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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]

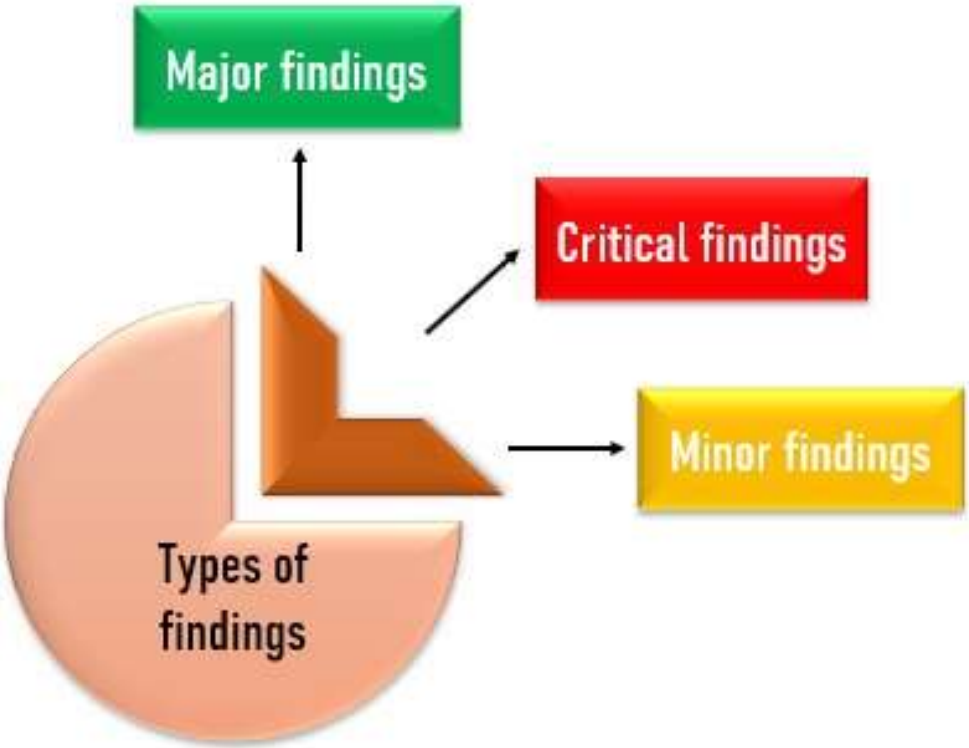

Figure 1. Types of finding during the USFD A inspections.

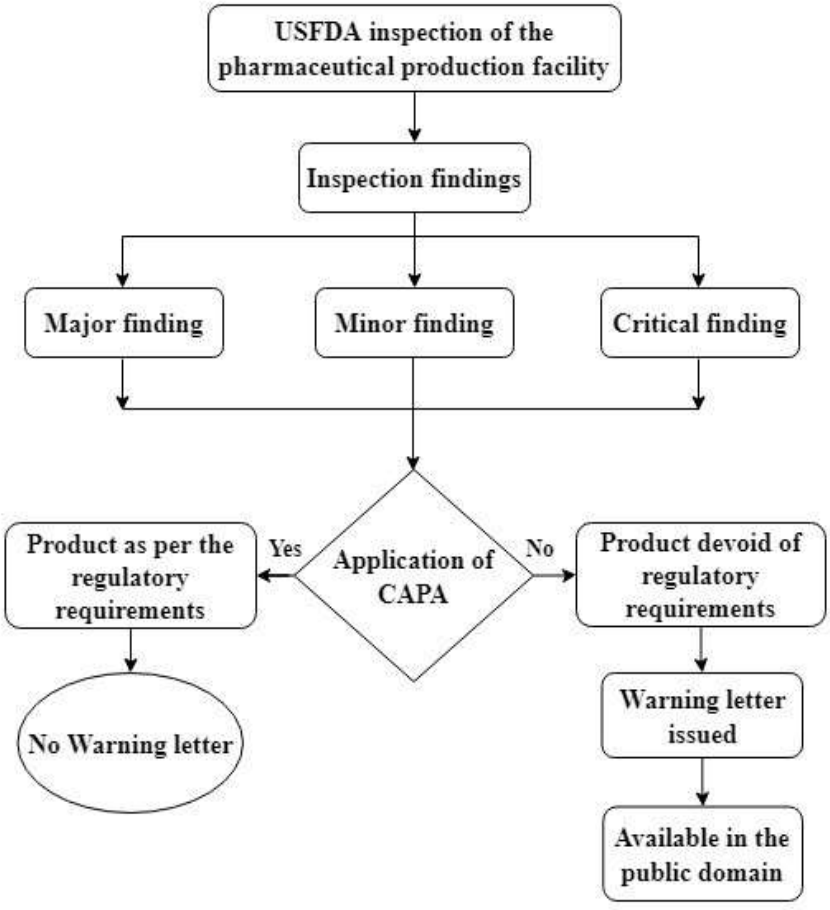

Figure 2. Overview of the process of USFDA inspection and issue of warning letters to facilities.

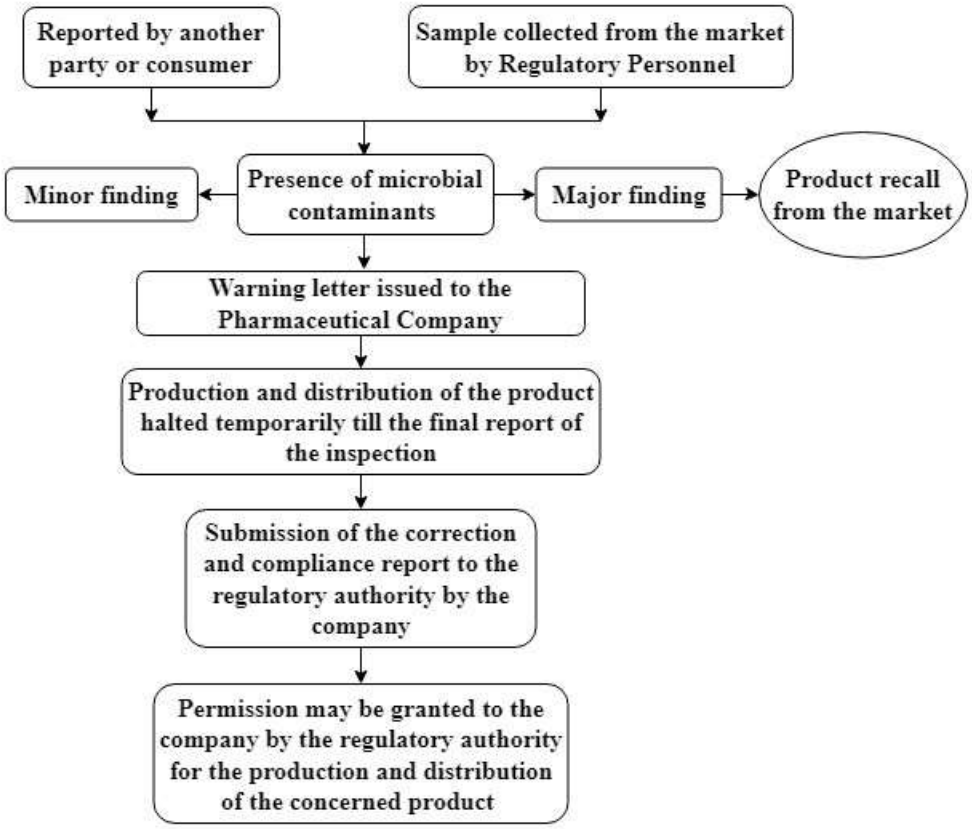

Figure 3.: Probable sampling strategies for sampling of products and inspection of facility.

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

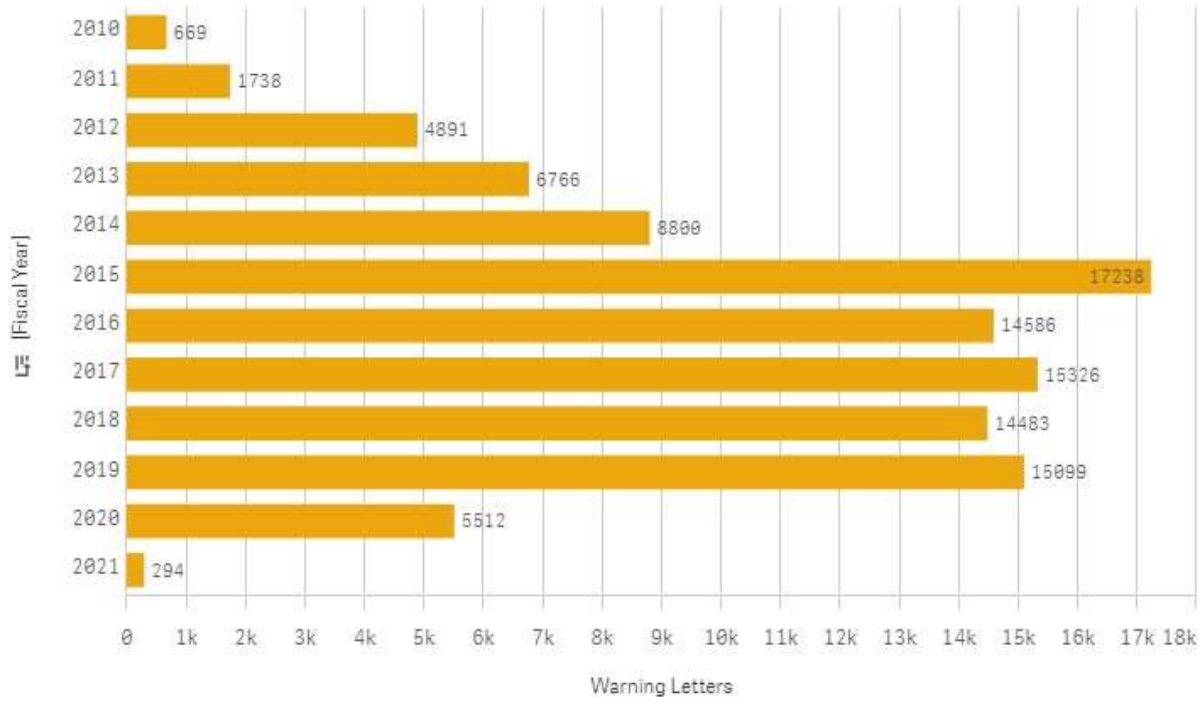

Figure 4. Warning letters issued to global Industry

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].

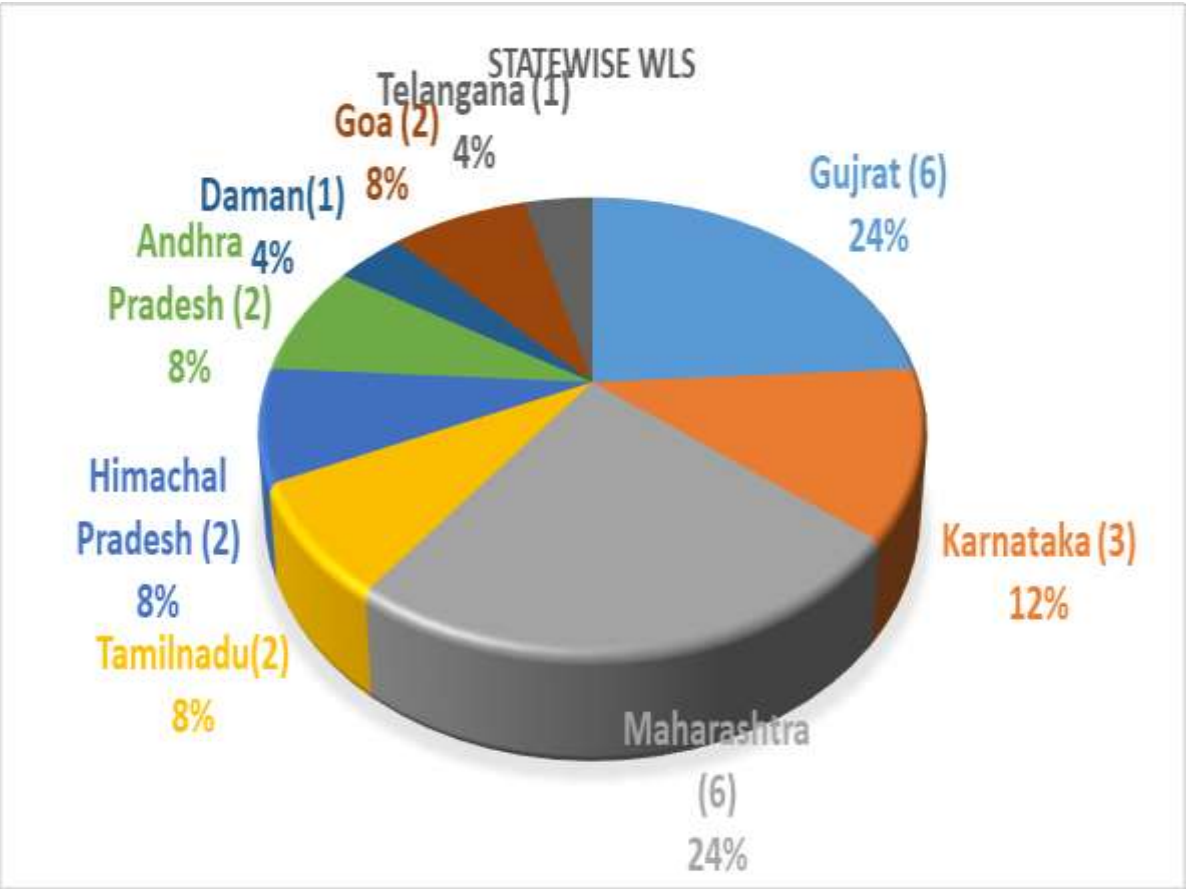

Figure 5. Warning letters issued to Indian Industry (state wise summary)

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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