TECHNO GEAR

A Pharmaceutical Magazine

Version 01

Published By: PRES

PREPARED FOR FDA INSPECTION

UNTOUCHED AREA OF DATA INTEGRITY

GLOBAL CHALLENGES FOR INDIAN PHARMACEUTICAL INDUSTRY

OVERVIEW OF STERILITY ASSURANCE

REGULATORY GUIDANCE ON SMOKE STUDY

FREQUENTLY ASK QUESTION

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From The Author's Desk

Dear Readers,

Through PRES we are trying to connect with the Global Pharma community. Where we discussed, share and explore lots of pharmaceutical hot topics. Being a Pharma professional it is very difficult to get time for own to do something different other than routine responsibilities. Hope you all paraprofessionals are agreed with my views.

That's you, the readers and followers of my blog, who always encouraged me a lot to do something different than my routine schedule. All the information are easily available web media, I am just trying too collating all those information in a single article.

I have collated the information's broadly from the major regulatory guidance document including FDA, PIC,s, MHRA and other pharmaceutical knowledge resources like ISPE , PDA Etc.

Once again I would like to thanks my readers, followers and seniors, who has encourage me a lot.

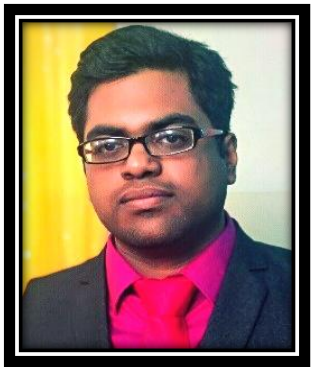
PRES Mission

To develop scientifically sound, practical, technical information and resources to advance science and regulation for the pharmaceutical industry

PRES Vision

To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical community

About Author



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Contents

Revision History

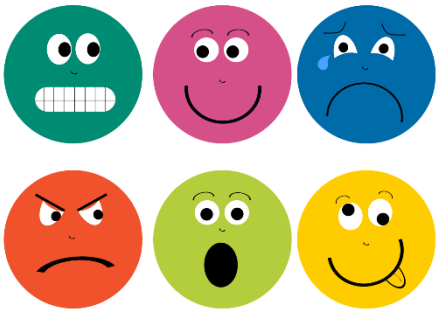
Revision	*Change Details*	*Date*
00	*Initial version*	*April 24, 2018*

1.Prepared for FDA Inspection:

Announcements of Inspection are always a nightmare for pharmaceutical industry. We did not feel that it was good news at all. Thought like 483, warning letter and recall are always come to our mind.

In this article we will discuss elaborately, how to overcome from this kind of circumstances. Fear, Anxiety, Panic, stress, pressure, tension and worry all are represent our mental state of mind. Normally two types of feelings we have, one is positive feeling one is negative feelings. Positive feelings always make us happy and it visible through our facial expression. Negative feelings always come up with stress and pressure.

The quality of your life is largely determined by the quality of the mental states you live in day to day – states like love, anger, happiness, fear and excitement. There are two main ways to control your state of mind. Either by controlling the way you use your physical body, or by controlling your focus of attention and the way you interpret it. What happens in your life does not determine how you feel. How you feel is only the result of how you are using your own mind and body at any moment.



No matter what happens in your life, you are in control of your own state of mind. Make sure to use that ability to put yourself in a state that is appropriate for what you want to achieve. In most cases, would it not be nice to be in a highly positive mood most of the time? People in our society often turn to external means such as food, alcohol, cigarettes or

drugs to elevate their mood, but with the techniques you are about to learn you will not have to depend on anything outside of yourself to change the way you feel.

For example, a person who is depressed will look down, talk slowly, have shallow breath, slackened facial muscles and will be physically hunched over. Conversely, a happy and positive person will smile, talk faster, raise their shoulders, lift their head and breathe deeply. We also become happy when we take action towards something that is important to us, while on the other hand depression comes from inertia. You cannot be sad and busy at the same time.

Are you surprise that in spite of discussing on technical aspect, we are discussing about behavioral aspects. Because the way we communicate to the auditor that matters a lot.

Effective communication is about more than just exchanging information. It's about understanding the emotion and intentions behind the information. As well as being able to clearly convey a message, you need to also listen in a way that gains the full meaning of what's being said and makes the other person feel heard and understood.

More than just the words you use, effective communication combines a set of 4 skills:

- Engaged listening
- Nonverbal communication
- Managing stress in the moment
- Asserting yourself in a respectful way

While these are learned skills, communication is more effective when it becomes spontaneous rather than formulaic. A speech that is read, for example, rarely has the same impact as a speech that's delivered (or appears to be delivered) spontaneously. Of course, it takes time and effort to develop these skills. The more effort and practice you put in, the more instinctive and effective your communication skills will become.

Common barriers to effective communication include:

- Stress and out-of-control emotion.
- Lack of focus.
- Inconsistent body language.
- Negative body language.

Till now we have discussed about the behavioral aspect, now we will be elaborating the technical aspect and planning part of audit.

Before Inspections:

One way to stay abreast is to **check out 483s**, available online, to understand what sort of issues are being **identified by inspectors**. There are various resource centers, blogs and webinars that offer insight, including an FDA Inspections group on LinkedIn which share information about the latest inspection trends.

Define roles for key employees such as the Director of Quality, Regulatory Director, Quality Assurance Manager or Production Manager. Identify one employee to serve as the main liaison or company representative with the FDA inspector to **reduce any possible miscommunication**.

Make sure employees who get promoted get briefed on their **new responsibilities** and make sure backups are trained, in case a key executive is away.

Conduct regular training sessions to keep employees aware of the changes and best practices. You might even consider conducting a mock inspection to ensure people know how to deal with the **stress and strain** of a real inspection.

Pre-Audit Preparation

- ❑ Review key procedures like, Investigations, CAPAs, Complaints, Change Control, Product Release
- ❑ Review critical/major investigations- Ensure these have been adequately addressed.
- ❑ Review new equipment validations.
- ❑ Review critical/major complaints.
- ❑ Auditors often ask for a list of these investigations etc.- Can and should be prepared ahead of time.
- ❑ Don't forget about the previous audit response - ensure all actions were completed.
- ❑ A review of the major changes since the last audit
  - ✓ Validation protocols/reports.
  - ✓ Risk Assessments.
  - ✓ Change Control Forms.
  - ✓ Ensure they are reviewed and available in the war room!

Keep in mind:

That inspections can happen any time, so your personnel must be prepared at all times.

At the Start of an Inspection:

The inspection process generally begins when the FDA Inspector presents a notice of Inspection (FD-482) and proper FDA credentials. But employees should know whom to notify – and should contact that person immediately – if they are approached by an FDA investigator outside of normal business hours (i.e. after 5:00 p.m. and/or outside of the facility on the company grounds.

If the investigator does not present an FD-482 or credentials, the investigator should not be allowed to begin the investigation until you can authenticate the person's identity with FDA Field Operations. The company should make sure that all relevant managers and departments are aware that the FDA inspector is on the premises.

Typically requested ahead of time

- ❑ Current Site Master File.
- ❑ Procedures for deviation, OOS management & Change Control.
- ❑ List of significant changes since the last inspection.
- ❑ Validation Master Plan.
- ❑ Validation schedules for equipment, facilities, processes, methods and utilities.
- ❑ List of sponsors for whom testing of medicines is performed (testing lab requirement).
- ❑ List of test methods relating to the licence.
- ❑ Quality Metrics

While regular company business must continue as normal during the regulatory audit, audit coordinator like Corporate QA (CQA) or audit and compliance team should focus on the FDA inspection only.

There is a requirement for an empty conference room for the inspector to use as the base of operation while the inspection is being conducted, to review records.

The company representative will need to provide adequate time for a brief company orientation and allow time to answer any other questions the inspector may have in order to conduct the Investigation. The representative should escort the investigator(s) on any tour of any areas of the facility.

Keep in mind:

Facility inspections are designed to determine that cGMP standards are being met and that you are maintaining **appropriate records**. In any interaction with the inspector, employees should be **cooperative and avoid conflict**.

It is important to maintain the **right attitude**; rather than grumble to the inspector about the disruption – since the inspector is just doing his or her job – think of this an opportunity to show that your company is meeting or exceeding cGMP standards. If you're not sure what the inspector is requesting, **don't guess: Ask for clarification.**

Identify personnel likely to be involved in the audit

- ❑ Presenters – Primary Contact,
- ❑ Area-specific presenters,
- ❑ Reception,
- ❑ People to be in the audit room (this should be limited),
- ❑ Note takers,
- ❑ Runners,
- ❑ People for the 'war room' (prep area).

During an FDA Inspection:

The company representative should determine from the investigator the scope and purpose of the inspection. This allows the company to organize the visit properly to determine the approximate length of time the inspector will need to be on site.

During the visit, the inspector will need to do a proper document review, conduct appropriate interviews, and other inspection activities.

Company policies and procedures that will or may have an impact on the inspection should be reviewed with the inspector, including:

- Access to restricted areas.
- Restricted behaviors including the wearing of lab coats (in required areas).
- The absence of food or eating in animal labs.
- Any policy prohibiting the use of cameras, tape recorders or other audio and/or photographic equipment.
- Requests for copies, materials, and/or drug samples must be made through the company representative.

Keep in mind:

The inspection usually involves a combination of physical plant inspection and document and record review, including complaints, production records, QC records and storage and shipping

records. The investigation may also explore into procedures related to equipment and process controls and vendor and design specifications.

The company should keep a detailed record of dates, times, areas inspected, observations made, questions or remarks by the FDA inspector, and responses or remarks by any employee during the inspection. Duplicate copies of all material provided to the investigator should be retained by the company.

During the Inspection, the company representative should request that the investigator(s) identify areas, procedures, or documents which are judged as not good practices. That way, the company can address and correct the issue during the inspection. The company should demonstrate the inspector that the practices are now in compliance.

Meanwhile company should assessed by implementing the changes or recommendations does not impacting the quality of previously manufactured products.

At the end of each day of the inspection, after the FDA inspector has left the facilities, senior management should apprised the team. If there were any issues identified by the inspector, the managers of the impacted department should, when practical, prepare and implement the appropriate corrective preventive actions.

If an issue has been corrected during the inspection, we should ask the inspector to review the corrective actions at the start of the next inspection day. The goal is to close out all non-compliances prior to the completion of the inspection. This demonstrates the company's commitment to quality and provide it with the opportunity to review the proposed corrective action with the inspector and make any corrections should the inspector feel the corrective action did not resolve the issue.

Information and Drug Sample Requests:

When copies of records or documents are requested, company personnel should be the ones to make copies. FDA personnel should not be allowed to make copies nor should they take or write on the original data or documents.

All materials given to the investigator must be marked "Confidential" and/or "Proprietary," and should be documented and listed by document title and number. The company should maintain a complete set of copied records and reports.

Requests for access to and copies of records and reports related to pre-clinical and clinical data conducted under the provisions of an IND are permitted under FDA authority.

No raw data or original documents may be taken off-site. The original documents should not be written on by the investigator.

Raw material, product samples or any other samples provided to the inspector should be listed by name, lot or batch number, and quantity on the FDA form (FDA 484). The company should retain a triplicate sample from the same lot for confirmatory testing. After the inspection is completed, a Freedom of Information (FOI) Request should be made to the FDA laboratory for a copy of its test results. The company may bill the FDA for samples taken.

Actual labels and labeling, (e.g. package inserts) and packaging may be collected by the investigator. Duplicates should be collected for the Company Record of the Inspection.

The inspector may ask for customer names and shipping records of products sold. This information should be provided. However, complete customer lists should not be provided during a routine inspection since this is confidential business information.

Exit Interview Protocol:

Upon completion of the inspection, the inspector will present a written FDA form (FDA 483) that contains a list of any negative observations that constitutes violation of Food and Drug law.

The inspector is then available for an exit interview to review any notes including any 483s. The senior management should attend this meeting.

During the exit interview, the company should take extensive notes and make sure that its people understand the issues around all 483 items, and how to correct those issues. Don't be afraid to ask clarifying questions as appropriate.

Any preliminary verbal response to a 483 observation by the company should be brief. It is not appropriate to vigorously argue a point with the FDA investigator during the exit meeting. However, if you feel a 483 observation is in error or the result of a misunderstanding or incomplete information, you should compile the proper documentation to support the company's position. If an issue remains unresolved, request the inspector to annotate the FDA 483 and his Establishment Report to reflect the differences.

If corrective action on an observation has been taken during the course of the investigation, this should be duly noted during the exit interview.

Post Inspection Protocol:

The inspection is over but there may still be work to be done.

The company representative should prepare a written report and maintain a file of the subjects, operations, documents, and activities that were inspected and/or performed during the FDA inspection.

The file shall contain duplicate copies of all records copied and taken by the FDA inspector. The report shall be reviewed by senior management and maintained by QA and should contain the following:

Reference the date of inspection and name(s) of members of inspection team, reason for written response, response to each cited deficiency, including observations resolved/corrected during the inspection and observed by the Investigator(s), description of preventive and corrective action to be taken regarding each observation for those items not resolved at the

time of written response and a schedule for completion, items still in dispute between the company and the FDA shall be addressed with necessary supporting information and documentation.

The Quality or Regulatory Director should submit the written response to the FDA within 10 working days of the exit interview.

After the inspection, the FDA inspector will write a narrative report called the Establishment Inspection Report (EIR). The Quality Director should submit a Freedom of Information (FOI) request for both a purged (confidential information removed) and an unpurged copy of the EIR. This should be sent directly to the FDA Freedom of Information Office in Rockville, Maryland.

The Quality Director should review all information received from the FDA after the inspection and coordinate all communication with the FDA. Any incorrect information should be communicated in writing to document the company's position.

Conclusion:

There are a lot of steps to ensure a successful FDA inspection. The most important is to ensure your facility implements current compliance procedures. Building on that, you need to develop and test your inspection plan, and train your employees so that everyone understands his/her role for before, during and after an inspection. Inspections can be a hassle but they are necessary to ensure the public safety.

With a detailed, thoughtful approach, you will be in a better position to pass inspections with a minimum of disruption.

2. Untouched area of Data Integrity in Pharmaceutical Industry

Now a days the topic “Data integrity and non compliance” is the hot topics. Lots of references available online that deals with the Data integrity issue.

One of the major example am going to give today, that can be control by the management only.

Extended shift/working hour or over time:

We know that “Human error” is the “Risk” for GMP. For this reason we always induced technology/automation everywhere and try to reduce the human intervention as much as we can.

As the human being are driven through emotion & sentiments. Mental peace and physical relaxation is just like preventive maintenance for human being. Usually we use to send our automobile for maintenance with defined interval, same our body deserves too.

We know that during audit preparation or other priorities we need to stay for extended hour. But if it is a regular or routine job then it caused frustrations and from where the chances Non compliance or data integrity begins.

We should not consider this as one of the reason of Data Integrity. Otherwise we can’t able to track and rectify the real reason for non conformance. We should focus on the time management and as a part of audit we should verify the attendance log.

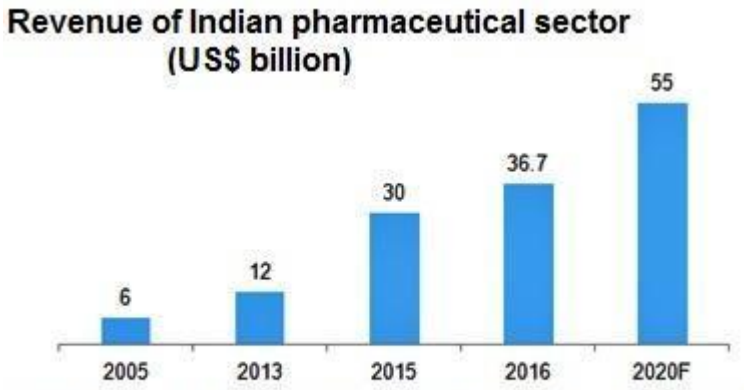
For Example: One of the major regulatory body ask for the attendance register for employee before one week of proposed audit date and they found that majority of people are staying more than 12 hr in the organization. Same has been come as a major observation and they ask for a justification from management. Why employees are started staying for an extended hour before audit.

3. Global Challenges for Indian Pharmaceutical Industry

[3]The Indian pharma industry is on a good growth path and is likely to be in the top 10 global markets by value by 2020. High burden of disease, good economic growth leading to higher disposable incomes, improvements in healthcare infrastructure and improved healthcare financing are driving growth in the domestic market.
Pharma companies are growing both organically and inorganically. Inorganic growth is happening through licensing and partnerships as high valuation of assets is making acquisitions difficult. Further, companies are organically improving their operations and productivity by increasing field force sizes, penetrating in Tier II and III cities and by expanding their product portfolios.

But now a day's pharmaceutical companies are facing trouble during audit. If we look into the growth rate of Indian pharmaceutical industries, it will fabulous.

[2]The Indian pharmaceuticals market increased at a Compound annual growth rate (CAGR) of 17.46 per cent during 2005-16 with the market increasing from US$ 6 billion in 2005 to US$ 36.7 billion in 2016 and is expected to expand at a CAGR of 15.92 per cent to US$ 55 billion by 2020.



Source: Department of Pharmaceuticals, PwC, McKinsey, TechSci Research
Notes: F - Forecast, CAGR - Compound Annual Growth Rate

By 2020, India is likely to be among the top three pharmaceutical markets by incremental growth and sixth largest market globally in absolute size.

[1]The Indian pharmaceutical industry is going through a period of significant volatility and uncertainty, requiring companies to re-visit their traditional growth strategies to succeed
Some of the key findings observed from the current audit faced by the major pharmaceuticals are summarized below,

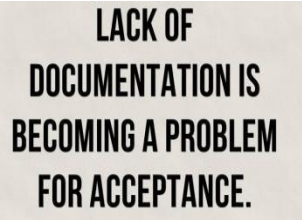
Subject knowledge:

As we all knows now a day's regulator are usually willing to discussed with the down the line team member. People like operator or line supervisor are not adequately trained. They are sufficiently knowledgeable sometime but they fear to open up their mouth in front of the auditor. Some time it was evident also the process what operator are following that was correct but it was not in line with the approve document or instruction. So, there is GAP in actual process and available document.

Assumptions: People are highly knowledgeable.

Reality: Doer is seeking for the support from their senior. But they don't have sufficient time because they engaged in meetings. Addition to this lack of problem solving skills and decision making capability.

Improper documentation/ instructions:



Available documents/records are not meeting with the principles of ALCOA+. In my views no one has come to job for doing wrong thing. Leaders providing less time to prepare good document and they are crazy about the output by executing the document. So, before proper review people are initiating the executions. Finally auditor are getting disputed document during review.

Assumptions: We should know our procedure and documentation are done as per ALCOA+ expectation.

Reality: Operating rocedures are not adequate. Sometimes SOP's are read first time by the operator or supervisor in front of auditor. So, during explanation people are literally struggling to find the exact paragraph what asked by the auditor.

Insufficient manpower:

Always we are ready to go with the less man power. Poor operators are unwillingly extending their working hour. We should not consider human as a machine, human are drive through emotions. They need mental and physical peace. Regular over-time can be caused non compliance to GMP.

Assumptions: We have sufficient manpower.

Reality: Always lack of man power was observed.

Work plan:

Poor work plan always hampered our work & life balance. Anyhow end of the day we need to deliver as per our commitment. But commitment is always coming with narrow timelines. Hence the timelines are not provided based on the proper work assessment. It was fixed by the higher management and further reduced by the team leader to make happy the management. So, closer of any work done in hurry and lots of deviation we left behind.

Assumptions: Things will move automatically move without plan.

Reality: Confusion what is the priority and what need to be close first?

Implementation of new Technology/Project:

Whenever we are going for new technology proper risk based assessment not considered. Our expectations are compromised based on the budget allocated for particular project by management. So, what we procured that in not meet our expectations. Teams allocated for the project are worked based on the targeted timelines not for the quality of technology. Sometime machines are procured for the audit commitment and after that people sent the machine in the scrap. Because that was not meeting the expectations of the user.

> Assumptions: Implementation was perfect within the timeline that is the assumption.
> Reality: Only the success mail floats over within the management group and people are appreciate for success. But reality was somewhat different.

Existing system up gradation:

As we already discussed implementation project completed with some gaps. For that we find lots of compliance issue during routine usages. So after several discussions managements allocate additional funds to fulfill those compliance gaps. But present as improvement or new requirement or continuous improvements. Based on that people are nominated to excellence award for the achievement during company annual meet.

Assumptions: Team was efficient for gap assessment

Reality: People in the shop floor dealing with number of complication for the up gradation

Over commitment to regulatory agency:

Regulators are god for us. After getting approval from regulatory, we can able to see growth in our business. So, during the regulatory inspections management members are giving lots of commitment to regulators. Once the audits end it result with lots of CA-PA (Corrective and preventive action). But further no evaluation for CA-PA allocation, timelines, closer and appropriateness.

Assumptions: All proposed action plans are closed. Compliance activity done as proposed to regulators.

Reality: Number of gaps will found if you review them carefully and improper evaluation & closer.

Selection of new assignments/project:

Usually selection of new project is done with lots of expectations. Initiation of new project gives impact to stock market. But numbers of project ware get aborted due to different reason. That will cause huge financial loss to organization.

Assumptions: Will give positive impact to the stock market.

Reality: But it caused financial loss.

Conclusion:

[3]The Indian market provides significant growth opportunities for the pharma industry. However, for the industry to sustain a robust growth rate of 15–20% till 2020, companies will have to rethink the way they have been doing business.

Pharma companies will continue to grow inorganically through alliances and partnerships. They will continue to focus on improving operational efficiency and productivity. However, to meet the requirements of changing business environment, they will have to adopt new business models and think of innovative ideas to service their evolving customers faster and better.

Developments in the health insurance sector, medical technology sector and mobile telephony can help the growth of the pharma industry by removing financial and physical barriers to healthcare access in India.

Overall, the various regulatory interventions require careful consideration by the pharma industry. How companies adjust to the regulatory environment as they seek to capitalise on the opportunities provided by the Indian market will be an interesting space to watch in the coming months.

As emerging markets become increasingly important and as India's role among these markets becomes progressively significant, both domestic and pharma MNCs will need to adapt their business models, organisations and processes and create customised strategies.

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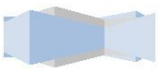
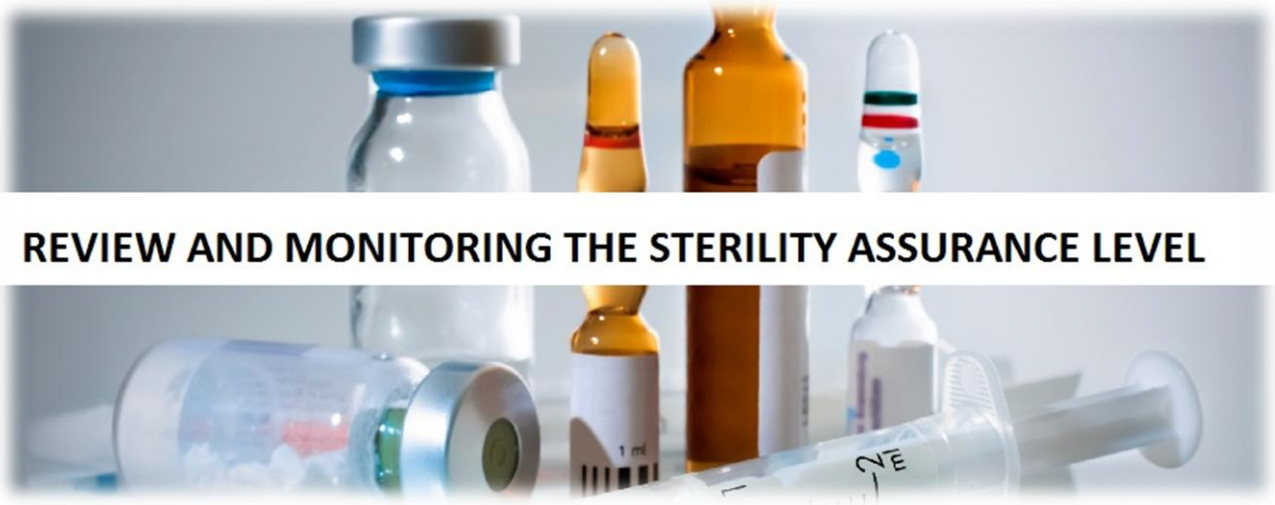




4.Sterility Assurance

One of the most critical operations in pharmaceutical manufacturing is the processing of sterile formulations. The productions of sterile formulations, specifically the ones that cannot be terminally sterilized, involve complex and demanding processes to prevent the products contamination and require a great amount of resources.

The objective of review includes

Obtain information on operations impacting on sterility, to identify areas for improvement and correction.

Evaluate current good manufacturing practices in the sterile drug industry. Initiate appropriate action against manufacturers observed to be out of compliance.

The inherent risk of microbiological contamination associated with aseptic operations is critical because it has a direct relation with patient health. The difficulty in detecting contamination makes the outcome of these processes less predictable, naturally having higher risk, and being more difficult to control and manage.

Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. In an aseptic filling process, the drug product, containers and closures are sterilized separately and then brought together under an extremely high quality environmental condition designed to reduce the possibility of a non-sterile unit. Aseptic processing involves more variables than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

Some types of aseptic processing involve manual manipulations of sterile components, containers, and closures in addition to routine operator interventions in the critical area. Humans are a significant

source of contamination in traditional aseptic processing, especially in production lines that require operators to routinely enter critical areas (Class 100, ISO 5, or Grade A) of the filling line. Aseptic processing systems based on more advanced control-based technologies, such as Restricted Access Barrier Systems (RABS) and Blow-Fill-Seal systems, are designed to reduce human interventions in the critical areas of the fill line while an isolator system completely separates the aseptic filling line from the external environment and minimizes employee interaction with the critical area.

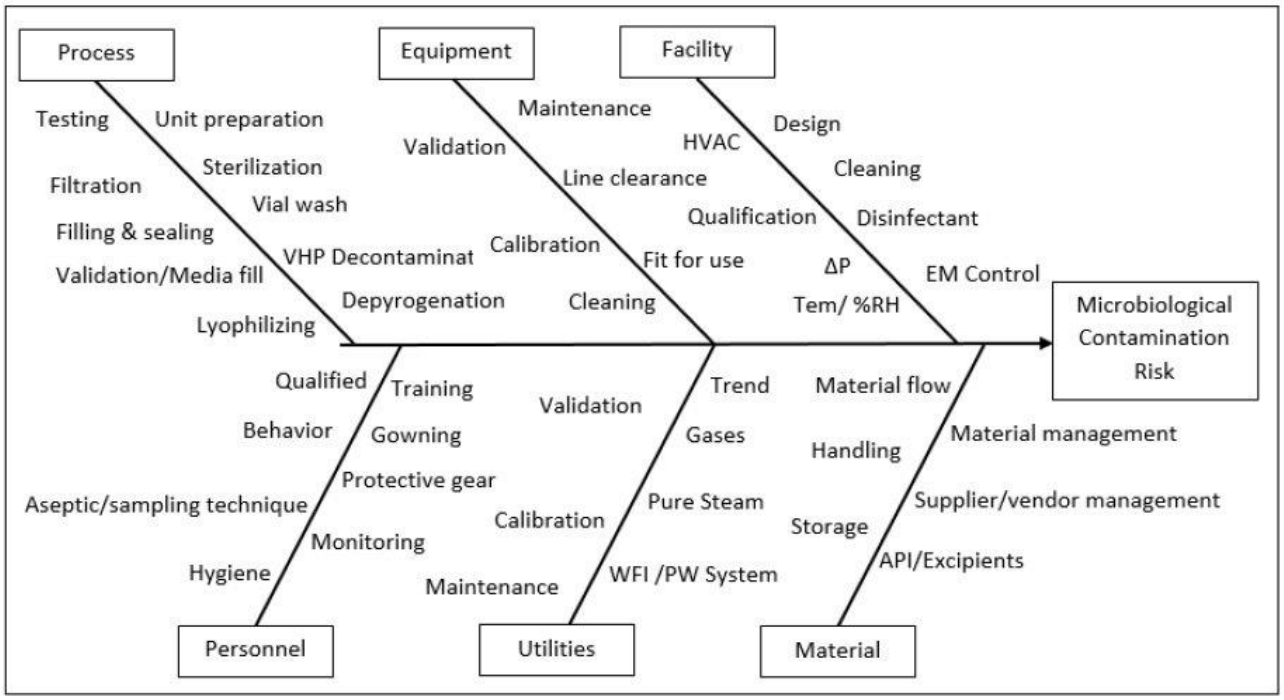


***Figure**: Fish Bone of Microbial contamination*

5.Regulatory guidance on Smoke study

Now the time has came to understand the principle of Smoke study or air flow visualization. Air pattern or “smoke” studies demonstrating laminarity and sweeping action over and away from the product under dynamic conditions should be conducted.

The studies should be well-documented with written conclusions. Videotape or other recording mechanisms have been found to be useful in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. However, even successfully qualified systems can be compromised by poor personnel, operational, or maintenance practices.

Smoke studies and multi-location particulate data are vital when performing qualification studies to assess whether proper particulate control dynamics have been achieved throughout the critical area.

Personnel should minimize interventions into the critical zones. Such interventions can adversely disrupt the unidirectional and should therefore be designed to minimize both the extent and frequency of occurrence.

Equipment should not obstruct airflow and, in critical areas, its design should not disturb unidirectional airflow.

Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended clean room design and control parameters. The principle of slow, careful movement should be followed throughout the clean room.

Keep the entire body out of the path of unidirectional airflow unidirectional airflow design is used to protect sterile equipment surfaces, container closures, and product.

Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility. Manufacturers should be aware of a device's air monitoring capabilities, and the air sampler should be evaluated for its suitability for use in an aseptic environment based on collection efficiency, cleanability, ability to be sterilized, and disruption of unidirectional airflow.

Exposure conditions should preclude desiccation (e.g., caused by lengthy sampling periods and/or high airflows), which inhibits recovery of microorganisms.

Evaluation methodology:

Evaluation of smoke study is equally important. Your study should review the study CD/DVD for follow criteria,

- Studies should demonstrating laminarity over the product path
- Sweeping action should to be away from the product path
- Activity/intervention should to be performed as per procedure
- Any Turbulence observed in smoke flow shall be relook
- Airflow should demonstrate unidirectional path
- Airflow should to be from supply and evacuate through return
- Clip should to demonstrate the complete interventions
- Adequate density of Smoke is preferred
- Continues smoke flow during intervention is preferred
- Visibility of intervention should to be part of evaluation

If in case poor visibility mentioned the reasons (i.e Reflection / less lighting/denser smoke)

Result shall be reported as Yes or No and in some cases rating can be done as Very good "+++", Good "++", Improvement req. "+" and Poor "-"

6.FAQ: Question and answer

6.1. What does the FDA inspect for?

The Food and Drug Administration (FDA) conducts careful inspections of regulated facilities to determine a firm's compliance with regulations and the Food, Drug and Cosmetic Act. Inspections are one of many ways FDA protects the public health.

6.2. What is an FDA 483?

An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts.

6.3. What is the FDA Form 482 for?

FDA may conduct an inspection of your operation for a variety of reasons, such as a routinely scheduled investigation, a survey, or a response to a reported problem. The investigator will present credentials and "Notice of Inspection" (FDA Form 482) upon arriving at your plant.

6.4. Why is the FDA important?

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

6.5. What is the purpose of an FDA warning letter?

Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes.

6.6. What is an EIR from the FDA?

An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts.

6.7. How does FDA classify inspection reports?

NAI – No action indicated

VAI – Voluntary action indicated (some deficiencies identified but not serious).

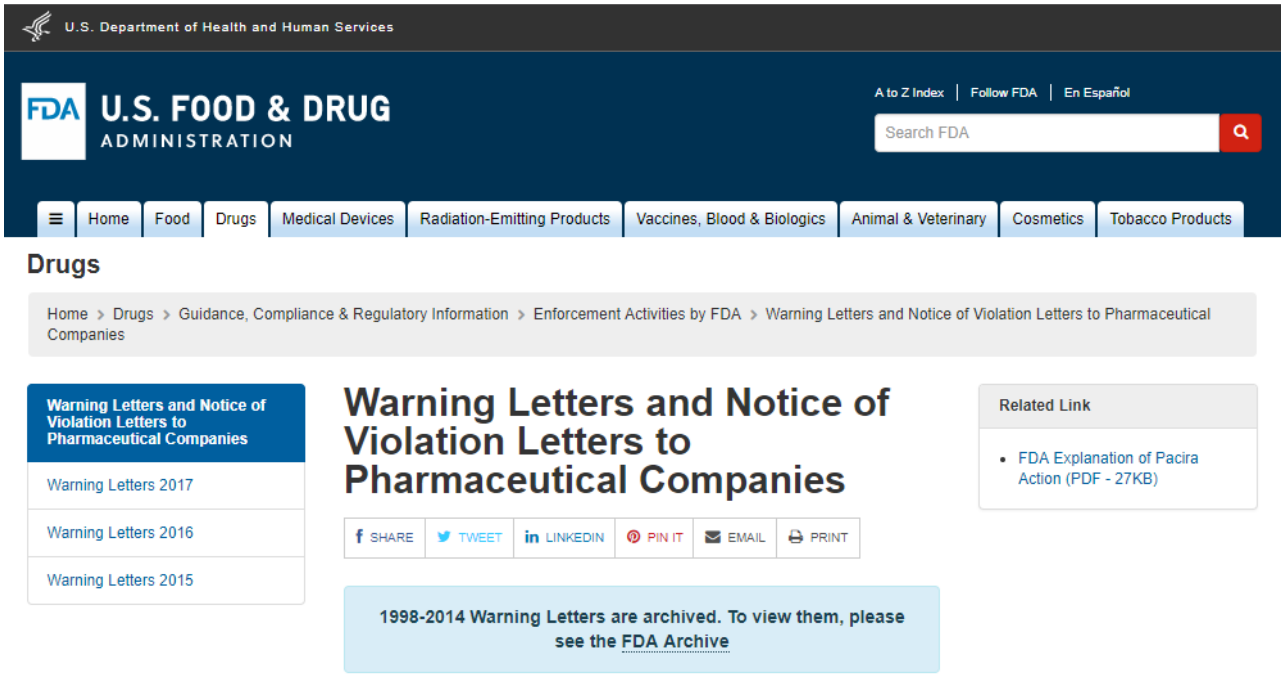
OAI – Official action indicated (serious deficiencies identified, and FDA must take action to assure correction).

6.8. Where you get information regarding all warning letters issued by FDA?

It is a free online resource, available at

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm

Screen shots are shared below for ready references,



6.9. What should I expect during an inspection?

FDA may conduct an inspection of your operation for a variety of reasons, such as a routinely scheduled investigation, a survey, or a response to a reported problem. The investigator will present credentials and "Notice of Inspection" (FDA Form 482) upon arriving at your plant. A knowledgeable person in your firm, such as the plant or production manager, preferably designated ahead of time, should accompany the investigator at all times. It is in your best interest to fully understand FDA's inspection procedures. When you are unsure of certain actions taken by the investigator, don't hesitate to ask questions.

Usually, the investigator will examine your production process, look at certain records and collect samples. At the conclusion of the inspection, the investigator will discuss with your firm's management any significant findings and concerns; and leave with your management a written report of any conditions or practices, which, in the investigator's judgment, indicate objectionable conditions, or practices. This list of "Inspectional Observations," also called an FDA Form 483, can be used by your firm's management as a guide for corrective action, since the FDA representative will not usually recommend specific corrective measures. Your firm can and should respond to the FDA-483 during the discussion with the investigator. In fact, corrective actions or procedural changes that were accomplished immediately in the presence of the investigator are regarded as positive indications of your concern and desire to voluntarily correct discrepancies.

If you do not agree with the actions being taken by the FDA or if you have a question about the jurisdiction of the agency in a particular matter, you can contact the FDA's Office of the Ombudsman to seek a resolution.

FDA Office of the Ombudsman,
10903 New Hampshire Avenue
WO 32, Room 4231
Rockville, MD 20903
Telephone: 301-796-8530
FAX: 301-847-8628
E-mail: ombuds@oc.fda.gov (sending confidential information by electronic mail is not recommended)

7.Free Online Resources

FDA Inspection guides available on the following mentioned link,

https://www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm

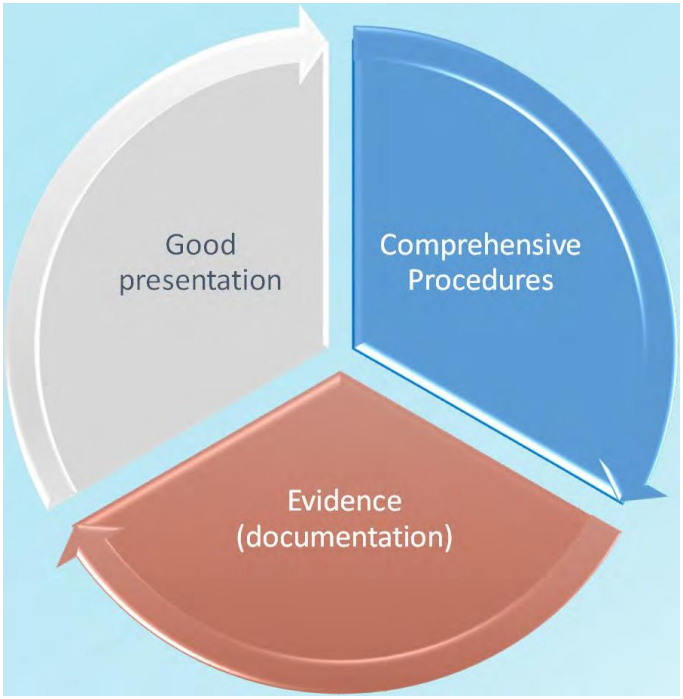
Guidance document link available under this section are mentioned below,

- High Purity Water System (7/93)
- Lyophilization of Parenteral (7/93)
- Microbiological Pharmaceutical Quality Control Labs (7/93)
- Pharmaceutical Quality Control Labs (7/93)
- Validation of Cleaning Processes (7/93)
- Dosage Form Drug Manufacturers cGMPs (10/93)
- Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)
- Sterile Drug Substance Manufacturers (7/94)
- Topical Drug Products (7/94)
- Oral Solutions and Suspensions (8/94)
- Computerized Systems in Drug Establishments (2/83)

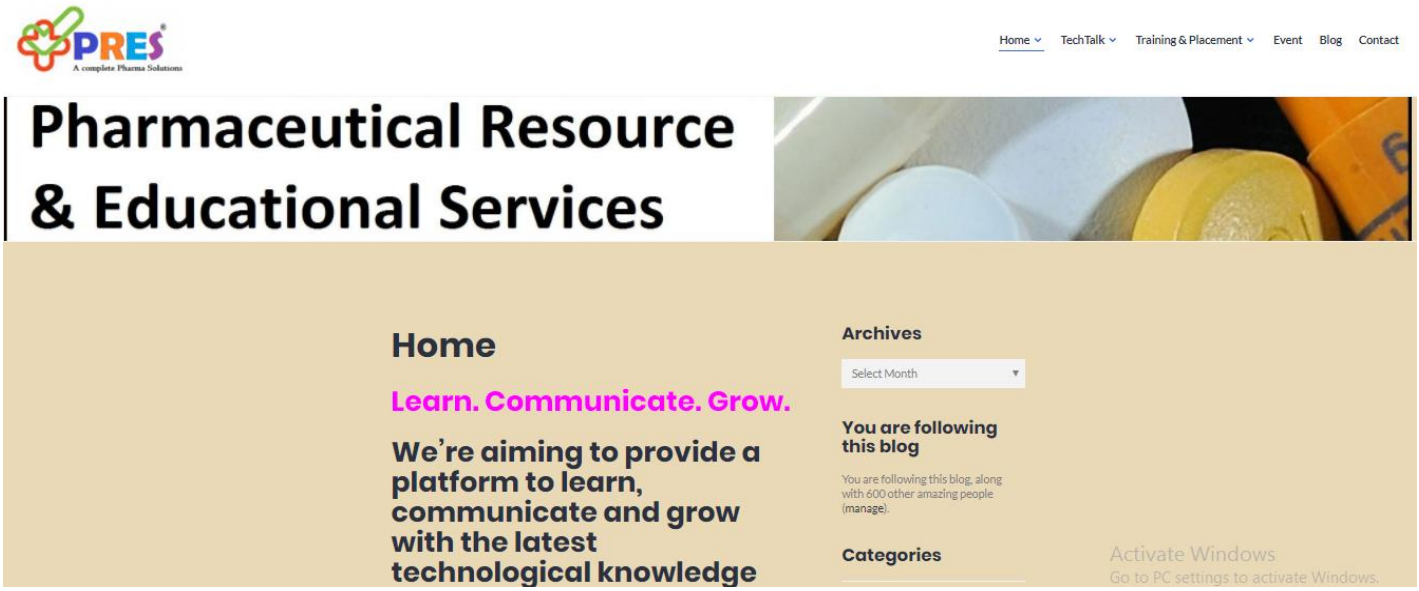
Note: These documents are reference material for investigators and other FDA personnel. The documents do not bind FDA and do not confer any rights, privileges, benefits or immunities for or on any person(s). An alternative approach may be used if such an approach satisfies the applicable statutes, regulations or both.

8. Reference

1. http://www.pharmacompliancemonitor.com/best-practices-handling-fda-inspections/7936/
2. https://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm237624.htm



Success in any audit require 3 things



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