia.

3.42 Quality system: Organizational structure, procedures, processes and resources needed to implement quality management.

3.43 Restricted Access Barrier System (RABS): An integrated system that possesses aseptic processing areas (critical areas) and is composed of some critical elements such as rigid wall enclosure (often equipped with gloves), unidirectional airflow least- to through HEPA filters and appropriate operation procedures.

3.44 Sanitation/sanitization: Hygienic means of facilities and equipment by disinfection, cleaning, hot waters, etc.

3.45 Standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain Standard Operating Procedures (SOPs) may be used to supplement product-specific master and batch production documentation.

3.46 Sterile: Free from viable microorganisms.

3.47 Sterility assurance level (SAL): Probability of a single viable microorganism being present in a product unit after exposure to the proper sterilization process, expressed as 10-n.

3.48 Sterilization: A process that destroys or eliminates all microorganisms which is used to render a product free from viable microorganisms.

3.49 Sterilizing filter: Either hydrophilic or hydrophobic filter to perform as required should be demonstrated through bacterial challenge testing. The filters should retain specified numbers of indicator bacteria under specified conditions. The nominal pore size of the filters ranges from 0.20 to 0.22 µm.

3.50 Terminal sterilization: A process whereby a product is sterilized in its final container or packaging, and which permit the measurement and evaluation of quantifiable microbial lethality. Typically, the sterility assurance level should be less than 10-6.

3.51 Unidirectional airflow: Air flow which has a singular direction of flow and may contain uniform velocities of air flow along parallel flow lines.

3.52 Working shift: Scheduled period of work or production, usually less than 12 hours in length, during which operations are conducted by a single defined group of workers.

4. Guidance and recommendations

4.1. Responsibilities of quality control unit (21 CFR 211.25)

In the pharmaceutical industry, quality control (QC) plays a vital role since it ensures that the pharmaceutical products are safe, effective, and complies with the predetermined specifications before the products are distributed in market. QC role should involves:

i. Effective QC systems and SOPs should be established in order to prevent microbiological contamination during processing of sterile drug products
ii. The quality system should include an audit process to detect deficiencies in the sterilization process and to evaluate uncontrollable deviations from standard procedures
iii. SOPs should be available with defining role and responsibilities for analysing, approving and rejecting the incoming material as well as finished product
iv. Training records of each employee engaged in quality control activity should be up to date
v. Risk management process should be in place to reduce the risk of microbial, endotoxin and particulate matter contamination of medicinal products
vi. Documentation management system should consist change control, SOP, process flow chart, testing process for intermediate products, finished products, equipment and equipment layout drawings, calibration data, EM data
vii. QRM (Quality Review Management) system should be in place to review periodic quality documents

4.2. Personnel qualifications (21 CFR 211.22) In a sterile area, personnel qualifications is crucial because it ensures that non-measurable factors like behaviour,

hygiene, attitude, and sensitivity are taken into account. In microbiological labs and sterile injectable facilities, personnel qualification is applicable to the aseptic processing and sterility testing sections. The essential components listed below should be taken into account for personnel qualifications:

i. Employees involved in the operation and monitoring of sterile pharmaceutical products must have the necessary education, training and experience to perform their duties

ii. The largest source of microbial contamination in sterile processing areas of manufacturing operations is humans. Therefore, human intervention should be minimized to eliminate the source of contamination. Employees must follow the hygiene rules iii. SOPs for aseptic processing should be prepared and implemented. The SOP should include a detailed description of the tasks that personnel must perform during aseptic procedures

iv. A training program should be developed and implemented for personnel involved in the production of sterile product

v. Employees should be trained for proper hand washing, changing and disposal procedures before entering and exiting a sterile workplace

4.3. Design and construction features (21 CFR 211.42)

21 CFR Part 211.42 on buildings and facilities mandates the proper design of production facilities. A facility qualification (FQ) ensures that an area, room, or building has the utilities and environmental conditions required for product manufacturing. Following are the prerequisites that must be met before producing a commercial product:

i. Buildings and facilities should be constructed appropriately and their ceilings should not leak. The wall should be smooth and dust should not accumulate on the wall/ceiling, and should be easy to clean

ii. A suitable and isolated area must be available to perform all necessary operations to prevent contamination or mixing during sterile product activity

iii. Temperature and humidity should be controlled to meet product storage needs.

iv. SOPs for cleaning and sterilization of products containers closures should be available

v. The pressure limits for critical areas (preparation, filling and sealing area) should be appropriate and established based on the worst case-criteria considering risk of contamination

vi. HEPA filter integrity must be maintained to prevent contamination

vii. Compressed gases used in sterile areas must be inert, clean, i.e. free of oil and condensation. Compressed air and nitrogen must be filtered through a pre-filter.

viii. In sterile areas, drainage is not recommended due to the risk of microbial growth

4.4. Sanitation (21 CFR 211.56)

Maintaining sanitation during the manufacturing of sterile products is important for preventing contamination of products. The objective of sterile manufacturing is to make sure that the finished products are free from contaminants, microorganisms, and particulates. Below critical parameters should follow with respect to sanitation in sterile area:

i. Employees engaged for sterile products processing should not apply cosmetics or use ornaments (such as rings, earrings, watches)

ii. Employees should be trained for proper hand washing and cleaning. Supervisors should regularly evaluate their performance to ensure they are following established SOPs

iii. Untoward man movement in critical areas should be restricted

iv. Appropriate, clean gowns should be worn in critical areas where sterile products are processed

v. Direct contact to the sterile materials is to be done with sterile instruments

vi. In the sterile area, man movement should be slowly and deliberately as rapid movement can generate unacceptable turbulence thereby be disturbing unidirectional airflow in the sterile area

4.5. Equipment design, size, and location (21 CFR 211.63)

Sterile facilities are designed to prevent microbial contamination during the manufacturing, packaging, and filling processes. The equipment design, size and location in sterile facilities is important for preventing contamination of products and materials. The following basic requirements that can be maintained while designing the equipment, including its location and size: i. Equipment used for product processing should be non-reactive to the product and there should not be any incompatibility between drug and equipments

ii. Equipment and instruments used in the aseptic processing area should be qualified

iii. A calibration schedule including its frequency should be prepared and followed for analytical equipment in quality control as well as equipment used in the production process

iv. Qualifications and certification procedures for sterile workplaces and production equipment must be ensured

v. The training program should be available for handling/operating instruments and equipment

vi. Any untrained personnel, including vendor engineers shall be accompany by trained and qualified personal

4.6. Equipment cleaning and maintenance (21 CFR 211.67)

21 CFR 211.67 mandates that utensils and equipment in sterile facilities be frequently inspected, cleaned, and sterilized or sanitized. This procedure serves to avoid any contamination or malfunctions that can alter the drug product's identity, strength, quality, purity, or safety. The

general guidelines for equipment cleaning and maintenance in sterile facilities are listed below:

i. Equipment should be cleaned, stored and disinfected regularly to prevent product contamination
ii. Each equipment should be validated for the processes used for sterile drug process
iii. The equipment should be designed to be easy to clean, maintain and operate.
iv. The performance of equipment should be reviewed periodically to ensure these are working for its intended use
v. After sterilizing the equipment, the integrity should not be compromised during transportation from one room to another room for processing

4.7. Automatic, mechanical, and electronic equipment general requirements (21 CFR 211.68) 21 CFR 211.68 mandates that drug products can be manufactured, processed, packed, and held using automated, mechanical, or electronic equipment as long as it is regularly examined, calibrated, or checked in accordance with a defined procedure. It is also necessary to maintain written records of these inspections and calibration checks. The prerequisites must to comprise:

i. Sterilization equipment must be equipped with computer to ensure the recording of online process data.
ii. Computer system should have provisions to prevent unauthorized access.

4.8. Control of components and drug product containers and closures (21 CFR 211.80)

Regulation 21 CFR 211.80 requires that drug product components, closures, and containers be handled and kept in a way that reduces the risk of contamination. Contamination may occur through contact with unclean surfaces, exposure to external contaminants, and crosscontamination between products. Following specific recommendations are helpful in this particular circumstance:

i. SOPs describing the receipt, identification, storage, processing, testing, approval or rejection of containers and closures should be in place
ii. Containers, closures and other product contact component should be tested for microbiological testing before use, should be cleaned, washed and sterilized by validated process before use

4.9. Components, drug product containers, and closures (21 CFR 211.84/94)

21 CFR section 211.84 211.94 deals with testing and the approval or rejection of components, drug product containers, and closures. Containers and closures for drug products are covered under 21 CFR 211.94. Below outline a few requirements for drug product closures and containers:

i. Sterilized containers and closures should be protected from microbial or pyrogenic contamination by appropriate preventive measures
ii. The depyrogenation/sterilization process of container closures should be validated to achieve sterility assurance level

4.10. Written procedures; deviations (21 CFR 211.100)

Written procedures have become necessary in sterile facilities to ensure that sterile products are free from microbiological contamination. They also improve the quality of pharmaceutical items, which is necessary for maintaining their strength, identification, purity, and quality. The few essential suggestions in this regard are listed below:

i. Written manufacturing processes must be in place to ensure the identity, potency, quality and purity of the sterile product
ii. While various production and control process studies are carried out, documentation of the production process and control process should be followed and recorded when completed
iii. Any deviations in the process should be documented and justified
iv. Change management system should address atypical situations caused by the shutdown of air handling unit and other electronic equipment and assess the impact

4.11. Sampling and testing of in-process materials and drug products (21 CFR 211.110)

As part of regular manufacturing procedures, in-process testing verifies that the final product fulfils predetermined requirements for product quality. To evaluate the quality of the pharmaceutical product and regulate process parameters, samples are collected at different stages of the manufacturing process. Here is a crucial suggestion in this regard.

i. Quality and purity of the materials used in the process must be checked and approved or rejected by the quality control department
ii. During manufacturing of sterile product, the QC unit has to approve or reject products, which are under the process, regardless of whether it is at the beginning or end of critical stages. Testing is required to ensure the materials' identity, strength, quality, and purity. Rejected materials have to be stored in quarantine and kept out of manufacturing or processing

4.12. Time limitations on production (21 CFR 211.111)

Time limits play an important role in sterile facilities in order to minimize the growth of microbes in products. For example, extended filtration times in the pharmaceutical manufacturing process could allow products that promote microbiological growth. For this context, the following are the important recommendations:

i. While establishing the hold time for intermediate and bulk solution, critical quality attributes such as impurities, bioburden, endotoxins should be ensured

ii. Manufacturing of drugs solutions, filtration, and sterilization, as well as other manufacturing procedures, should be completed as soon as possible in order to produce sterile pharmaceutical products. The maximum period of time that can be allowed between filtration, storage, filling, and sealing should be established by evaluating the risks associated with each operation, as well as the manufacturing procedures, storage conditions

iii. While establishing the hold time for sterile product, critical quality attributes such as the endotoxins and bioburden must be assessed

4.13. Control of microbiological contamination (21 CFR 211.113)

Microbiological contamination is the most commonly violated aspect in sterile facilities. The US FDA recently sent WL to Kilitch Healthcare India Ltd. in March 2024 for cGMP violations, particularly for the company's failure to establish and follow standard processes in order to prevent microbiological contamination of sterile pharmaceutical products. The key recommendations in this perspective are listed below:

i. Sampling plans and testing procedures should be designed to produce sterile products, which maintains the sterility of the product throughout shelf life. Scientifically based specifications limits for microbiological tests should be in place

ii. Validation of sterility methods should include microbial testing to demonstrate reproducibility

iii. Sterile environment should be available for sterility testing of product.

iv. The EM location of critical areas should be defined in the SOP. The EM plan should include sampling of a variety of surfaces for microbial quality, including contact surfaces, floors, walls, and equipment, and should be tested regularly

v. Manufacturing process controls should be designed to minimize bioburden on unfiltered bulk and raw materials

vi. SOPs should be established to control unintentional introduction of microorganisms for sterile pharmaceutical products

vii. EM of non-viable particles should include worst-case area where there is most risk to exposed product, container and closures. Disinfectants used in critical areas should be in a sterile form to avoid contamination

viii. Any unexplained deviation or non-conformity to any of its specifications should be thoroughly investigated and documented

ix. Product process should be selected to have a low microbial load in the unfiltered bulk product. For example, for incoming raw materials, control limits for bioburden is to be required to avoid a sterility failure of the finished product.

x. Content of viable and non-viable particles should be monitored during environmental monitoring

xi. For sterile products, each operations involved in aseptic processing i.e. sterilization of equipment, components, packaging materials shall adequately validated

xii. An aseptic processing operation is also called as media fill should be performed to validate the process that involves all intervention covered in product processing including operator movement, number of operator, maintenance, stoppages, equipment adjustments, duration of product process

xiii. SOPs related to aseptic processing should be available

4.14. Labeling issuance (21 CFR 211.125) Labeling ensures product identification and is an aspect of trademark. Labeling that includes particular content determined by regulatory agencies or labeling and packaging that functions in a specific manner. Some recommendations are included below.

i. Issuance of product labels must be strictly controlled

ii. The information listed on the product must be independently checked and conform to the information listed in the batch manufacturing record

4.15. Expiration dating (21 CFR 211.137) Unopened sterile products must retain their quality throughout the duration of the declared expiration date. Drug applicants submit the stability results for supporting the suggested expiration date to the US FDA. The FDA determines that the applicant provides sufficient data to back up the requested expiration date. Here are some recommendations for expiration dating:

i. Drug product including packaging, raw materials and other materials must have an expiration date

ii. For the reconstituted at the time of dispensing, label must contain information about the in-use period after reconstitution and the expiration date of the reconstituted drug

4.15. Warehousing procedures (21 CFR 211.142) Proper storage of all the materials as well as finished product is essential to maintain their quality. The product should be stored according to prescribed storage conditions on the label. The following are suggestions regarding warehousing procedures:

i. SOP should be available for receiving, storage and issuance of all materials in warehouse

ii. Before release of materials, it should be quarantined and to be kept under restricted use

iii. Storage of drug products under appropriate conditions of temperature, humidity, and light to maintains its quality

4.16. General requirements laboratory control (21 CFR 211.160)

The US FDA issues WLs in case violations observed for the inadequate laboratory controls. Below are the recommendations to avoid the issuance of WLs:

i. The quality control unit should have the specifications of materials and finished drug products
ii. Sampling plans, procedure and standard testing procedures should be available in laboratory
iii. The SOPs should be available for laboratory personals with defined duties and responsibilities

4.17. Testing and release for distribution (21 CFR 211.165)

According to 21 CFR 211.165, QC must ascertain that each batch meets the final specifications prior to the release of a drug product in to the market. This includes each active ingredient's identification and potency. The recommendations for avoiding the issuance of WLs are listed below:

i. The SOPs or standard testing procedure must be available for testing of batches before release into the market
ii. Prior to release drug product batch in the market, each batch shall be tested and ensured for satisfactory compliance to predefined specifications

4.18. Stability testing (21 CFR 211.166) Inadequate stability studies that failed to provide a product's shelf life could result in a WL from the USFDA to the sterile facility. Below is a list of suggestions for preventing the issuing of WLs:

i. Written master stability plan should be available for each product to be placed on stability for determination of the shelf life/expiration dates
ii. Sufficient number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained
iii. Accelerated studies, photostability and thermal excursion studies shall be designed to determine the storage conditions of drug product

4.19. General requirements -records and reports (21 CFR 211.180)

General requirements for records and reporting are covered by 21 CFR 211.180. According to the regulations, industries must maintain the records that includes:

i. APQR i.e. annual product quality review system and process validations, trend report for critical quality attributes (CQA) should be available for each product
ii. Re-validation criteria should be defined in the process validation protocol and reports.

4.20. General recommendations during US FDA inspections of sterile facility.

Here are a few important recommendations based on the findings of the WLs and my own presence of sterile facility inspections in couple of Indian pharmaceutical Industries:

i. A brief introductory presentation can be made on the first day showing company history, compliance history, organization chart, number of employees, operating hours, product list, major equipment and computer/software list, and facility layout. This will assist the investigator in familiarizing themselves with the facility prior to commencing the investigation
ii. Before meeting the US FDA inspection team, discuss the question with the site staff in the "backroom" and prepare answers for it. Ask for clarification if a question or request is unclear. Listen carefully to what is being asked and answer the question directly. Do not delay or refuse to provide requested documents/data as this may lead to further legal action by the agency
iii. To ensure the timely completion and evaluation of all relevant activities and documentation, it is essential to assign an inspection readiness team along with an inspection coordinator
iv. The inspection coordinator should regularly take updates regarding assistance of operational plans to facilitate seamless inspection preparations and promptly address any arising issues
v. It is not uncommon for US FDA inspectors to request documents, particularly before an inspection. Investigators may expect the firm to have all necessary documents prepared on the initial day of the inspection. Document readiness before the start of inspection must be ensured
vi. US FDA inspectors have quite different preferences when it comes to document retrieval; some require both physical copies and electronic files, while others prefer electronic files. These requirements should be understood and preparations done accordingly
vii. As per the US FDA's Investigations Operations Manual (IOM), [i] it is advised that investigators make reasonable attempts to communicate all observations to facility management on a daily basis. This is done in order to minimize unexpected findings, mistakes, and misunderstandings when issuing Form 483.
viii. The discussion related to Form 483 observations should cover any notes made on the form and will only be addressed with management during the closing meeting. The company can use this time to ask questions about the observations, ask for clarification, and let the inspection team know what corrections have been, or will be, made during the inspection
ix. Ensure that the most senior employee in the facility is present during the final audit meeting. This shows that firms take the inspection outcomes seriously and are interested in learning more about the outcomes of the inspection so that deficiencies can be addressed
x. The US FDA typically allows 15 business days to respond to Form 483 comments. Form 483 observation should be communicated to a crossfunctional (CFT) team immediately
xi. Responses to observations should be as detailed as possible. If there is more than one part to an observation, respond to each part
xii. Responses to Form 483 must include corrections to any incorrect statements in the form. If possible,

explain how and why the current existing systems meet cGMP standards and therefore are not deficient. In the firm's response, provide the CAPA as well as a realistic timeline for completion of each CAPA action

4.21. Suggestions to the pharmaceutical manufacturers of the sterile products to avoid issuance of the warning letters due to the cGMP violations

Based on review of WLs issued to sterile products' manufacturers, above brief guideline document is prepared that provides essential recommendations and can be used as a manual for avoiding cGMP violations pertaining to sterile products. Along with the specific guidance for each issue, the following suggestions are recommended to the pharmaceutical manufacturers of the sterile products to avoid issuance of the warning letters due to the cGMP violations:

i. **Quality by Design (QbD) approach:** The focus needs to be shifted on comprehensive quality management rather than isolated, expedient compliance efforts. For this, the principles of QbD may be used to enhance the product and process quality. QbD involves thorough understanding of the processes involved. Objectives are defined before the actual start of process. Based on the real time risk assessment, implementation of QbD will help risk reduction. This in turn will help in avoiding the warning letters [ii,iii]

ii. **Automation:** Though regulatory authorities issue guidance documents on the topic of automation of processing as well as data management, the compliance continues to be poor.[iv] Automation uses technology to perform repetitive tasks quickly and accurately, eliminating the risk of human error. Automation enables companies to minimize human errors by eliminating manual activities in aseptic area. The use of automation, however, is not very common because of the high cost involved in automation and a general notion that no automated system can substitute for human supervision.[v] Awareness trainings for decision makers on resource constraints, explaining the cost of non-compliance vs. that of the cost of compliance using case studies, need to be conducted. On the other hand, while these innovations enhance efficiency and reduce the risk of human error, they also require a workforce that is adept at using them optimally. The need for ongoing training and development in new technologies will instill skill and confidence in the workforce that still feels intimidated by the rapid pace of change.[vi]

iii. **Use of artificial intelligence (AI) and Machine learning (ML):** The integration of advanced technologies, such as artificial intelligence (AI) and Machine learning (ML), into aseptic manufacturing processes is set to transform the regulatory compliance of the industry. AI and ML can support in dossier compilation, data retrieval and processing, auditing as per latest regulatory requirements, and even quality control. AI can also assist in identification of critical quality attributes (CQA), critical material attributes (CMA), and critical process parameters (CPP) by extensive analysis of earlier production datasets and scientific literature.[vii]

iv. **Trained personnel**: Aseptic manufacturing is a critical process in the production of sterile products. As demand for sterile products continues to rise, so does the need for skilled professionals in aseptic manufacturing. However, there is a lack of adequately trained professionals who possess the necessary skills in aseptic techniques and sterile processing.[viii] Most of the training programs offered frequently do not fully address the complexities of aseptic manufacturing, leading to a gap between industry needs and workforce capabilities. Recruitment, training and engagement of the right people for aseptic process operations will avoid the issuance of warning letters. The US FDA needs to work with industry to train people in the finer nuances of the process so as to avoid the issuance of WLs.

v. **Formation of expert committee:** Establish an indigenous expert committee of sterile product facility pre-audit from the professionals of sterile product manufacturing firms who can share their expertise and experience with the industry. This committee may provide insight into the expectations of the US FDA for facility audits and how to overcome warning letter issuance[ix]

4.22. The changes need to be done in cGMP to avoid the warning letters

As indicated by the addition of 'c' indicative of the word "current", before GMP, cGMP is constantly evolving and pharmaceutical companies are expected to stay updated with the latest changes to ensure compliance. Following are the changes that may be done in cGMP to avoid the warning letters:

i. The cGMP regulations require that training be conducted on cGMPs on a periodic basis. However, the cGMP guidelines are complex, and quite exhaustive. Training on cGMPs is not adequately imparted in terms of frequency as well as extent. Hence there is need of changes in cGMP to have continuous trainings on cGMP from the USFDA on the key areas such as facility design, aseptic practices, good documentation and laboratory practices. Furthermore, these trainings should include the lessons learned and remedial programs put in place by other company who had warning letters and are now compliant with the cGMP (as case studies).

ii. The study of USFDA warning letters pertaining to sterile products reveals that the top reasons for issuance of WLs include the poor environmental monitoring,

lack of sterility assurance and poor aseptic practices. Hence, there is need of bring change in cGMP with respect to detailed process for environmental monitoring to introduce continuous microbiological environmental monitoring, thereby reducing interventions and future replacement of Grade A settle plates and non-remote active air sampling. The replacement of traditional monitoring with biofluorescent particle-counting systems provides an improvement in process understanding and product safety and reduces operator manipulations, assuring product quality and real-time process verification.[x]

iii. Artificial intelligence (AI) has emerged as a powerful tool that harnesses anthropomorphic knowledge and provides expedited solutions to complex challenges. Remarkable advancements in AI technology and machine learning present a transformative opportunity in the drug discovery, formulation, and testing of pharmaceutical dosage forms.[xi] Hence it is need to bring a change in cGMP to introduce continuous processing executed with the assistance of AI. Environmental monitoring (EM) requires the introduction of the AI concept, which will allow automated data collection and interpretation of EM samples, generate precise, usable data for prompt decision-making, and enhance data integrity (DI) and also compliance through the use of auditable electronic records[xii]

4.23. The reasons why pharmaceutical companies are not able to comply requirements of US FDA but easily comply with requirements of other countries including India The GMP requirements of US FDA and other countries including India for manufacturing of sterile products are broadly similar except for environmental factors and water system. The guidelines from these countries are focused on high quality requirements for the manufacturing process for sterile products. USFDA focuses more on clean area classification, microbial monitoring, validation aspects and personnel training. In spite of similar GMP requirements, the reasons why pharmaceutical companies are not able to comply requirements of USFDA but easily comply with requirements of other countries including India Are mentioned below:

i. The US FDA GMP inspections are considered as more stringent and they take quick enforcement actions such as issuing warning letters, import alerts or initiating product recalls. US FDA inspections typically include extensive review of documentation and focus on holistic Corrective and Preventative Action (CAPA) and remediation plan against any deviations of the process whereas Indian and other countrys' GMP inspections are considered as relatively flexible and focused on end product quality

ii. Lack of up-to-date knowledge of the USFDA cGMP requirements seems to be another reason for higher non-compliance issues. Employees are generally not very well aware of the USFDA requirements that are relevant to their jobs. This may result in inadvertent non-compliance. On the other hand, Indian regulatory agency, Central Drugs Standard Control Organization (CDSCO) is situated in India and their experts are readily available for responding to queries raised from the Indian manufacturers. No training programs from USFDA are conducted in India for imparting the awareness to the drug product manufacturers with respect to current expectations of GMP practices

5. Summary and Conclusion

Pharmaceutical industry involved in the manufacture of sterile products across the globe has been receiving a number of WLs from the US FDA. This phenomenon has, however, increased in recent years, which is a major concern for the pharmaceutical industry worldwide. Because sterile products are administered directly into human blood, any compromise in the quality of such products poses a very high risk to the patients. In light of this, any WLs received in context to sterile products assume much higher significance. There are several available studies on WLs issued by the US FDA. However, there are no specific reports on WLs associated with sterile products.

The study observed that a larger number of WLs were issued to drug product as compared to devices and biologics product. The major reasons for this were poor cGMP compliance related to sterile product. Content analysis of reviewed WLs issued to pharmaceutical manufacturers shows that US FDA closely monitor operations of quality control unit, validation of manufacturing process, and data record and integrity**Error! Bookmark not defined.**.

The major findings of WLs evaluations indicate that there are significant cases of cGMP violations resulting in sterility breach and other non-compliance issues with the sterile product market. Various cases demonstrate the current state of cGMP through risk assessmentbased problem detection, classification of data by nonconformance type, and audit to determine the cause of the nonconformity. Frequent data breaches, human error, lack of training, and improper use and maintenance are reasons for deviations from many cGMP regulations. Thus, if cGMP labs are well managed in a strict control of EM, they would be able to improve quality and eliminate the risk of sterility failures.

Our study shows that the pharmaceutical companies must improve their quality systems and expand its knowledge of handling sterile products. Firms must work out to have greater control over aseptic practices, specifically to maintain product sterility and environmental monitoring. Any finding of a sterility violation will shake the confidence of the regulator and result in a shutdown of the US market. Root causes of WLs in sterile facilities are shown in the fault tree diagram below:

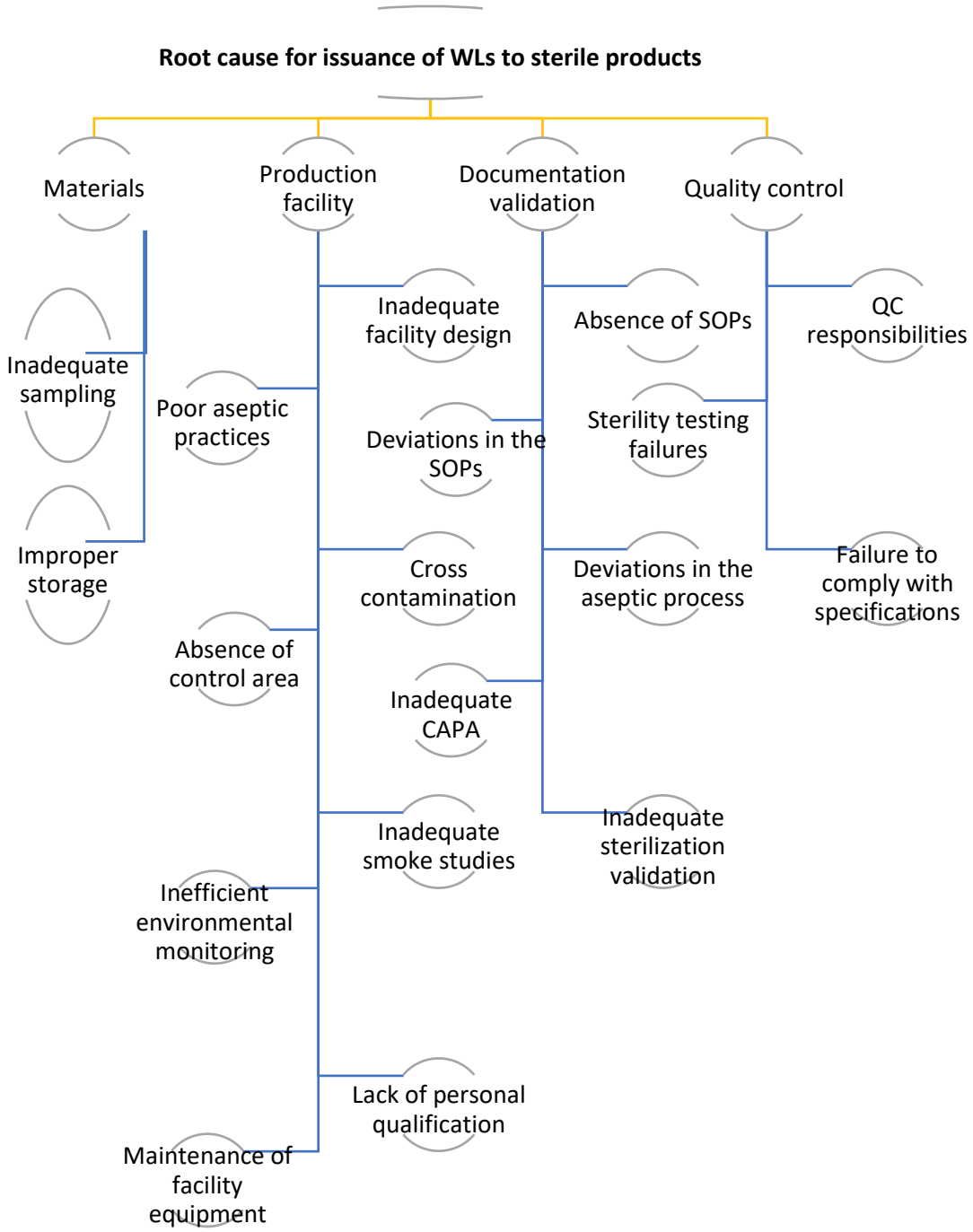

Figure 1: Fault tree diagram showing root causes of WLs for sterile product facilities

A paradigm shift in quality culture is needed to reduce WLs related to sterile products. Companies must further control aseptic technique and microbial contamination. Interactions during inspections should be completely transparent. Observed violations of the sterility assurance could undermine the regulatory confidence of the US FDA and lead to a reduction in the potential operations of the pharmaceutical industry in the US market. It is suggested that firms involved in the sterile product manufacturing that are not US FDA approved should also regularly review sterile product related WLs issued to other such manufacturers to understand and implement preventive measures to provide high quality products in the market.

Based on analysis of WLs issued to sterile products, specific guidelines are framed which may serve as an ongoing information of the most recent US FDA inspection and enforcement trends, specifically in the area of cGMP violations related to sterile products. Based on the WLs that are issued to manufacturers of sterile products, these guidelines may be revised after a period of every five years to keep them relevant and meaningful to the industry.

Reference Guidance Documents

Some relevant FDA guidance documents include:

1. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice September 2004

2. Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
3. Guideline for Validation of Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices
4. Guide to Inspections of Lyophilization of Parenterals
5. Guide to Inspections of High Purity Water Systems
6. Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories
7. Guide To Inspections of Sterile Drug Substance Manufacturers
8. Pyrogens: Still a Danger; (Inspection Technical Guide)
9. Bacterial Endotoxins/Pyrogens; (Inspection Technical Guide)
10. Heat Exchangers to Avoid Contamination; (Inspection Technical Guide)
11. Compliance Program Guidance Manual 7356.002 A, Sterile Drug Process Inspections
12. ICH Q5A, Guidance on Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
13. See also the draft guidance Container and Closure Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, which was issued in 1998. Once final, it will represent the Agency's thinking on this topic.

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Impact of USFDA Warning Letters on Economic Growth of Indian Pharmaceutical Industries

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Abstract:

The drug companies which sell their medicines in the United States are expected to adhere to the regulations which are entailed by the FDA. The manufacturing units which are engaged in the supply of drugs are frequently inspected by the FDA. Common issues for pharmaceutical industries around the world (including US and India) include inadequate or poor quality systems implementation, data integrity issues, inadequate validation of various processes used in manufacturing or testing, and product contamination. In any region, some drug manufacturers meet US requirements, while others do not. When USFDA determine that there are significant violations at pharmaceutical industries, USFDA take appropriate action to protect the public health through issuing waring letters(WLs) and enacting import alerts to the drugs manufacturing units resulting the financial loss. The WLs not only impacts particular industry but it has direct implications on society where the lot of human being earnings are directly or indirectly depends on the pharmaceutical industries. The

Indian pharma firms need to persistently evolve with the variations in the global regulatory compliances and accordingly adjust cost and resources to adhere to those standards. The overall economical impact of issued WLs on the pharmaceutical industries are to be studded in the article.

Keywords: Warning letter; Import Alert; economical impact, global pharmaceutical industries

Introduction

The US FDA (Food and Drug Administration) is the agency responsible for regulating the pharmaceutical market in the US, aiming to safeguard the health safety of the consumers. The Federal Food, Drug and Cosmetics Act is the basic food and drug law followed in the country.

The United States is the world's leading pharmaceutical market. The US pharmaceutical industry, as the largest, most diverse and globalized industry, is the economy's most competitive and vital sector. Therefore, exporting to the US is a great opportunity that is leveraged by many nations, and to verify the quality standards of medicines, the US FDA was created.

Every pharmaceutical drug marketed in the US has to pass through an approval process, which comprises four stages, viz. pre-clinical, clinical, new drug application review and post marketing. The various types of applications that need to be submitted to the US FDA for drug development and approval include:

- New Drug Application (NDA)
- Investigational New Drug Application (IND)
- Abbreviated New Drug Application (ANDA)
- Over-the Counter Drugs (OTC)
- Biologic License Application (BLA)

NDA is the primary means by which a drug sponsor puts forward to the US FDA for approval of marketing and sales of the drug in the United States. The entire information and data collected while the animal studies and human clinical trials are conducted constitute a part of the New Drug Application

According to the Federal Law, the marketing application of a drug must be approved, before it can be transported or distributed across state lines. Nevertheless, the sponsor of an investigational drug is likely to ship the drug to clinical investigators across various states. So, the Investigational New Drug application is the means by which a pharmaceutical company acquires the permit to ship an experimental drug across state lines (typically to clinical investigators) prior to the approval of marketing application of the drug. The three types of INDs include an Investigator IND, Emergency Use IND and Treatment IND.

For marketing a generic drug, companies need to submit the Abbreviated New Drug Application to the FDA to gain approval. These applications are referred to as ‘abbreviated’

as there is no compulsion of incorporating the preclinical (animal) and clinical (human) data to demonstrate safety attributes. The matter of concern for the drug companies is to confirm scientifically that the performance of their product is comparable to that of the innovator drug.

Over the counter drugs, which refer to the drugs which are available to patients without the need of a prescription, constitute a substantially important segment of the American healthcare market. There exist greater than 80 therapeutic categories of OTC drugs, extending from drugs for the cure of acne to weight loss. CDER's Office of Drug Evaluation IV is essentially responsible for the assessment of the OTC drugs. FDA evaluates the active ingredients and the labelling of more than 80 therapeutic varieties of drugs such as analgesics or antacids, rather than reviewing individual drug products. FDA has developed an OTC Drug Monograph for each category of these drugs, which is published in the Federal Register. Firms undertaking the manufacture of biologics for sale in interstate commerce are expected to hold a license for the product. These products receive an approval for marketing under the provisions of the Public Health Service Act. The application requires

Regulatory Compliance

Regulatory compliance has emerged as a critical challenge for the pharmaceutical industry, particularly in the regulated markets. Noncompliance is cost intensive, and may expose the companies to revenue losses, reputational risks, patient safety issues, criminal sanctions, and can jeopardize the future of the entire business unit. Compliance issues facing the pharmaceutical industry include government policies, drug safety, counterfeiting, information security and privacy, intellectual property protection, corruption and adulteration, and other third-party risks.

Under such a scenario, meeting the evolving regulatory stipulations such as Current Good Manufacturing Practices (cGMPs) should be given prime importance by the pharmaceutical companies. Along with addressing the emerging legal requirements, the companies need to lay emphasis on following the policy of substantial compliance and risk management. The Indian pharma firms need to persistently evolve with the variations in the global regulatory compliances and accordingly adjust cost and resources to adhere to those standards.

The pharmaceutical firms should be facilitated with an updated repository enumerating regulatory requirements notified by each country's regulatory organisation. The repository can be formulated in a manner that lists down the common requirements as well as the variations in standards, such that minimum set of regulatory adherence can be identified to address the compliance across various global agencies. For ensuring the compliance to standards, skill development of various stakeholders is crucial. Preparedness and proficiency in documentation and following statistical techniques as per regulatory requirements are also of considerable importance in this regard. Moreover, to demonstrate and justify that the manufacturing process being applied by the firm is in compliance with good manufacturing

practices, it is essential for them to have a comprehensive record of their production information, which can be presented to the inspectors and auditors.

Warning Letter:

The manufacturing units which are engaged in the supply of drugs are frequently inspected by the FDA. At the completion of the inspection, if the investigator concludes that there exist violations of the Food Drug and Cosmetics Act, then a FDA Form 483 is issued to the management of the concerned firm. The FDA expects a response to the Form 483 observations within a period of 15 days. In the circumstance when the FDA is unsatisfied with the response furnished by the manufacturer in reply of the Form 483, then the FDA might issue a warning letter to the firm.

Import Alert: FDA Import Alert signifies that the product does not comply with FDA laws and regulations. As a result, the products will be detained at the border without physical examination, as there exist adequate evidence regarding the regulatory noncompliance of the product.

Import Alert:

This import alert represents the Agency's current guidance to FDA field personnel, regarding the manufacturer(s) and/or products(s) at issue. This alert is applicable when an evidence exists related to the marketing or promotion of unapproved drugs, to individuals residing in the United States. In this circumstance, the products should be considered for detention without physical examination.

Table 1: Implications of Violating GMPs

Business Loss	Issuance of warning letters can lead to product recalls or import alerts, as well as a fall in the stock prices of listed companies
Reputational Damage	List of companies violating guidelines are posted on a regulator's website, making the information publicly available, which can be further picked up by the media, thereby tarnishing the company's reputation
Regulatory Influence	Additional inspections can be carried by other regulatory bodies or customers tarnishing the company's reputation
Competitive Disadvantage	Competitors can leverage this opportunity to enhance their market share
Diversion to Remediation and Increase in Attrition Rate	Diversion of management and employees' attention from their daily activities, to focus on Corrective Action and Preventive Actions. The lengthy remediation process tends to cost time, money and often loss of talent

Source: Analysing the State of Data Integrity Compliance in the Indian Pharmaceutical Industry, EY

Indian Pharmaceutical Industry

India is a prominent and rapidly growing presence in global pharmaceuticals. It is the largest provider of generic medicines globally, occupying a 22% share in global supply by volume, and also supplies 64% of global demand for vaccines. India ranks 3rd worldwide for production by volume and 14th by value. India is the source of 60,000 generic brands across 60 therapeutic categories and manufactures more than 500 different Active Pharmaceutical Ingredients (APIs). The country is home to more than 3,000 pharma companies with a strong network of over 10,500 manufacturing facilities. The domestic pharmaceuticals market turnover reached $20.03 bn in 2021, up 9.3% from 2018.

Chinese Pharmaceutical Industry

The pharmaceutical industry of China is the second largest market in the world and the largest among the emerging countries. The pharma industry is valued at USD 135 billion in 2018 and is projected to touch USD 175 billion by 2022, with an annual growth rate of 6%. There are nearly 2000 pharma companies and over 5000 drugs manufacturers. The pharma companies in China are primarily involved in the production of generic medicine, active pharmaceutical ingredients, therapeutic medicines and traditional Chinese medicines. Over 90% of drugs registered in China are generic by nature. In the next decade, the global position of Chinese pharmaceuticals is likely to incline towards R&D from manufacturing.

Russian Pharmaceutical Industry

The pharma market of Russia is expected to touch USD 42 billion by 2022 with an annual compound growth rate of 14%. The domestic pharmaceuticals market of Russia is dominated by generic medicine, accounting to 70% of the Russian pharma industry.

Brazilian Pharmaceutical Industry

The Brazilian pharmaceuticals market is projected to touch USD 40 billion by 2022 with a CAGR of 7%. The market share for generic medicine in Brazil is over 33% in 2020. The focus of pharma companies in Brazil is shifting from generic medicine to innovative research.

South African Pharmaceutical Industry

The pharmaceuticals industry in South Africa is valued at USD 7 billion in 2020 with a CAGR of 9.2%. The generic medicine share in the South African pharma market is over 60% and the remaining 40% share is of originator drugs.

GCC Countries

The pharmaceutical industry in the gulf is still in the early development stages compared to international standards. Despite that, it is changing through reform and simplifying government regulations, increasing its efficiency and expanding the infrastructure of health care.

Population growth in the GCC will be a key growth driver for the pharmaceutical sector. Population is anticipated to expand from 37.5 million in 2021 to nearly 50 million in 2020. High levels of urbanization and a strong expatriate presence also support pharmaceutical sales growth in the region. Population aged 60 years and above is projected to increase from 1.9 million in 2012 to 17.8 million in 2050.The elderly population forms a big slice of the overall pharmaceutical spending in the GCC and will also drive growth.

The size of the pharmaceutical industry reached USD 8.5 billion by the end of 2012, compared to USD 7.7 billion in 2011. Saudi produces 59.4% of medicine in the region, followed by 18% in UAE, 9.2% in Kuwait, 5.6% in Oman, 4.5% in Qatar and Finally 3.1% in Bahrain. Health care spending in the GCC will increase as the sector grows, which will lead to a decrease in the percentage spent on pharmaceuticals compared to the total health care spending to match those of the developed world, expecting a decrease from 14.3% in 2010 to 12.4% by 2021.

Literature Review:

According to a recent blog by the USFDA, quality issues have been a major challenge for Indian Pharmaceutical sector **(USFDA, 2021)**. More than 42 warning letters have been sent to the manufacturing units last year. Since 2012, the USFDA inspections have been doubled in India and China, from 11 percent to 20 percent **(Export-Import Bank of India, 2020).** Apart from the quality related problems, the USFDA has additionally recognized the data integrity downside with the drug companies in India. As per the examination reports by the USFDA and MHRA over the previous few years, varied warning letters have been issued to organizations for lack of documented educational program as well. Further, there should be zero tolerance by the prime organization authorities to any non-compliance and ought to be cross practical coaching by the external consultants on the compliance matters.

The study by (**Bhatt et al.2012)** provides an insight on the inspection of Indian sites by the FDA which is still a huge challenge since Indian regulators use low stringent methods for audits and inspections, hence they underestimate the inspections carried out by the FDA. It has been reported that the inspections carried out by Indian regulatory bodies in the past have been inconsistent and moreover, duration of each inspection has also been insufficient to cover non-compliance. Inspections of clinical sites are made to safeguard the human rights, well-being, and safety of the participants involved in the FDA-regulated clinical trials, also to verify the reliability and accuracy of clinical trial information defer to the FDA, to evaluate the backup of clinical research, and to judge the compliance with the FDA's regulations which prevails the techniques of clinical trials.

However, **Patel et al., (2012)** have been reviewed to identify the challenges that the FDA faced as a result of limited resources available. The study highlights that the GDUFA fees

will facilitate the global inspections and provides the speedy and timely review of the generic applications. It also pointed out that the GDUFA statute is a ground-breaking for the generic industry and the main subsidy for American buyers, as it will step-up the market admittance of those drugs that are tiny in stock with the improved quality, consistency, thereby resolving the problem of drug shortages.

Additionally, a study by **(HDFC Bank Investment Advisory Group, 2017)** also highlight the increased cases of the big companies in India facing compliance issues like warning letters by the FDA and the surge of warning indicative of lacking implementation of cGMP standards in Indian Industry. Frequent inspections by the USFDA on the global facilities lead to the consistent and improved quality of medicines in supply.

The study conducted by **Deloitte, (2015)** has shown that India today have about 546 facilities approved by the USFDA, 857 facilities approved by UK MHRA and 1,295 facilities approved by the WHO-GMP. To manage such large number of facilities and its compliance standards, The USFDA has setup two local offices with the investigators in India to carry out the inspections. Many instances of the non-compliance have been found among Indian Pharmaceutical Industry pertaining to the manufacturing practices, data management, and quality control practices. In December 2021, three (3) Pharma companies had received the warning letters.

From the survey, it has been pointed out that most of the compliance challenges are typically due to the shortage of skilled resources, which might hamper the company's growth. Deloitte, (2015) it is important for the companies to work together with the regulatory bodies so as to set-up the training and the development courses to train the professionals. For this purpose now MNCs have established alliances with academic institutions for the research endeavors and the faculty development. But the recent the regulatory actions taken by the USFDA have brought these issues so as to take necessary actions in order to maintain the forthcoming compliance requirements. These compliance issues have greatly affected the Pharma stocks. It has been found that in the last one year BSE Healthcare has declined close to 4 percent.

Analysis, discussion and conclusion

An overview of Global Pharma Industry & India's Role Pharmaceutical industry globally during the year 2020 has been a bit sluggish. However, India's Pharmaceutical exports during Fy-21, has recorded a growth of over 18%, which happens to be the highest during the last seven years. Global market has recorded a turnover of $ 1265.2 billion during the calendar year of 2020(Source: Iquiva report on Global Medicines & usage trends) and has grown by just 1% with an incremental value of $12 bn. General grouping of different markets constituting global market is shown in the table below [https://pharmexcil.com/uploads/annualreports/17thAnnualReport.2021Final.pdf]

Group	**$ bn**

Developed Market	959.5
Pharma Emerging (India is a part of this)	290.8
Rest	15
Global market	1265.3

In the next Five years Global market is forecasted to grow at a CAGr of 3-4% and touch $1,600 billion by 2025,which would be an increase of around $ 350 billion in value.

India's Role in Global Pharma

India is predominantly a generic Player. India during Fy-21 has exported $18.85 billion with a growth of 19.53% which is over six times the global generic estimated growth rate. India's Pharma Industry during 2020-21 has touched $ 49 billion (domestic and Exports). India's Pharma exports during 2020-21 was $24.47 billion comprising of Bulk Drugs, Finished dosage formulations, Ayush& Herbals &Surgicals . India's Pharma exports contributed 8.38% of Merchandise exports. Drug formulations & Biologicals is the second largest Principal commodity being exported by India. Eight of India based companies feature among top 20 Generic companies in the world based Calendar year of 2019 turnover. They are as follows. (Sourced from generics bulletin/informa Dated December 2020).

India Based Companies Featuring among top 20 Generic companies $ Million			
S.No	**Rank**	**Company**	**Turnover $ Million**
1	6	Sun Pharma	4539
2	8	Aurobindo Pharma	3257
3	11	Cipla	2360
4	12	Dr.Reddy's Laboratories	2311
5	13	Lupin	2135
6	14	Intas	2108
7	16	Zyduscadila	1692
8	20	Glenmark	1471

India's Pharmaceutical industry during 2020-21 has produced $40.85 billion worth of finished dosage forms of Generics, out of which $ 18.85 billion has been exported and is self-sufficient as far as generic formulations are concerned. However, India Imported Bulk Drug & Drug Intermediates (Mostly Lower intermediates) to a tune of $ 3841 million.

India is the largest exclusive generic exporter in the world.

USFDA has Granted 1438 market authorizations in Fy-21. Out of these India based companies have bagged 36% of them. India houses 741 Drug manufacturing facilities registered with USFDA. Following are Top Ten formulation exporting countries

Top Ten formulation exporting Countries $ Mn						
Rank	**Country**	**2017**	**2018**	**2019**	**Change%**	**Cont bn%**
1	Germany	56961.31	65338.68	60111.28	1-8.00	13.91
2	Switzerland	42152.05	46136.43	48552.34	5.24	11.23
3	Belgium	34508.94	36229.25	40091.69	10.66	9.28
4	France, Monaco	28244.62	31178.96	33052.77	6.01	7.65
5	USA	27369.25	29194.60	31648.88	8.41	7.32
6	Ireland	24754.31	30868.20	26666.31	-13.61	6.17
7	Italy	20337.26	21303.39	26310.45	23.50	6.09
8	United Kingdom	27075.72	25260.68	23357.81	-7.53	5.40
9	Netherlands	16145.64	18408.62	20435.75	11.01	4.73
10	India	12773.85	14116.80	15966.50	13.10	3.69
	World	**387759.50**	**420164.53**	**432157.05**	**2.85**	**100.00**

Source: Uncomtrade

The analysis of the FDA warning letters of the last 10 years (January 2010 to Dec 2021) issued to Indian pharmaceutical industries is undertaken for evaluation to see the economical impact. The details of warning letters pertaining to Indian pharmaceutical industries are summarized in below Table 3.

Table 3. Summary of Warning letters issued by US FDA to Indian Pharmaceutical Industry

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
	3015394334	Biotek India	05/13/2021	613295
	3009876430	Shilpa Medicare Limited	10/09/2020	607877
	3007187282	Panacea Biotec Pharma Limited	09/25/2020	607837
	3010910756	Mayon'S Pharmaceuticals Pvt Ltd	09/04/2020	607388
	3003227156	Mylan Laboratories Ltd. (Unit 7)	08/20/2020	607508
	3003821988	Wintac Limited	08/13/2020	606700
	3016998483	Kegan Wellness	07/13/2020	608737
	3015658387	Vega Life Sciences	06/17/2020	604469
	3011108348	Dr. Dhole's Sushanti Homeopathy Clinic	05/04/2020	607348
	3009167769	Kumar Organic Products Limited	04/23/2020	598683
	3002808145	Shriram Institute for Industrial Research	04/15/2020	597629
12	3016551424	Alpha Arogya India Pvt. Ltd. (The	04/13/2020	606253

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
		GBS Group)		
13	3016601904	Homeomart Indibuy	04/01/2020	605888
14	3008316085	Pfizer Healthcare India Private Limited	03/24/2020	594972
15	3005339091	Windlas Healthcare Private Limited	03/10/2020	595494
16	3014466792	ESSND GLOBAL	02/14/2020	595850
17	3009223273	JHS Svendgaard Hygiene Products Ltd	02/13/2020	593473
18	3004081307	Cipla Limited	02/12/2020	597511
19	3008311641	Gpt Pharmaceuticals Private Ltd	12/17/2019	590938
20	3002785310	Mylan Laboratories Limited (Unit 8)	11/05/2019	589297
21	3002984011	Cadila Healthcare Limited	10/29/2019	584856
22	3005029956	Torrent Pharmaceuticals Limited	10/08/2019	585255
23	3005757050	Glenmark Pharmaceuticals Limited	10/03/2019	582701
24	3002807511	Lupin Limited	09/10/2019	572345
25	3012390454	Lantech Pharmaceuticals Limited	08/08/2019	580027
26	3005151215	Emcure Pharmaceuticals Limited	08/02/2019	576961
27	3006254924	CTX Lifesciences Private Ltd.	07/12/2019	577416
28	3006644152	Indoco Remedies Limited (Plant I)	07/09/2019	575313
29	3012448465	Strides Pharma Science Limited	07/01/2019	576722
30	3004611182	Aurobindo Pharma Limited	06/20/2019	577033
31	3005269310	Rxhomeo Private Limited	06/13/2019	575889
32	3009729392	Glint Cosmetics Pvt Ltd	05/31/2019	573468
33	3008342939	Centurion Laboratories Private Limited	05/04/2019	571255
34	3006217304	Contacare Ophthalmics & Diagnostics	04/23/2019	570360
35	3010212308	B. JAIN PHARMACEUTICALS PRIVATE LIMITED	03/21/2019	567957
36	3006895982	Jubilant Generics Limited	03/06/2019	569799
37	3008386908	Pfizer Healthcare India Private Ltd.	03/04/2019	557890
38	3007450508	Anicare Pharmaceuticals Pvt Ltd.	02/28/2019	569251

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
39	3003090962	Vipor Chemicals Private Ltd.	01/29/2019	555392
40	3003658163	Skylark CMC Private Limited	12/03/2018	567229
41	3004974700	Wilson Medicine Company	09/11/2018	557206
42	3006076314	Apotex Research Private Limited	08/09/2018	547439
43	3005543404	P Banerji Mihijam Pharmaceuticals	08/07/2018	547958
44	3011783104	JT Cosmetics & Chemicals Pvt Ltd.	07/27/2018	554478
45	3004610460	Baxter Pharmaceuticals India Pvt Ltd	07/05/2018	543187
46	3011543431	Reine Lifescience	05/09/2018	548293
47	3009336980	Goran Pharma Pvt Ltd	04/24/2018	545331
48	3003677831	Keshava Organics Pvt. Ltd.	03/15/2018	540146
49	3005115135	Malladi Drugs & Pharmaceuticals Ltd.	03/09/2018	541915
50	3005216842	Alchymars ICM SM Private Limited	02/16/2018	542879
51	3007931994	Fleming Laboratories Limited	02/14/2018	537647
52	3006210232	Fresenius Kabi Oncology Limited (Baddi)	12/18/2017	526863
53	3003519498	Fresenius Kabi Oncology Ltd	12/04/2017	538641
54	3004819820	Lupin Limited	11/06/2017	532465
55	3007549629	Lupin Limited	11/06/2017	535014
56	3006370331	Kim Chemicals Private Ltd.	10/16/2017	535531
57	3007474872	Vital Laboratories Pvt Ltd Plant II	10/11/2017	527253
58	3008307735	Hetero Labs Limited (Unit V)	08/15/2017	520359
59	3003978209	Vista Pharmaceuticals Limited	07/05/2017	515652
60	3004982352	Vikshara Trading & Investment Ltd.	04/28/2017	516856
61	3003916387	Sal Pharma	04/20/2017	516205
62	3004149463	Divi's Laboratories Ltd. (Unit II)	04/13/2017	518434
63	3005124189	Indoco Remedies Limited	03/31/2017	514601
64	3005587313	Mylan Laboratories Limited	03/31/2017	517906
65	3004086192	USV Limited	03/10/2017	510159
66	3004058356	Badrivishal Chemicals & Pharmaceuticals	03/06/2017	511820

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
67	3006688078	Megafine Pharma (P) Limited	02/24/2017	510862
68	3004483648	Resonance Laboratories Private Limited	02/03/2017	511907
69	3006254924	CTX Lifesciences Private Ltd.	01/18/2017	496393
70	3002808500	Wockhardt, Ltd.	12/23/2016	495920
71	3005048741	Srikem Laboratories Pvt. Ltd.	11/10/2016	496015
72	3010532174	Pan Drugs Limited	08/25/2016	490052
73	3004414652	Unimark Remedies Limited	08/12/2016	483816
74	3008117347	Unimark Remedies Limited	08/12/2016	483816
75	3007931994	Fleming Laboratories Limited	06/21/2016	438607
76	3012278106	Anil Gangwani	06/02/2016	495560
77	3005694111	Megafine Pharma (P) Limited	05/19/2016	479195
78	3007287078	Polydrug Laboratories Pvt. Ltd.	04/14/2016	477491
79	3005280525	Sri Krishna Pharmaceuticals Ltd. - Unit II	04/01/2016	472869
80	3005151215	Emcure Pharmaceuticals Limited	03/03/2016	455201
81	3002807297	Ipca Laboratories Limited	01/29/2016	442963
82	3005977675	Ipca Laboratories Limited	01/29/2016	442963
83	3007574780	Ipca Laboratories LTd	01/29/2016	442963
84	3002984011	Cadila Healthcare Limited	12/23/2015	471062
85	3006595385	Cadila Healthcare Limited (Zyfine)	12/23/2015	471062
86	3002809586	Sun Pharmaceutical Industries Ltd.	12/17/2015	458804
87	3005447965	Dr. Reddy's Laboratories Limited	11/05/2015	481160
88	3002949085	Dr. Reddy's Laboratories Limited CTO VI	11/05/2015	481160
89	3006549835	Dr. Reddy's Laboratories Ltd.	11/05/2015	481160
90	3003737804	Sandoz Private Limited	11/02/2015	445532
91	3004944629	Sandoz Private Limited	11/02/2015	445532
92	3005202703	Unimark Remedies Ltd.	09/29/2015	429340
93	3003263118	Pan Drugs Ltd.	09/02/2015	446630
94	3007512701	Mylan Laboratories Limited	08/07/2015	464863
95	3003813519	Mylan Laboratories Limited (Sterile Products Division)	08/07/2015	464863
96	3007648351	Mylan Laboratories Limited, Speciality Formulation Facility	08/07/2015	464863

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
97	3004544153	Sipra Labs Limited	07/23/2015	431553
98	3003802404	Mahendra Chemicals	07/13/2015	438517
99	3005925733	Sharon Bio-Medicine Limited	06/22/2015	471663
100	3003978209	Vista Pharmaceuticals Limited	06/22/2015	471701
101	3006076314	Apotex Research Private Limited	01/30/2015	437669
102	3005210225	Micro Labs Limited	01/09/2015	437438
103	3004161432	Sharp Global Limited	10/15/2014	428474
104	3002806711	Cadila Pharmaceuticals Limited	10/15/2014	429369
105	3006257565	Amanta Healthcare Ltd.	08/26/2014	438593
106	3006257565	Amanta Healthcare Ltd.	07/08/2014	418268
107	3005466325	Apotex Pharmachem India Pvt Ltd.	06/16/2014	423752
108	3005409363	Sun Pharmaceutical Industries Limited - Karkhadi	05/09/2014	418746
109	3004896392	Smruthi Organics Limited	03/06/2014	416931
110	3003297374	Canton Laboratories Pvt. Ltd.	02/27/2014	413940
111	3003255171	Usv Limited	02/06/2014	413332
112	3002808503	Wockhardt Limited	11/25/2013	412858
113	3007648351	Mylan Laboratories Limited, Speciality Formulation Facility	09/09/2013	409756
114	3008250236	Sentiss Pharma Pvt. Ltd.	08/12/2013	398060
115	3006418686	Aarti Drugs Limited	08/02/2013	397189
116	3009688205	Aarti Drugs Ltd	08/02/2013	397189
117	3001329340	Posh Chemicals Private Limited	08/02/2013	398629
118	3005289335	Wockhardt Limited	07/18/2013	396819
119	3007972864	AMRUTAM LIFE CARE PRIVATE LIMITED	07/15/2013	395196
120	3003519498	Fresenius Kabi Oncology Ltd	07/01/2013	393890
121	3008386908	Pfizer Healthcare India Private Ltd.	05/28/2013	382438
122	3003269328	RPG Life Sciences Limited	05/28/2013	392574
123	3008314161	RPG Life Sciences Limited	05/28/2013	392574
124	3010004588	Discount Online Pharmacy	02/12/2013	392439
125	3009966662	buy-pharma.com	02/04/2013	391562
126	3003916387	Sal Pharma	05/30/2012	301698
127	3003263118	Pan Drugs Ltd.	02/28/2012	284758

Sr. No.	FEI Number	Firm Name	WLs Date	Case/Injunction ID
128	3003821988	Wintac Limited	02/23/2012	241074
129	3003747592	Xylo Chem Industries	11/16/2011	218896
130	3004896339	Yag Mag Labs Private Limited	09/12/2011	213033
131	3002984011	Cadila Healthcare Limited	06/21/2011	192132
132	3004021263	Aurobindo Pharma Limited, Unit VI	05/20/2011	180094
133	3008494993	Synbiotics Limited	12/16/2010	136712
134	3004610460	Baxter Pharmaceuticals India Pvt Ltd	11/01/2010	134950
135	3008299032	Choksi Laboratory	09/30/2010	135190
136	3004983128	Stericon Pharma Pvt. Ltd.	08/24/2010	122649
137	3008186667	Shreeji Homeo Clinic	04/13/2010	95710

Source:https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters

Exports of pharmaceutical products from Indian region to USA for the period of 2010-20 was evaluated as case study.

[Fiscal Year]	**Warning Letters-Global**	**WLs Count-(India)**	**India's exports to United States of America**
2010	669	2	1,656
2011	1738	3	1,543
2012	4891	2	2,417
2013	6766	8	11,155
2014	8800	4	44,684
2015	17238	11	68,251
2016	14586	8	97,641
2017	15326	9	98,059
2018	14483	4	98535
2019	15099	15	87154
2020	5512	8	101454
2021	294	2	Data not yet available

Total	105402	75	

Unit: US Dollar thousand, Source: ITC Geneva; Exim Bank Analysis

From the above data, it can be concluded that although there are WLs cases in India for the period of 2018-2020, in spite of this there is no impact on the exports ultimately the economical growth. This might be due to the exports was happened from the other pharmaceuticals where the WLs not imparted.

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AN OVERVIEW OF US FDA WARNING LETTERS TO INDIAN PHARMACEUTICAL INDUSTRIES FOR cGMP VIOLATIONS PERTAINING TO STERILE PRODUCTS

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ABSTRACT

Background: In the process to ensure the quality of pharmaceuticals, United States Food and Drug Administration (USFDA) notifies the manufacturers by the means of warning letters (WLs) in case of any significant violation of any of its regulations. For sterile products, careful compliance with Current Good Manufacturing Practices (cGMP) regulations needs to be done. Indian pharmaceuticals industries involved in the manufacturing of sterile products have been receiving a number of WLs from USFDA. This phenomenon has shown an upward trend in recent years. Increased number of warning letters to sterile product manufacturer is a matter of great concern due to the fact that any compromise in the quality of such products poses an exceptionally high risk to the patient, the product being generally administered directly into the human blood. It was, therefore, decided to analyze these letters and decipher the significant reasons for these WLs.

Methods: Publically available USFDA letters (available under the law of the freedom of Information Act) sent to various Indian pharmaceutical companies were accessed from the USFDA website. Letters were manually screened and those related to sterile products violations of cGMP were selected based on their subject and content. The typical data collection tool (Excel Spreadsheet) with all letters of warning issued from January 2010 to May 2021 was used.

Results: Overall, 105,402 warning letters for cGMP violations worldwide issued between January 2010 and May 2021 were reviewed. Out of these, Indian companies were found to have received 75 warning letters for the period from January 2010 to May 2021. Out of 75 warning letters issued to Indian pharmaceutical industries, 25 warning letters were found to be associated to sterile products, indicating that around 33% warning letters issued to Indian companies are associated with sterile products.

Conclusion: Studied letters indicate that the USFDA is applying a systematic approach while assessing cGMP compliance and paying very close attention to aseptic practices. Another significant conclusion is that the Indian pharmaceutical industry needs to pay greater attention to maintenance of quality checks in the aseptic processing of products.

Keywords- Warning letter; Sterile products; Import Alert; Indian pharmaceutical industries

INTRODUCTION

The United States Food and Drug Administration (USFDA) being the Federal agency of the Department of Health and Human Services in the Unites States of America enforces the regulatory guidelines on the conduct of clinical trials on humans, marketing authorization approval and post marketing surveillance related to the pharmaceutical products intended to be used for humans. It ensures the quality of drug products, medical devices, and dietary supplements by carefully monitoring compliance with Current Good Manufacturing Practice (cGMP) regulations and enforcing the regulatory framework.

As compared to other pharmaceutical formulations, the sterile products are considered to be the most precarious owing to their potential administration directly in to the blood stream. Pharmaceutical sterile products are generally intended to be used in the form of injectable, infusion and/or application to the eye.

The United States Pharmacopeia General Chapter <1211>, i.e., "Sterilization and sterility assurance of compendial articles", indicates that a specimen should be deemed sterile only if there is complete absence of viable microorganisms and visible particulate matter from the formulation. The chapter further states that the sterility of a batch, claimed to be sterile, defined in probabilistic terms, which means the likelihood of a contaminated unit or article is acceptably remote. The assurance of such state of sterility can only be established by the application of adequate number of sterilization cycles and subsequent aseptic processing under appropriate cGMP norms. The state of sterility can be expected not only by relying solely on sterility testing, but also on the proper validation of the sterilization process as well as the aseptic process. This, in turn, requires a high level compliance within the cGMP and thorough knowledge of sterilization process along with the concept of clean room.[i] It is pertinent to add here that the Corona Virus Disease (COVID19) pandemic has increased the demand of the sterile products including vaccines and injectable formulations of lifesaving drugs more than ever before.

CATEGORIES OF THE STERILE PRODUCTS

Based on various factors e.g. the volume to be administered, specific organ to be targeted and the method of sterilization employed to make the product free form the viable contaminants, the sterile products are divided into following categories:

- Small Volume Parenteral (SVP) and Large Volume Parenteral (LVP) [both aqueous and non-aqueous including oil-based products]
- Products processed by the different sterilization techniques, i.e., membrane filtration, moist and dry heat sterilization, ionizing radiation and, gaseous method of sterilization
- Ophthalmic formulations
- Topical impalpable formulations
- Aqueous solution-based inhalations
- Sterile Active Pharmaceutical Ingredients (APIs), sterile medical devices and sterile dusting powders.

In the event of any breach in the compliance of sterility in the above stated categories of the products, FDA issues Warning letters to the concerned facility. Although the issued warning letters to the production facilities are publicly available, no comprehensive reports containing a summary of the data related to the warning letters issued due to the non-compliance related to the sterile products are available. In the present investigation, an effort has been made to compile the data of warning letters issued by USFDA to the facilities, based on the issues raised/regulatory finding during the audits/inspections and deciphering them to suggest the required measures for avoiding any further non-compliance. It is expected by the USFDA that products' bio-burden should be evaluated in the sterile products before the release of the product to the public domain. As per the Code of Federal Regulation (CFR)211.113(b) of USFDA, Control of

Microbiological Contamination states that the "appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed". Such procedures should be inclusive of the validation of all aseptic and sterilization procedures. The cGMP regulations specify the minimum requirements for the methods, facilities, and control measures to be applied in the manufacturing, processing and packing of the sterile products. (https://www.cacmap.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/complianceactions-and-activities/warning-letters).

It has been reported in the literature that China and India were amongst the topmost countries which received the warning letters form the USFDA during the tenure of year 2015 to 2017. Apart from the above South Korea followed by Canada and Japan were the countries in the list. As a total percentage of the warning letters issued by USFDA, China and India together were accounted for approximately 80% of warning letters associated with import alerts. It recent years it has been observed that the trend of the issuance of letters by the USFDA has increased substantially for drug substance and drug products, whereas

the trend was found to be reversed in the case of medical devices and biological products. [ii]

Recommended methods for sterilization of the pharmaceutical sterile products

As recommended by the United States Pharmacopeia (USP) General chapter <1211>, "Sterilization and sterility assurance of compendia articles", and the literature reported by the various researchers, there are five methods of sterilization. These include:

Dry-Heat Sterilization

The method of dry heat sterilization works on the principle of denaturation of proteins of the cell wall of microorganisms with the application of the dry heat. The batch of the pharmaceutical products required to be sterilized is kept in the specially designed oven supplied with heated, filtered air distributed uniformly at the required temperature for a specific period of time as per the type of product.[iii] Using this method a microbial survival probability of 10^{-12} is achievable for heat-stable products. Although this method is effective, it suffers from certain limitations such as high sterilization time, warping or charring of heat sensitive material, damage of rubber and plastic closure systems and relatively poorer penetration of heat to denature of cell wall of microorganism as compared to the moist heat sterilization.

Although no warning letter issued to an Indian pharmaceutical company could be traced wherein discrepancy in dry heating cycles led to such an action by USFDA, a warning letter issued to Cytosol Laboratories Inc. was found wherein discrepancies in documentation of Sterilization Cycle Parameters have been mentioned.

Moist Heat Sterilization

Sterilization of the pharmaceutical products with the application of moist heat is carried out by employing saturated steam under specific pressure in a specially designed autoclave. The basic principle of sterilization by using this method is the denaturation of structural proteins and enzymes of the microorganisms. Though it is the most widely used method of sterilization, the heat sensitive products cannot be sterilized by this method. Moreover, it is time consuming and cumbersome in comparison to other heat sterilization methods. [iv, v] In November 2010, a warning letter was issued to Claris Lifesciences Ltd., Ahmedabad, Gujarat for failing in the calibration of thermocouples of the terminal sterilizers. During the validation process, the step of thermocouple calibration of the terminal steam sterilizers was found to be missing before as well as after the autoclaving cycles. [vi]

Gaseous method of Sterilization

Application of gas for the purpose of the sterilization of the pharmaceutical products is an alternate to heat based methods to overcome the limitations associated with them. It is generally used when the material to be sterilized is not capable of withstanding the high temperatures reached during the

processes of steam or dryheat sterilization. Ethylene oxide (EtO) is most commonly used in the process of gaseous sterilization. However, it is pertinent to add here that the gas used must be of acceptable sterilizing quality. [vii,viii] The biggest limitation of EtO is that it is highly flammable in nature. Because of this, it is generally mixed with suitable inert gases. Other limitations of EtO include its mutagenic potential, and the left over presence of its traces in the treated materials. The probability of retention of EtO residues is higher in materials containing chloride ions. The process of gas sterilization is generally carried out in a pressurized chamber which is quite similar in its design to an autoclave. However, certain additional features are included to ensure post sterilization degassing, to facilitate monitoring of any microbial residue, and to minimize exposure of operators to EtO. The program for qualification of a sterilizing process using EtO is more comprehensive than for the other sterilization procedures. This is attributed to the involvement of additional control of EtO concentration which requires a rigid monitoring. Adequacy of all critical process parameters in the chamber during the cycle must be demonstrated. [ix]

Though no WL issued to an Indian industry could be traced wherein discrepancy in gas sterilization led to such an action by USFDA, a WL issued to Cardiomed Supplies, Inc. was found wherein discrepancies in residual levels of EtO after sterilization have been found out. [x].

Sterilization by Ionizing Radiation

As certain articles like medical devices are not able to withstand heat sterilization and the safety of EtO sterilization in such cases is questionable, the need for radiation sterilization was felt. Radiation sterilization is also used for certain drug substances and final dosage forms. The major advantages of sterilization by irradiation are its low chemical reactivity, low residues, and less number of variables to control. The assessment of absorbed radiation, whose precise measurement is possible, is used to determine the sterilizing dose. Any additional controls and safety measures are still being evaluated with regards to this sterilization technique. Though the rise in temperature caused by Irradiation is generally minimal, it may affect certain grades of materials like plastics and glass. Ionizing radiations used for sterilization are categorized into two types, namely radioisotope decay (gamma radiation) and electron-beam radiation. Radiation dose in both the cases must be established for assurance regarding the required extent of sterility while the properties of the article being sterilized are preserved.[xi] Validation procedure of sterilization by gamma irradiation includes the establishment of following parameters:

- Compatibility with the article materials
- Pattern of product loading
- Mapping of dose in the sterilization container
- Identification of the minimum and maximum dose zones inside the sterilization container
- Establishment of timer setting, and demonstration of the
- Delivery of the required sterilization dose

Additional parameters in case of validation of electron-beam irradiation include the on-line control of voltage, current, conveyor speed, and electron beam scan dimension. In case of sterilization by gamma radiation, generally 2.5 megarads (Mrad) of absorbed radiation is used. It is, however, desirable in certain cases like those for devices, drug substances, and finished dosage forms to use lower doses. Another essential parameter to be kept in mind is the natural resistance of the microbial population present in the product to radiation. Specific product loading patterns must be established, and minimum and maximum dosage distribution absorbed must be determined by use of chemical dosimeters. Commonly used dosimeters include dyed plastic cylinders, slides, or squares that exhibit intensification of color in proportion to the amount of absorbed radiation energy. Preferred absorbed dose is set on the basis of pure cultures of resistant microorganisms and using an inoculated product like spores of *Bacillus pumilus* as biological indicators. A fractional experimental cycle approach provides the data to be utilized for determination of the D10 value of the biological indicator. This information is then used to extrapolate the amount of absorbed radiation to establish the appropriate microbial survivor probability. The natural heterogeneous microbial burden contained on the product

in question is considered to calculate the radiation dose in the procedures to be adopted for gamma radiation sterilization. Refinement of these procedures is still going on, especially to handle the issue of radiation-resistant organisms. These include inoculation with standard resistant organisms such as *Bacillus pumilus,* exposure of finished product samples taken from production lines and sub-lethal dose exposure. Exposing the article to a less than totally lethal sterilization dose eliminates the less resistant microbial fraction. This, in turn, results in a residual homogeneous population with respect to radiation resistance and yields consistent and reproducible results. In another approach, the resistance of the microbial population is not determined, and dose setting is based on a standard arbitrary radiation resistance assigned to the microbial population, derived from data obtained from manufacturers and from the literature. The assumption is made that the distribution of resistances chosen represents a more severe challenge than the natural microbial population on the product to be sterilized.

No WL issued to an Indian industry could be traced wherein discrepancy in gas sterilization leading to such an action by USFDA was reported.

Sterilization by Filtration

Filtration through microbial retentive materials is commonly employed for the sterilization of heat-labile solutions. This is achieved by physical removal of the contained microorganisms. A filter assembly consists of a porous material within an impermeable housing. Efficiency of a filter medium or substrate depends upon its pore size and sometimes on adsorption of bacteria to the filter matrix or even on the mechanism of filtration. Fiber-shedding filters, e.g. those containing asbestos, are to be avoided unless there is no alternative available. In such cases, wherein a fiber-shedding filter is used, it must include a nonfibershedding filter subsequent to the initial filtration steps.

Pore sizes of filter membranes indicate their capability to retain microorganisms of size represented by specified strains. Sterilizing filter membranes are membranes capable of retaining 100% of a culture of 107 microorganisms of a strain of *Pseudomonas diminuta* (ATCC 19146) per square centimeter of membrane surface under a pressure of not less than 30 psi (2.0 bar). Such filter membranes are labeled 0.22 µm or 0.2 µm, depending on the manufacturer's practice. Bacterial filter membranes capable of retaining only larger microorganisms are labeled as 0.45 µm. These are capable of retaining particular cultures of *Serratia marcescens* (ATCC 14756) or *Ps. diminuta*. Test pressures used vary from low (5 psi, 0.33 bar for Serratia, or 0.5 psi, 0.34 bar for *Ps. di*minuta) to high (50 psi, 3.4 bar)[xii] (Coté, 1999).

Though no WL issued to an Indian industry could be traced wherein discrepancy in sterilization by filtration led to such an action by USFDA, a WL issued to Abraxis Bioscience, Inc. was found to be issued in 2006 wherein discrepancies for not conducting bacterial filtration retention validation for aseptically filled products manufactured in their site have been found out. [xiii]

Aseptic Processing

Despite the fact that sterilization of the final filled container or final packaged device is the preferred process for ensuring the minimal risk of microbial contamination, a number of products cannot be subjected to terminal sterilization and need to be prepared by a series of aseptic steps. These are designed to prevent the introduction of viable microorganisms into components. An aseptically processed product consists of components that have been sterilized by any one of the sterilization processes. The most significant factor in aseptic processing is the environment to which these pre-sterilized components are exposed during the preparation and filling of the finished dosage form. An air environment free from viable microorganisms, a proper design to permit effective maintenance of air supply units, and the provision of trained operating personnel who are adequately equipped and gowned are the essential prerequisites to accomplish this process. The desired environment is achieved by the use of high-level air filtration technology to deliver the air of the requisite microbiological quality. The facilities require both primary as well as secondary barrier systems. Primary barrier systems are required in the vicinity of the exposed article while secondary barrier

systems are required where the aseptic processing is carried out. Significant features of aseptic processing facility include nonporous and smooth surfaces, including walls and ceilings amenable to regular sanitization; sufficient space for personnel and storage of sterile garments in the gowning rooms; sufficient separation of preparatory rooms for personnel from final aseptic processing rooms, availability of airlocks and air showers; proper pressure differentials between rooms, positive pressure in the aseptic processing rooms; laminar (unidirectional) airflow in the immediate vicinity of exposed product or components, and filtered air exposure with adequate air change frequency; humidity and temperature controls; and a documented sanitization program. Validation of the aseptic process and facility need to be done. Monitoring of the aseptic facility includes periodic environmental filter examination as well as routine particulate and microbiological environmental monitoring and sterile culture medium processing (https://www.fdalabelcompliance.com/letters/ucm076222).

In a warning letter issued to the Ankleshwar plant of Wockhardt Ltd. issued in December 2016, presence of air turbulence inside the laminar flow area led to the issuance of WL.[xiv]

Warning letters

A warning letter is an official message from the USFDA to a manufacturer or other organization that has violated some rule in a federally regulated activity. cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

As a part of verification of cGMP compliance, investigators from the agency perform inspections of the drug substance and drug product manufacturing sites. Mainly three types of inspections are conducted by the USFDA. These are:

Pre-approval inspection after a company submits an application to FDA to market a new product Routine inspection of a regulated facility

"for-cause" inspection to investigate a specific problem that has come to FDA's attention

During inspection, if any non-compliance is observed, the investigator issues the observation on form 483. Because of this reason, the observations are popularly known as 483 observations. The manufacturer then, has to submit a response within 15 calendar days explaining the reasons for existence of non-compliance, their impact on the product quality and appropriate corrective actions taken to avoid recurrence. In case the response is not found satisfactory or observations are critical in nature and have direct impact on product quality, patient safety and data integrity, the USFDA issues warning letters to the manufacturers. [xv]

USFDA Inspection

FDA ensures the quality of sterile products by carefully monitoring compliance with Current Good Manufacturing Practice (cGMP) regulations. These regulations contain minimum requirements for the methods, facilities, and controls used in the manufacturing, processing and packing of a regulated product. In short, cGMP rules ensure the safety of a product. FDA believes that the inherent flexibility of the CGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations. [xvi]

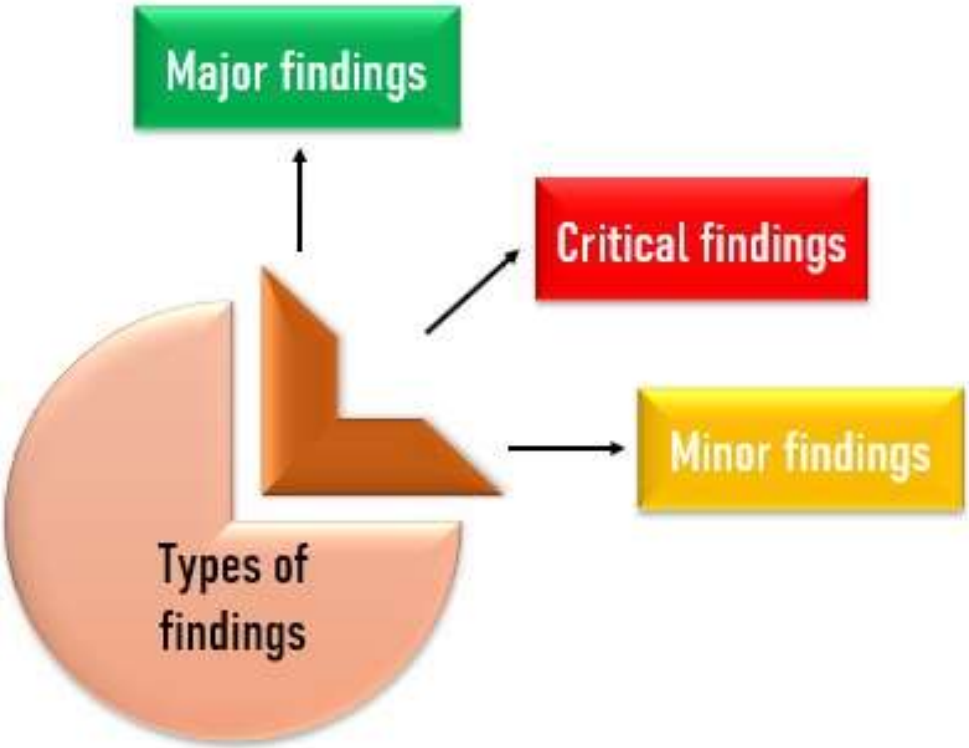

Figure 1. Types of finding during the USFD A inspections.

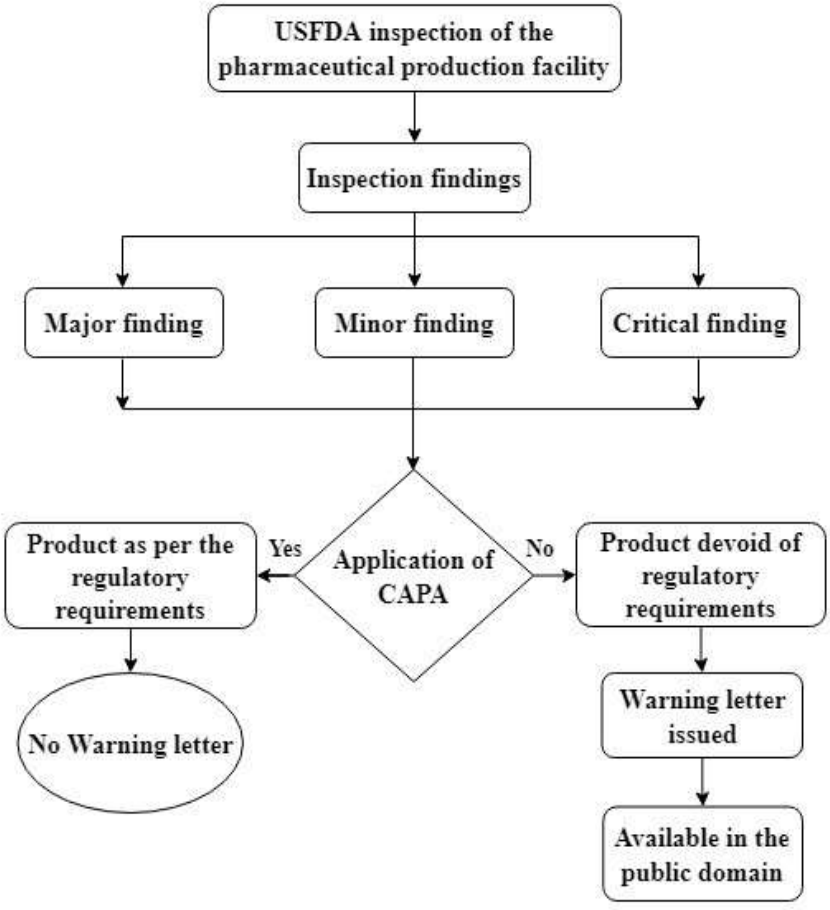

Figure 2. Overview of the process of USFDA inspection and issue of warning letters to facilities.

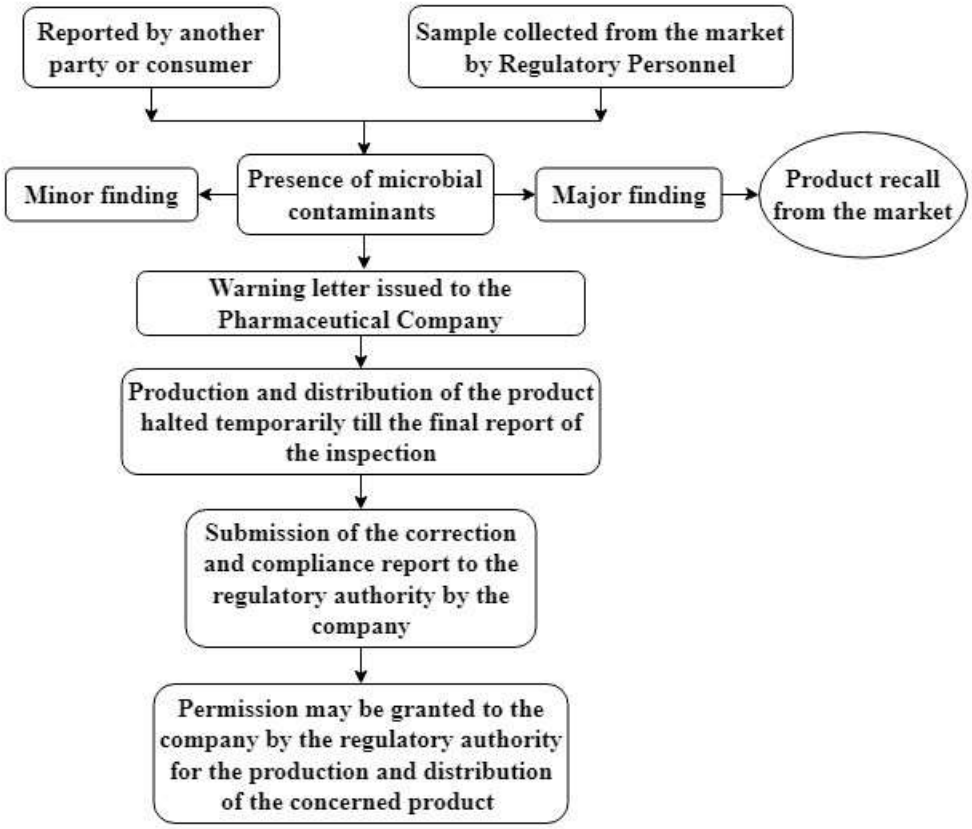

Figure 3.: Probable sampling strategies for sampling of products and inspection of facility.

Issuance of warning letters by the FDA Committee has increased drastically in recent years. Notably, there has been a significant increase in the number of warning letters referring to "data integrity" and "sterility assurance" in relation to environmental monitoring (EM). The increase is attributed to a stricter approach of the USFDA to infringement handling. Those of significance to the warning letter issued in year of 2016 to drug sector and relating to EM are highlighted in bold in Table 1.

TABLE 1. Warning letter issued in year of 2016 to drug sector and relating to EM

21 CFR211.22(D): The responsibilities and procedures applicable to the quality control unit are not writing or followed.
21 CFR211.160(B): Inadequate scientifically sound laboratory controls.
21 CFR211.192Failure to review investigation of discrepancies or batch failures.
21 CFR211.100(A): Absence of written procedures.
21 CFR211.42(C)(10)(IV): Aseptic processing areas deficient for environmental monitoring systems.
21 CFR211.68(A): Calibration, inspection, or checking is not done.
21 CFR211.165(A): Procedures designed for testing and release for distribution are not established, written, or followed.
21 CFR211.113(B): Equipment and utensils are not maintained at appropriate intervals to prevent problems that would alter the safety, identity, strength, quality or purity of the drug product.
21 CFR211.67(A): Equipment and utensils are not maintained or cleaned at appropriate intervals.
21 CFR211.166(A): There is no written testing program designed to assess the stability characteristics drug products.

21 CFR211.67(B): Written procedures not established and /or followed for cleaning and maintenance of material
21 CFR211.42©(10)(V): Aseptic processing areas are deficient regarding the system for cleaning and disinfecting to produce aseptic conditions.
*21 CFR211.68(B): Appropriate control are not exercised over computer or related system to assure that changes in **matter** production and control records or other records are institute only by authorized personnel*

Source: Accessed from https://www.pharmaceuticalprocessingworld.com/prevention-of-fda-483s-andwarning-letters-with-proper-aseptic-processes-and-environmental-monitoring/

The FDA expects that the product bio-burden be assessed and evaluated. CFR 211.113(b) Control of Microbiological Contamination states that the "appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed".
These procedures must include validation of all aseptic and sterilization processes. [xvii]

Microbiological Contamination Control (MCC)
Gilberto Dalmaso in 2017 reported that MCC must be established through detection testing so that the product meets microbiological quality standards (see USP 37, <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms).
A "specified" microorganism has several elements that require evaluation on a case-by-case basis for each drug manufacturer. The key elements to be considered include microbial species, number of microorganisms, dosage form, intended use, patient population, and route of administration. Four types of modern monitoring systems are in place that offer various limitations on personnel interaction with the product.
In traditional cleanroom production, the presence of people in a Grade A area is allowed, with a mandatory installation of a surrounding Grade B environment. In open Restricted Access Barrier Systems (oRABS), there is a physical separation of people from Grade A areas, but Grade A air is exhausted into Grade B. oRABs must be installed with a Grade B surrounding environment. In closed Restricted Access Barrier Systems (cRABS), there is a physical separation between people and Grade A production areas and Grade A air recirculation. cRABS must be installed with a Grade B surrounding environment.
In an isolator system, the production inside the isolator is completely separated from people and air circulation in a Grade A area. The isolator can be installed in a Grade C environment. Out of these, only the isolator system is capable of offering complete sterility assurance. However, with an increase in human intervention of the system, risk is enhanced while the ability to ensure a sterile final product is decreased. Only about 10% of pharmaceutical industries are reported to utilize isolators as part of their production process while some use traditional cleanroom techniques and the majority follows a form of RABS. Microbiological monitoring methods that offer advanced sensitivity with real-time results help in avoiding any interventions.[xviii] . Environmental monitoring systems constitute an integral part of the aseptic processing as they support in controlling the presence, distribution and a result, the survival of microorganisms. Critical factors, such as process waters (deionized, RO and WFI), air and compressed gases, working surfaces (personnel, gloves, equipment) constitute the critical features that should be the primary focus in a monitoring program. Early evaluation of the surface, personnel, and additional critical points of the aseptic manufacturing area prevents any need of corrective action. Additional benefits to a strong EM program include undelayed product release, enhanced efficiency and productivity (labor and time), overall cost reduction, and data integrity. [xix]
A recent warning letter to one of the manufacturers states that, "During our inspection, we reviewed reports from multiple investigations that you conducted into complaints regarding the presence of visible particulates in several of your sterile injectable products. The presence of visible particulates in sterile injectable products is an indication of a significant loss of control in your manufacturing

process and represents a severe risk of harm to patients. We documented that your investigations into these product
quality defects were inadequate and failed to spur appropriate corrective actions and preventive actions." [xx] In another warning letter, the FDA quotes 1,500 complaints from 2012 to 2016 related to leaking, underfilled or empty bottles of a sterile solution. In its root causes investigation, the company has indicated issues with the bottle within the filling process i.e. inappropriate filling when the bottle isn't correctly placed in the filling machine. Several manual interventions in the aseptic process were necessary, whereby defects haven't always been detected, particularly when cracks occur in the glass bottle under the cap. Moreover, such cracks may develop a few days after the filling process, as noticed in the investigation [xxi].

Analysis, discussion and conclusion

The analysis of the FDA warning letters of the last 10 years (January 2010 to May 2021) is undertaken for evaluation. The total list of warning letters issued to global industry is given in below in Table -2.

TABLE 2. Warning letters issued to global industry

[Fiscal Year]	Warning Letters
2010	669
2011	1738
2012	4891
2013	6766
2014	8800
2015	17238
2016	14586
2017	15326
2018	14483
2019	15099
2020	5512
2021	294
Total	105402

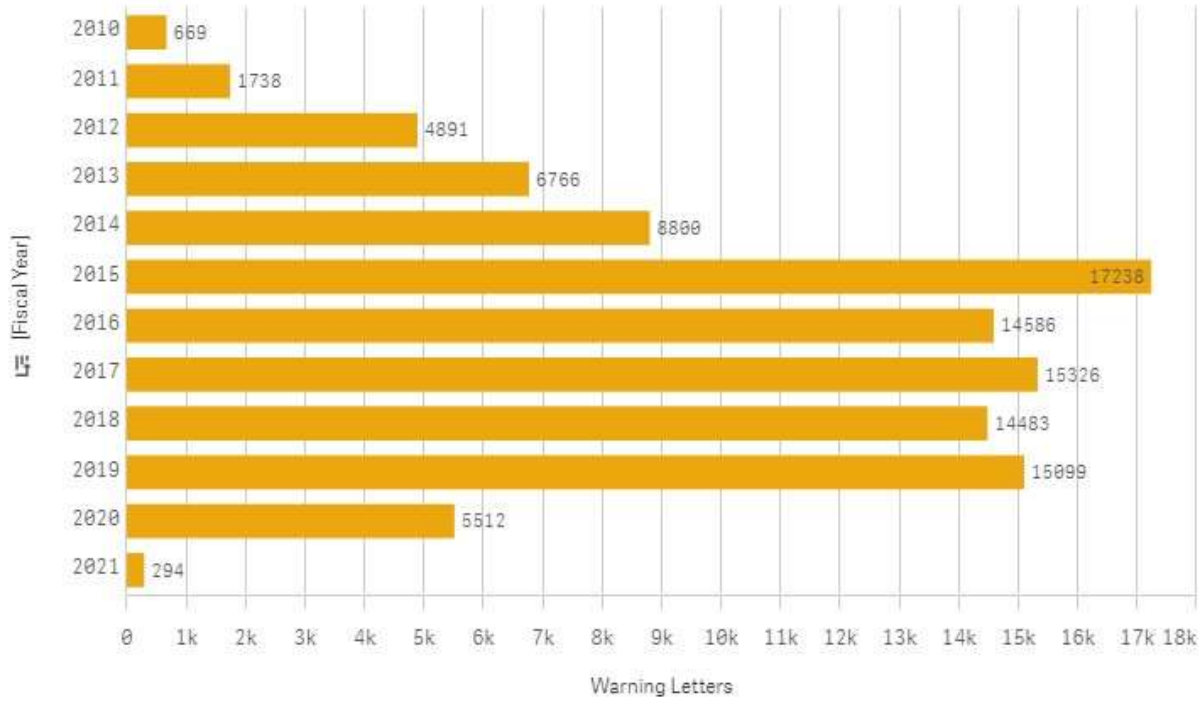

Figure 4. Warning letters issued to global Industry

From the data presented in table 2 (figure 4), it is appeared that no. of WLs decreased after 2015. We believe that the no. of WLs decreased after 2015 due to GADUFA (Generic Drug User Fee Amendments) implemented in July 2012.

The details of warning letters pertaining to sterile products manufactured in Indian pharmaceutical industries are summarized in below Table -3.

TABLE 3. Summary of Warning letters issued by US FDA to Pharmaceutical Industry (Global/Indian)

Year	WL count-global	WL count-India	Sterile drug related (India)	Company
2010	669	2	1	Claris Lifesciences Limited Chacharwadi - Vasana Ahmedabad, Gujarat 382 213
2011	1738	3	1	Cadila Healthcare Limited, located at Sarkhej Bavla N.H. No.8 A, Moraiya, Tal: Sanand, Dist. Ahmedabad, Gujarat382210
2012	4891	2	1	Wintac Limited located at 54/1 Boodihal Village, Nelamangala, Bangalore 562 123
2013	6766	8	3	Wockhardt Limited (FEI 3002808503) located at L-1, M.I.D.C. Area, Chikalthana, Aurangabad, Maharashtra Promed Exports Private Limited located at Promed Exports Private Limited, Khera Nihla Village, Tehsil Nalagarh, Solan District, Himachal Pradesh Hospira Healthcare India Pvt., Ltd., located at Plot No. B3, SIPCOT Industrial Park, Irungattukottai, Sriperumburdur Tamil Nadu
2014	8800	4	0	--

2015	17238	11	4	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway, Halol, Gujarat A. Dr. Reddy's Laboratories Limited CTO Unit VI, located at APIIC Industrial Estate, Pydibhimavarma (Village), Ranasthalam Mandai, Srikakulam District, Andhra Pradesh B. January 26-31, 2015: Dr. Reddy's Laboratories Limited CTO Unit V, located at Peddadevulapally Village, Tripuraram, Mandal, Miryalguda Taluk, Nalgonda District, Telangana; and C. February 26 to March 6, 2015: Dr. Reddy's Laboratories Ltd., Unit-VII located at Plot No. P1 to P9, Phase III, Duvvada, VSEZ, Visakhapatnam, Andhra Pradesh A. Mylan Laboratories Limited OTL, Plot No. 284-B (19A) Bommasandra Jigani Link Road, Ind. Area, Anekal Taluk, Bangalore, 560 105 B. September 23, 2014 through October 3, 2014: Agila Specialties Private Ltd., Specialty Formulation Facility (SFF) 19A, Plot No. 284-B/1 Bommasandra Jigani Link Road, Anekal Taluk, Bangalore, Karnataka C. August 1-8, 2014: Agila Specialties Private Ltd., Sterile
				Product Division, Opp II M, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka A. Sandoz Private Limited, MIDC Plot Nos. 8-A/2 & 8-B, TTC Industrial Area, Kalwe Block, Village Dinghe, Navi Mumbai, Maharashtra (Kalwe facility) B. August 12-28, 2014: Sandoz Private Limited, Plot Nos. D31 & D32, MIDC, TTC Industrial Area, Turbhe, Thane-Belapur Road, Navi Mumbai, Maharashtra (Turbhe facility)
2016	14586	8	2	Emcure Pharmaceuticals Limited, located at Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune, Maharashtra Wockhardt Limited, Plot No. 138 G.I.D.C. Estate District Bharuch, Ankleshwar, Gujarat
2017	15326	9	3	USV Private Limited at H-17/H18, OIDC, Mahatma Gandhi Udyog Nagar, Dabhel, Daman Indoco Remedies Limited, Plants II & III, L-32, 33, 34 Verna Industrial Estate Area, Verna, Goa Fresenius Kabi Oncology Ltd at D-35, Industrial Area, Kalyani, Nadia, West Bengal
2018	14483	4	2	Goran Pharma Private Limited at GDIC-I, Bhavnagar Road, Sihor, Gujarat Claris Injectables Ltd. at Ahmedabad, Gujarat

2019	15099	15	3	Hospira Healthcare India Pvt. Ltd., at Plots B3, B4, B5 (pt); B6 (pt); B11-B18 and B21-B23, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur, Tamil Nadu Emcure Pharmaceuticals Limited, located at Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune, Maharashtra Cadila Healthcare Limited, FEI 3002984011, at 419 & 420 8a Village-Moraiya, Ahmedabad, Gujarat
2020	5512	8	5	Cipla Limited, FEI 3004081307, at L138; Ll39 - 146; L147/A; L147/1 - 147/3; S103 - 105; S107 - 112; M61 - 63, Verna, Goa Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116-117-118-119-111-123 (part), Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam, Andhra Pradesh Wintac Limited, FEI 3003821988, at 54/1 Bodhihal Village, Nelamangala, Bangalore, Karnataka Panacea Biotec Limited, FEI 3007187282, at Tehsil Nalagarh, Village Malpur, Baddi, District Solan, Himachal Pradesh Shilpa Medicare Limited, UnitIV, FEI 3009876430, Plot No. S20 to S-26, Pharm, Formulation SEZ, TSIIC, Green Industrial Park, Polepally (Village), Jadcherla (Mandal), District Mahabubnagar, Telangana
2021	294	1	0	-
Total	105402	75	25	-

The findings of the warning letters associated to sterile drug products for the year of 2010-2021 has been studied, the summary of these is given in Table 4.

Table 4. Summary of Warning letters studied for the year 2010-2021

Sr. No	Letter Issue Date	Company Name	Crux of warning letter
1	01/10/2010	Claris Lifesciences Limited Chacharwadi - Vasana Ahmedabad, Gujarat	It lacks sufficient evaluation of several complaints of intravenous (IV) bag contamination Metronidazole Injection USP IV bags (lot A090744) were contaminated with a swirling mass, which the complainant identified as the fungus *Cladosporium* species The technician from the pharmacy observed that fungi were in the IV bag (as well as inside the overwrap)
2	21/06/2011	Zydus Group Zydus Tower Satellite Cross Roads Ahmedabad, Gujarat	The microbiological growth found on settle plate MS 4 was incorrectly identified and reported as a typical microorganism when compared against your firm's library/photographs of typical environmental flora Environmental monitoring is inadequate in relation to personnel monitoring Firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile
3	23/02/2012	Wintac Limited #163 Reservoir Street Basavanagudi, Bangalore, Karnataka	*In situ* air pattern analysis (smoke studies) does not demonstrate unidirectional airflow and sweeping action over and away from the critical processing areas under dynamic conditions An operator performing critical aseptic operations with exposed skin at the forehead, posing an unreasonable risk of the product becoming contaminated Operators moving very quickly in the aseptic area, which may create unacceptable turbulence in the area, and disrupt the unidirectional airflow

Sr. No	Letter Issue Date	Company Name	Crux of warning letter
			Operators leaning halfway in and out of the class 100 area while performing interventions over opened bottles
4	18/07/2013	Wockhardt Limited Biotech Park, Plot H-14/2 M.I.D.C. Area: Waluj Aurangabad, Gujarat	Incomplete training records were found for critical GMP activities, including: Handling of sterilized materials and materials to be sterilized Handling and transfer of media fill vials Line clearance for the manufacturing, filling, washing and sealing areas, sanitized container storage area and sanitization area
5	09/08/2013	Sentiss Pharma Pvt. Ltd. (formerly Promed Exports Private Limited) Khera Nihla Village, Tehsil Nalagarh, Solan District, Himachal Pradesh	The aseptic processing environment is not adequately monitored. For example, there is no viable air monitoring inside of the Class 100 (ISO 5) filling barrier on the "(b)(4) Line (b)(4)." This is the critical area where drug product and pre-sterilized components are exposed and it is important that your firm collect air samples that adequately represent filling conditions The environmental monitoring (EM) program is not adequate to ensure the environment is suitable for aseptic processing of sterile product. The data generated does not sufficiently demonstrate that an ISO 5 environment is maintained
6	28/05/2013	Hospira Healthcare India Pvt., Ltd., located at Plot No. B3, SIPCOT Industrial Park, Irungattukottai, Sriperumburdur, Tamil Nadu	Aseptic manufacturing interventions are not performed in a manner to protect sterile drug products from contamination No dynamic airflow studies (e.g., smoke studies) have been performed to demonstrate unidirectional airflow and to determine risk to product sterility for certain routine aseptic interventions
7	17/12/2015	Sun Pharmaceuticals Industries Ltd. Halol-Baroda Highway, Halol, Gujarat	Significant airflow turbulence, including air moving in an (b)(4) direction, in the laminar airflow (LAF) unit in which aseptic (b)(4) and tubing connections are made for the (b)(4) process. Also, the studies lacked dynamic simulation of this critical intervention No dynamic smoke studies to demonstrate unidirectional airflow during the manual aseptic transfer of (b)(4) units into the (b)(4) used for transport to the (b)(4) Inadequate evaluation of airflow patterns in your stopper (b)(4) area, and turbulence around the stopper (b)(4)
			Lack of smoke studies during aseptic filling line setup activities
8	06/08/2015	Mylan Laboratories Limited OTL, Plot No. 284-B (19A) Bommasandra Jigani Link Road, Ind. Area, Anekal Taluk, Bangalore, Karnataka	Non-integral (b)(4) gloves were used in Suites (b)(4) and (b)(4) for conducting aseptic processing operations Reviewed environmental monitoring (EM) data that showed excursions in your ISO 5 area, which you attributed to gloves. Finally, during the inspection, we observed unidentified white particles on (b)(4) gloves exposed to critical areas inside the Restricted Access Barrier Systems (RABS) There is a lack of assurance that you maintain your manufacturing environment in a state of control suitable for aseptic processing
9	05/11/ 2015	Dr. Reddy's Laboratories Ltd. 8-2-337, Road No 3 Banjara Hills, Hyderabad, Andhra Pradesh	During the filling operation, our investigator observed an operator repeatedly using forceps and an (b)(4) hand to (b)(4) the (b)(4) manually and align the (b)(4) with the (b)(4) conveyor belt. The operator intervened again to (b)(4) the (b)(4) onto the (b)(4) conveyor belt. Because the conveyor belt was not operational, an operator manually intervened to (b)(4) the vials into the (b)(4) loading area, where the (b)(4) the (b)(4) into the (b)(4) You did not simulate these critical manual interventions during media fills The media-fill records do not include reasons why filled vials were rejected
10	22/10/2015	Sandoz Private Limited, Plot Nos. D31 & D32, MIDC, TTC Industrial Area, Turbhe, Thane-Belapur Road, Navi Mumbai, Maharashtra	You failed to perform adequate unidirectional airflow studies (smoke studies) on the aseptic filling line used to produce sterile finished drug products Media fill batch record (filling end date July 3, 2012), 359 media-filled vials were rejected after interventions due to machine set-up and periodic adjustments, and after the end of the filling process. None of these vials were incubated as part of the media fill You have inadequate scientific justification for your environmental monitoring sampling plans in manufacturing areas

Sr. No	Letter Issue Date	Company Name	Crux of warning letter
			for aseptically-filled injectable drug products. This includes the locations of viable airborne particulate sampling, settle plates, and contact surface monitoring
11	03/03/2016	Emcure Pharmaceuticals Ltd., Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune, Maharashtra	Poor Aseptic Processing Techniques Our investigators observed poor aseptic processing techniques during the manufacture of (b)(4) injection USP (aseptically filled for U.S. market) batch (b)(4), and (b)(4) injection (aseptically filled for U.S. market) batch (b)(4) Your operator placed a (b)(4) cup on the floor of an ISO 7 area (Grade B) to collect water (b)(4) from a
			(b)(4) unit. As operators set up ISO 5 (Grade A) filling line, they used the cup contents to wet the mechanical assembly in the piston drive Operators crawled on the floor on their hands and knees under the filling line during routine aseptic filling operation activities An operator directed vials to the (b)(4) with his hand located directly above open vials During set up, an operator moved un-bagged sterilized tools from the ISO 7 to the ISO 5 area, which he placed in the filling area near the stoppering equipment
12	23/12/2016	Wockhardt Limited Bandra Kurla Complex, Bandra (East) Mumbai, Maharashtra	Sterile API Violations-During the airflow analysis (smoke study) of aseptic connections on your (b)(4) equipment inside the laminar air flow (LAF) ISO-5 area, our investigator identified air flow disturbances and turbulence. Under dynamic conditions, air did not sufficiently sweep across and away from sterile connections, so the sterility of any product processed under these conditions could be compromised Our investigator observed employees working in gowns that had unraveled stitching extending from hoods, zippers, and pants. Your firm approved these gowns for operations. Employees wore them while manufacturing sterile (b)(4) USP API and sterile (b)(4) API. Five of 10 garments released for use in aseptic production areas had loose fibers or other damage. Per your procedures, you should have discarded these garments. You determined that inadequate lighting and ineffective operator training were root causes
13	17/12/2017	Fresenius Kabi Oncology Limited Baddi at Kishanpura Village, Baddi, Gurumajra, Himachal Pradesh	Firm, failed to adequately investigate the sterility failure of injectable product. This test, performed in January 2017 as part of routine stability testing, reported Bacillus subtilis, Pseudomonas putida, and Pseudomonas entomophila growth. Microbiological growth was observed in both the media canisters. Investigation was deficient in that it did not sufficiently address these factors and thoroughly investigate potential manufacturing root causes. Company's manufacturing investigation substantively assessed environmental data for only the week before and the week after the product's manufacture date. It did not sufficiently address whether adverse trends or related incidents had occurred in the manufacturing area over a longer period and did not address the atypical findings of gram negative bacteria (e.g., Pseudomonas, spp.) earlier in the year in the production RABS (restricted access barrier systems). Your review of environmental data was insufficient as it only addressed near term data trends and relied too heavily on cumulative contamination rates in assessing the potential routes of contamination in your manufacturing operation
14	03/10/2017	USV Private Limited at H17/H-18, OIDC, Mahatma Gandhi Udyog Nagar, Dabhel, Daman	Firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity Firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes

Sr. No	Letter Issue Date	Company Name	Crux of warning letter
15	27/03/2017	Indoco Remedies Limited, Plants II & III, L-32, 33, 34 Verna Industrial Estate Area, Verna, Goa	Firm failed to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product, including provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products Unreliable process compromises the quality, integrity, and sterility of solution. Although the company implemented various corrective actions and preventive actions (CAPA) since 2013, they continued to receive a large number of non-integrity complaints. It is unclear whether the latest CAPA sufficiently addresses the root causes of this recurring container-closure integrity defect and will correct the problem
16	05/07/2018	Baxter (Claris Injectables Ltd.) Nr. Parimal Railway Crossing Ellisbridge Ahmedabad- 380006 Gujarat	Our investigators observed significant evidence of water damage in your facility, including warped ceiling panels, puddles of water, and water stains. For example, water damage was evident over the (b)(4), and in sky lights, vents, and ceilings above the finished drug product packaging area and in the personnel corridor outside the Quality Control laboratory In addition, our investigators observed ceiling panels over the personnel corridor and (b)(4) that were not sealed, allowing ingress of air from the building's plenum into post-sterilization areas
17	24/04/2018	Goran Pharma Private Limited GDIC-I, Bhavnagar Road Sihor, Gujarat	Your (b)(4) system was not appropriately designed. The system, which you indicated was "sterilized" (b)(4), contained (b)(4) piping with dead legs. This inappropriate system design fosters the development of biofilms. Moreover, due to the deficiencies noted in laboratory controls during the inspection, such as inappropriate storage of media, lack of growth promotion testing, and lack of positive controls, it is not certain you would be able to reliably detect bioburden or microbial limits failures
18	29/10/2019	Cadila Healthcare Limited, FEI 3002984011, at 419 & 420 8a Village-Moraiya, Ahmedabad	Firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements Firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes
19	03/04/2019	Hospira Healthcare India Pvt. Ltd., at Plots B3, B4, B5 (pt); B6 (pt); B11-B18 and B21B23, SIPCOT Industrial Park, Irungattukottai, Sriperumbudur, Kancheepuram District, Tamil Nadu	Microbiology laboratory did not accurately report test results. On a particular day, during inspection, during a walk-through of the laboratory, microbial growth was observed on personnel and environmental monitoring media plates associated with aseptic processing lines. However, our review of laboratory records found that analysts had recorded a result of "Nil" (no growth) for each of these plates. On the same day, company's investigator also observed that the microbiologist had significantly underreported microbial results for three samples.
20	08/02/2019	Emcure Pharmaceuticals Limited at Plot No. P-1 & P2, I.T.B.T. Park, Phase II, M.I.D.C., Hinjwadi, Pune, Maharashtra	Sterility failure investigations lacked sufficient data to support its conclusions. For example: Sterility testing was performed using a closed testing system inside an ISO 5 laminar air flow environment. These conditions minimize the potential introduction of adventitious contamination during a sterility test. The investigation did not adequately address the specific breaches that could have occurred in such a closed testing system No microbial contamination was observed in the negative controls Environmental monitoring data in the ISO 5 environment did not show microbiological contamination during performance of the sterility test The investigation did not identify aseptic breaches during the sterility tests

Sr. No	Letter Issue Date	Company Name	Crux of warning letter
			The investigation did not identify faults in the testing procedure, material, or technique used in conducting the sterility tests Potential manufacturing failure modes were not adequately assessed
21	25/02/2020	Cipla Limited, FEI 3004081307, at L138; Ll39 - 146; L147/A; L147/1 - 147/3; S103 - 105; S107 - 112; M61 - 63, Verna, Goa	The firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or established requirements
22	25/03/2020	Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116117-118-119-111-123 (part), Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam, Andhra Pradesh	Firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. Firm did not adequately investigate serious deficiencies in microbiology laboratory conditions and practices. Among the deficiencies were excessive occurrences of negative control plate contamination, high levels of contamination in environmental monitoring (EM) samples of the sterility test
23	13/08/2020	Wintac Limited located at 54/1 Boodihal Village, Nelamangala, Bangalore	Firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Smoke studies performed for aseptic processing operation lacked simulation of interventions and other related activities that occurred during aseptic manufacturing operations FDAs inspection found that interventions and other operations simulated for procedures conducted during media fills were not sufficiently representative of commercial aseptic manufacturing
24	24/09/2020	Panacea Biotec Limited, FEI 3007187282, at Tehsil Nalagarh, Village Malpur, Baddi, District Solan, Himachal Pradesh	Firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. Firm lacked an effective system to ensure adequate control of differential pressures in aseptic processing facility
25	10/09/2020	Shilpa Medicare Limited, Unit-IV, FEI 3009876430, Plot No. S-20 to S-26, Pharm, Formulation SEZ, TSIIC, Green Industrial Park, Polepally (Village), Jadcherla (Mandal), Telangana	Firm failed to follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product, including the review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of sterility specifications

Key problem areas and trends in twenty five WLs observations mainly included sterility assurance (Compounding and conventional lack of sterility) [10], aseptic technique failures [3], environmental monitoring failures [3], design and qualification of facilities [2], rudimentary CGMP (Release testing) [2], cleaning, equipment maintenance [2], basic sanitation failures [2], cross-contamination risks [1].

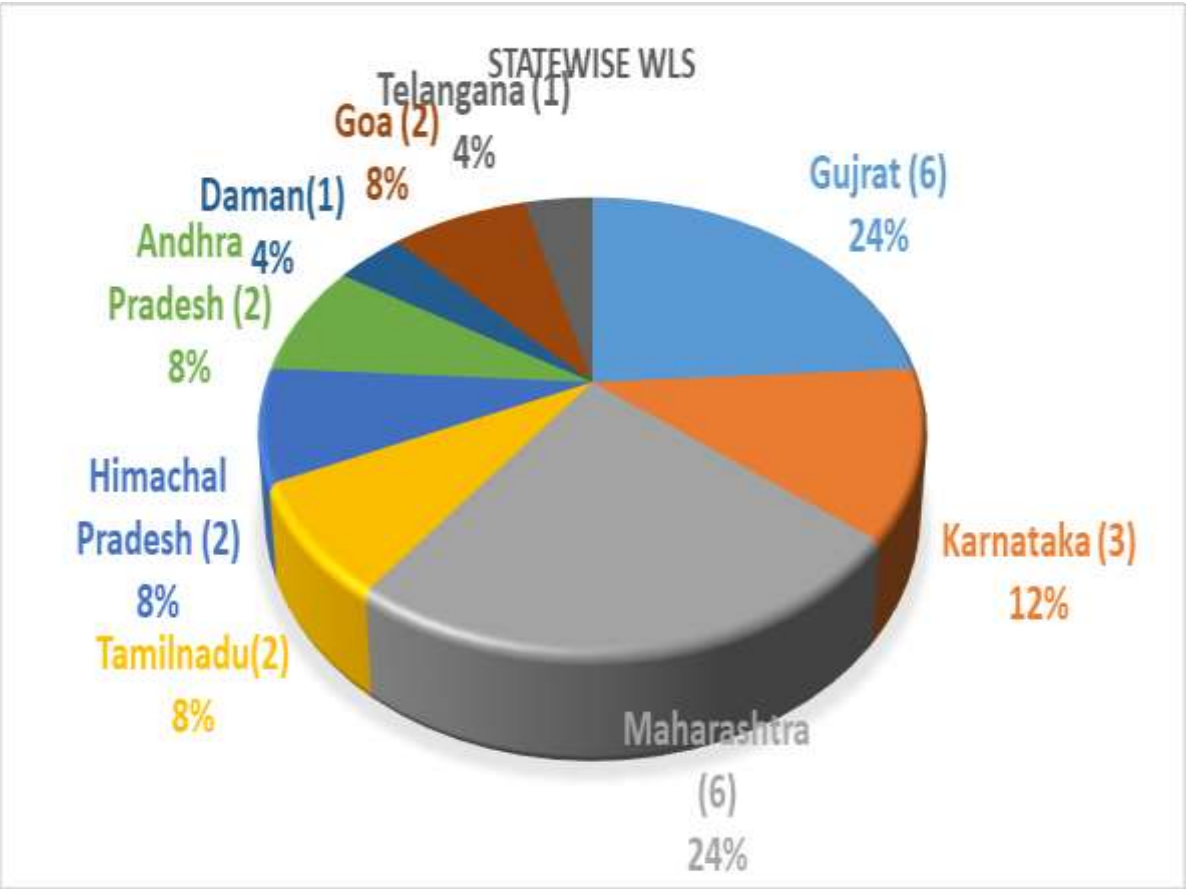

Figure 5. Warning letters issued to Indian Industry (state wise summary)

CONCLUSION

USFDA observations in Indian pharmaceutical industry, particularly for sterile products, mainly concerned the sterility assurance, environmental monitoring issues and violation of 21 CFR part 210 and 211. We present the concise observations which can help the industry to put more quality control parameters and utmost care in design of standard operating procedures and maintenance of raw an authentic traceable data. For sterile manufacturing operation where the risk is high w.r.t. product quality and patient safety, the highest issues were related to compounding and conventional lack of sterility. Almost 40% observations cited in the warning letters were attributed to these parameters.

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Appendix III
List of Conferences attended

U.S. FOOD & DRUG ADMINISTRATION

CERTIFICATE OF ATTENDANCE

CDER Small Business and Industry Assistance (CDER SBIA)

Hanumant Gambhire

attended the

Understanding FDA Inspections and Data Webinar

September 6, 2023

This event has been:

- pre-approved by RAPS as eligible for a maximum of 12 credits for a two-day event (appropriate to real-time attendance) towards a participant's RAC recertification upon full completion.
- pre-approved by SOCRA who accepts documentation of candidate participation in continuing education programs for re-certification if the program is applicable to clinical research regulations, operations or management, or to the candidate's clinical research therapeutic area.
- pre-approved by SQA as eligible for 1 non-GCP or non-GLP unit for every 1 hour of instructional time towards a participant's RQAP re-registration.
- approved by ACRP for continuing education in clinical research. ACRP will provide 1 ACRP contact hour for every 45-60 minutes of qualified material.

Brenda Stodart

Brenda Stodart, PharmD, MS, BCGP, RAC-US
Captain, United States Public Health Service
Director, CDER Small Business and Industry Assistance Program
Division of Drug Information | Office of Communications
Center for Drug Evaluation and Research
Food and Drug Administration

Pharma Summit 2022 :
Drug Discovery & Community Trial
27th & 28th August 2022

CERTIFICATE

OF BEST ORAL PRESENTATION

ASSOCIATION OF PHARMACEUTICAL RESEARCH

PHARMA SUMMIT 2022

DRUG DISCOVERY AND COMMUNITY TRIAL

27th & 28th August 2022 | Virtual Conference & Expo

BioLEAGUES UNITED innovators

This is to certify that Mr/Ms/Mrs. **Hanumant Gambhire** has presented his/her research paper titled ***Content analysis of USFDA warning letters issued to sterile products pharmaceutical*** ..... which has been awarded as **Best Oral Presentation** in International Conference on "Pharma Summit 2022: Drug Discovery and Community Trial" organized by Association of Pharmaceutical Research (APR) on 27th & 28th August 2022.

Dr. Anil Kharia
Partner - Modern Laboratories
Director - Nandani Medical Laboratories Pvt Ltd
Chairman - Modern Group of Institutions
Indore, Madhya Pradesh, India

Ms. Priyamvada Jain
Associate Director-Regulatory Affairs
Jubilant Generics Limited
Greater Noida, Uttar Pradesh
India

Dr. Md Salahuddin
Principal
Al-Ameen College of Pharmacy
Bangalore, Karnataka
India

Mr. Rudra Bhanu Satpathy
CEO & Founder
Association of Pharmaceutical Research (APR), India

CERTIFICATE

OF PARTICIPATION

SFE
SOCIETY FOR EDUCATION

International Conference On Medical, Biological And Pharmaceutical Sciences (ICMBPS-22)

30th January 2022,Delhi, India

This is to certify that **Hanumant Gambhire**

of *Lovely Professional University, Phagwara , Punjab, India* has done his/her excellence in presenting the research paper titled *" Impact of USFDA Warning Letters on Economic Growth of Indian Pharmaceutical Industries"*

on 30th January 2022 at Delhi, India.

Dr. James Crusoe
President

SOCIETY FOR EDUCATION
SFE
INTERNATIONAL CONFERENCE

Shraddhasrinath
Convener

Certificate of Attendance

This certifies that

Hanumant Gambhire

Has attended the Webinar on USFDA Warning Letters and Inspectional Trends of Sterile Manufacturing Sites that was held on 9 March 2021 .

Sougata Pramanick

Certificate of Attendance

THIS CERTIFICATE PRESENTED TO

Hanumant Gambhire

FOR ATTENDING THE WEBINAR ON

WARNING LETTER & FDA 483 RECOVERY

Larry Stevens.

SENEIR CONSULTANT , THE FDA GROUP

SEPTEMBER 17, 2021