BACHELOR OF PHARMACY

SENGAL ADHYA
SHAH AESHA
BASU AISHANI
GOHEL ARPAN

2024

REVIEW ON 483 NOTIFICATIONS ISSUED BY FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS

SENGAL ADHYA H (20BPH003)
SHAH AESHA A (20BPH004)
BASU AISHANI R (20BPH005)
GOHEL ARPAN N (20BPH012)

BACHELOR OF PHARMACY

UNDER THE GUIDANCE OF

DR. PRITI J MEHTA

INSTITUTE OF PHARMACY
NIRMA UNIVERSITY

MAY 2024

REVIEW ON 483 NOTIFICATIONS ISSUED BY US-FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS

Thesis submitted to the Institute of Pharmacy, Nirma University,
in partial fulfillment of the requirements for the Degree of

BACHELOR OF PHARMACY

SENGAL ADHYA HARSHIDABEN (20BPH003)
SHAH AESHA ALPESHBHAI (20BPH004)
BASU AISHANI RANBIR (20BPH005)
GOHEL ARPAN NILESHBHAI (20BPH012)

Semester VIII
(PROJECT WORK BP808ET)

UNDER THE GUIDANCE OF

DR. PRITI J MEHTA

INSTITUTE OF PHARMACY
NIRMA UNIVERSITY

May, 2024

DECLARATION

We, **SENGAL ADHYA (20BPH003), SHAH AESHA (20BPH004), BASU AISHANI (20BPH005) AND GOHEL ARPAN (20BPH012),** hereby declare that B.Pharm project work (BP808PW) entitled **"REVIEW ON 483 NOTIFICATIONS ISSUED BY FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS"** being submitted to Institute of Pharmacy, Nirma University for the award of degree of B.Pharm was carried by us under the supervision of Dr. Priti J Mehta, Institute of pharmacy, Nirma University. The content of this project work, in full or in parts, have not been submitted to any other University for the award of any degree. We also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.

SENGAL ADHYA (20BPH003)

SHAH AESHA (20BPH004)

BASU AISHANI (20BPH005)

GOHEL ARPAN (20BPH012)

Institute of Pharmacy
Nirma University

Date: 27/05/2024

CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work (BP808ET) entitled **"REVIEW ON 483 NOTIFICATIONS ISSUED BY FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS"** submitted by **SENGAL ADHYA (20BPH003), SHAH AESHA (20BPH004), BASU AISHANI (20BPH005), GOHEL ARPAN (20BPH012)** B.Pharm. semester VIII is a bonafide research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of "Dr. Priti J Mehta". We are aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad.

SENGAL ADHYA (20BPH003)

SHAH AESHA (20BPH004)

BASU AISHANI (20BPH005)

GOHEL ARPAN (20BPH012)

Institute of Pharmacy
Nirma University

Guide:

Dr. Priti J Mehta
M.Pharm, Ph.D.,
Chair Professor and Head,
Department of Pharmaceutical Analysis,
Institute of Pharmacy,
Nirma University

Date : 27/05/2024

CERTIFICATE

This is to certify that BPharm Project Work (BP808PW) entitled **"REVIEW ON 483 NOTIFICATIONS ISSUED BY FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS"** being submitted by SENGAL ADHYA (20BPH003), SHAH AESHA (20BPH004), BASU AISHANI (20BPH005), GOHEL ARPAN (20BPH012) for the award of degree in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy under my direct supervision to my full satisfaction. The content of thesis in full or in parts, have not been submitted to any other University for the award of any degree.

Guide:

Dr. Priti J Mehta
M.Pharm, Ph.D.,
Chair Professor and Head of Department
of Pharmaceutical Analysis,
Institute of Pharmacy

Nirma University

Date : 27/05/2024

CERTIFICATE

This is to certify that BPharm Project Work (BP808PW) entitled **"REVIEW ON 483 NOTIFICATIONS ISSUED BY FDA FOR DRUGS, MEDICAL DEVICES AND BIOLOGICS IN LAST FIVE YEARS"** being submitted by SENGAL ADHYA (20BPH003), SHAH AESHA (20BPH004), BASU AISHANI (20BPH005), GOHEL ARPAN (20BPH012) to the Institute of Pharmacy, Nirma University for the award of degree in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy under the supervision of Dr. Priti J Mehta to the fullest satisfaction. The content of thesis in full or in parts, have not been submitted to any other University for the award of any degree.

Dr. GOPAL NATESAN
M.Pharm., PhD.,
Director
Institute of Pharmacy
Nirma University

Date : 27/05/2024

ACKNOWLEDGEMENTS

In the pursuit of this endeavor, we are profoundly grateful for the divine guidance and strength bestowed upon me.

The completion of this thesis has presented a truly significant opportunity for intellectual growth. In this regard, we extend our deepest gratitude to our guide Dr. Priti J Mehta, whose invaluable mentorship, encouragement, and unwavering support have been instrumental in shaping this project.

Furthermore, we are deeply indebted to our beloved parents, for their unwavering love and belief in our abilities. Their constant support has served as a cornerstone of strength throughout our academic pursuits.

Our sincere appreciation extends to the President of Nirma University, Mr. Karsanbhai Patel, for providing this valuable opportunity to undertake this research. Additionally, we are grateful to Dr. Anup K Singh, Director General, and Dr. Gopal Natesan, Director of the Institute of Pharmacy, for their insightful feedback and constructive criticism. Finally, we would like to express my gratitude to the Institute of Pharmacy, Nirma University, for providing the necessary resources and facilities that facilitated the completion of this research.

List of Tables :-

List of Figures :-

LIST OF ABBREVIATIONS :-

US-FDA :-United State Food and Drug Administration

ORA : Office of Regulatory Affairs

DHHS : Department of Health and Human Services

FD&C : Food, Drug, and Cosmetic

CGMP : Current Good Manufacturing Practice

IRBs : Institutional Review Boards

CFR : Code of Federal Regulations

CAPA : corrective and preventive actions

QMS : Quality Management System

SOPs : Standard Operating Procedures

EIR : Establishment Inspection Report

CAP : Corrective Action Plan

HACCP : Hazard Analysis and Critical Control Points

GMP : Good Manufacturing Practices

GLP : Good Laboratory Practices

QA : Quality Assurance

QC : Quality Control

ABSTRACT:

This study examines trends in inspectional observations documented on FDA Form 483 over the past five years (2019-2023) with a focus on human drugs, medical devices, and biologics. This research aims to identify overarching patterns in 483 observations across different product categories (drugs, medical devices, biologics, delve deeper into specific regulations by analyzing the most frequent CFR code violations within designated focus areas and intends to assess the effectiveness of current quality system practices in the pharmaceutical industry based on identified trends.

This study analyzes publicly available data on USFDA website related to 483 notifications for five-year period. All observations were categorized in eight subgroups namely documentation practices, GMP/GLP compliance, contamination control, quality control/Quality assurance, personnel qualifications, labelling regulations, clinical trial conduct and management oversight. One additional subgroup was created for biologics namely donor factors. Data analysis will be conducted using Microsoft Excel with the aid of charts and graphs.

An analysis of the data revealed a general decrease in observations across medical devices, drugs, and biologics. However, for medical devices, documentation and Good Manufacturing Practices require the most attention. Documentation, Contamination, and Quality Assurance/Quality Control (QA/QC) were the most frequent observations for drugs, with QA/QC violations showing a positive downward trend. For Biologics, issue related to donors, indicates a need for a comprehensive review and potential tightening of procedures related to blood or tissue donation.

The most frequent citations in 21 CFR in medical devices to Quality System Regulation and investigational devices, while biologics citations focused on stringent quality control for blood products. For drugs, the emphasis remains on enforcing good manufacturing practices throughout production, with a high number of citations for adulterated medications.

In conclusion, to ensure a sustained decrease in 483 notifications, a culture of

continuous improvement is vital. Manufacturers must delve deeper by conducting root cause analyses to pinpoint and rectify underlying problems. Implementing stricter contamination control protocols alongside robust documentation procedures and electronic data capture systems are crucial steps. F ostering a quality-centric environment requires regular review of inspection findings, implementing corrective actions, and establishing a systematic quality improvement program encompassing all facets of manufacturing. This comprehensive approach will solidify a focus on quality and minimize the likelihood of future notifications.

TABLE OF CONTENT

CHAPTER 1:- INTRODUCTION

Public confidence in the safety and effectiveness of drug products, medical devices, and biological products is fundamental to the healthcare sector. The Food and Drug Administration's (FDA) Office of Regulatory Affairs (ORA) is a crucial component within the regulatory framework governing the safety and efficacy of consumables in the United States. Functioning under the auspices of the Department of Health and Human Services (DHHS), the ORA is tasked with safeguarding public health by ensuring that FDA-regulated products comply with relevant statutes and regulations.

Office of Regulatory Affairs (ORA) serves as the principal office that enforces a multifaceted approach that incorporates field operations such as inspections of manufacturing facilities, testing of regulated products, and the implementation of corrective actions in instances of non-compliance.

Conditions that ORA investigators find unacceptable may be observed during an inspection. When an investigator determines that conditions or activities seen suggest that an FDA-regulated product may be in violation of FDA regulations, these observations are recorded on an FDA Form 483. It is a cornerstone of the FDA's regulatory toolkit.

The Food and Drug Administration (FDA) Form 483, titled "Inspectional Observations," serves as a critical document within the regulatory oversight framework for ensuring the safety and efficacy of human drugs, medical devices, food products, and cosmetics in the United States. During FDA inspections, investigators are empowered to issue Form 483 upon identifying conditions or practices that potentially contravene the Food, Drug, and Cosmetic (FD&C) Act and associated legislation.

Form 483 enumerates observed violations of the relevant Current Good Manufacturing Practice (CGMP) regulations or other statutory requirements. These meticulously documented observations constitute a formal notification to

the establishment of deviations from regulatory standards and potential public health risks. The observations focus on conditions that, in the investigator's professional judgment, could signify adulteration of food, drugs, devices, or cosmetics, or their preparation, packaging, or storage under circumstances that could lead to adulteration or compromise public health.

In the interests of transparency and public health promotion, FDA disseminates findings from these inspections. This disclosure serves a threefold purpose. Firstly, it enhances public comprehension of the FDA's role in safeguarding public health. Secondly, it furnishes a rationale for the Agency's enforcement activities. Thirdly, it empowers informed decision-making by both the public and industry stakeholders. This transparency allows for more informed marketplace selections and fosters a culture of compliance. The disclosed citations pertain to finalised inspections conducted at facilities manufacturing, processing, packaging, or holding currently marketed FDA-regulated products, as well as clinical trial investigators and Institutional Review Boards (IRBs).

However, while the total number of 483 observations offers a general overview, a more granular analysis is necessary to comprehend the specific areas where manufacturers of products are encountering difficulties. This review seeks to address this gap by investigating trends in 483 observations over the past five years (2019-2024). The Focus Product Areas in this review include the following:

- Biologics Products
- Drug Products
- Medical Devices

(Inspection Observations data set, www.fda.gov)

1.1 THE CODE OF FEDERAL REGULATIONS (CFR):

It is a compendium of US Regulatory Law and within the United States legal framework, the Code of Federal Regulations (CFR) occupies a critical position. It serves as a codified collection of the general and permanent rules and regulations promulgated by all federal executive departments and agencies, encompassing a vast array of subject areas.

The Code of Federal Regulations is meticulously organized into 50 distinct titles, each representing a broad regulatory domain. These titles function as overarching categories, providing a foundational framework for the regulations that follow. Each title is further subdivided into progressively more specific components. Parts constitute the initial level of subdivision, addressing specific regulatory areas within the broader title.

Parts are further segmented into sections, which represent the most granular level of detail within the CFR. Sections outline the specific regulatory requirements applicable to a particular facet of the part's subject matter. Furthermore, sections may be further divided into paragraphs for enhanced clarity and precision. Citations to the CFR employ a standardized format to pinpoint the exact regulatory provision.
(Inspection Observations data set, www.fda.gov)

1.1.1 CODE OF FEDERAL REGULATIONS TITLE 21 OR 21 CFR:

Occupying a pivotal position within the expansive Code of Federal Regulations (CFR), Title 21 stands as a cornerstone of the regulatory framework overseen by the Food and Drug Administration (FDA). This detailed title delineates the regulations governing a diverse array of products that directly impact public health.

Title 21 is subdivided into numerous parts, each dedicated to a specific product category or regulatory area under the FDA's purview. Each part is further segmented into progressively more granular sections. These sections detail the

specific regulatory requirements applicable to their corresponding part's subject matter. For enhanced clarity, sections may be further subdivided into paragraphs, ensuring utmost precision in regulatory language.

The chapters of 21 CFR include the following:

CHAPTER I: Food and Drug Administration, Department of Health and Human Services.

- Subchapter A - General
- Subchapter B - Food for Human Consumption
- Subchapter C - Drugs: General
- Subchapter D - Drugs for Human Use
- Subchapter E - Animal Drugs, Feeds, and Related Products
- Subchapter F - Biologics
- Subchapter G - Cosmetics
- Subchapter H - Medical Devices
- Subchapter I - Mammography Quality Standards Act
- Subchapter J - Radiological Health
- Subchapter K - Tobacco Products
- Subchapter L - Regulations Under Certain Other Acts Administered by the Food and Drug Administration

CHAPTER II: Drug Enforcement Administration, Department of Justice.

CHAPTER III: Office of National Drug Control Policy.

- Part 1401: Public Availability of Information
- Part 1402: Mandatory Declassification Review

(FDA Code of Federal Regulation Title 21, www.ecfr.gov/current/title-21)

CHAPTER 2:- REVIEW OF LITERATURE

A review of this literature provides details on the inspection process and 21 CFR. Included are topics such as the importance of 21 CFR in the context of an FDA 483 inspection, FDA inspection preparation, the FDA 483 inspection procedure, how to reply to Form 483 and how to prevent receiving Form 483.

2.1 Importance Of 21 CFR In FDA 483 Inspections:

During inspections, investigators meticulously assess a company's adherence to the relevant Code of Federal Regulations (CFR) – particularly those outlined in Title 21, which governs the FDA's regulatory framework. CFR citations within the FDA 483 form (often referred to as "observations") play a critical role in ensuring public health and product safety. Role of these citations are as follows:

A. Pinpointing Non-Compliance:

   CFR citations within the FDA 483 form function as a highly specific communication tool which pinpoint the exact regulatory requirements (sections within a part of Title 21) where the investigator has observed potential deviations. This specificity provides companies with a clear and focused understanding of the areas requiring corrective action and avoids ambiguity and ensures all parties involved are on the same page regarding the observed deficiencies.

B. Communication and Transparency:

   It establishes a common language between the FDA and the inspected company so parties can readily reference the specific regulation in question, facilitating a productive dialogue and ensuring a clear understanding of the expectations. It also fosters transparency in the inspection process by allowing companies can verify the validity of the observations by referencing the CFR themselves.

C. Streamlining Corrective Actions (CAP):

   FDA 483 form with its citations pinpoints CFR violations allowing companies to develop targeted corrective and preventive actions (CAP) plans which ensures that plan directly addresses the identified non-compliance issues, leading to a more efficient and effective resolution.

Companies' use of the cited CFR sections also demonstrates remediation and understanding of the specific regulations violated and the corrective actions taken when responding to the FDA 483 form.

D. Legal Significance:

These citations within the FDA 483 form serve as a documented record of observed non- compliance and in the event of further non-compliance or unresolved issues serve as a basis for more serious enforcement actions, such as warning letters or product recalls. Accurate citations are essential for accountability against violation of the correct regulations and ensuring subsequent enforcement actions are legally sound.

Understanding the importance of CFR citations empowers companies to proactively address potential issues and navigate FDA inspections effective.
(FDA Code of Federal Regulation Title 21, www.ecfr.gov/current/title-21)

2.2 HOW TO PREPARE FOR AN FDA INSPECTION:

The prospect of an FDA inspection requires a well-structured and proactive approach can significantly enhance an organization's preparedness and minimize the risk of receiving a Form 483, signifying potential regulatory non-compliance. Strategies for a rigorous preparation process are:

1. Solidifying Internal Processes:
   1.1. Scrutinize Quality Management System (QMS): Conduct a comprehensive review of the existing QMS. This entails evaluating the effectiveness of documented procedures, data integrity practices, and internal audit programmes. Identify any gaps or areas requiring improvement to ensure robust compliance with relevant regulations.
   1.2. Review Standard Operating Procedures (SOPs): Verify that all critical processes have clearly defined and up-to-date SOPs. Assess employee adherence to these SOPs through training records and observation.

Address any discrepancies or outdated procedures.

1.3. Data Integrity Assessment: Evaluate data integrity controls throughout the organisation. This includes scrutinising record-keeping practices, data security measures, and procedures for handling deviations.

2. Mock Inspections:

2.1. Simulate an FDA Inspection: Conduct simulated inspections to familiarise employees with the inspection process and identify areas for improvement. Utilise experienced personnel to act as inspectors, posing realistic questions and requesting relevant documentation. This empowers staff to respond confidently and efficiently during a real inspection.

2.2. Refine Communication Protocols: Establish clear communication protocols for employees to interact with the inspector during an actual inspection. This includes designating a point person responsible for facilitating communication and ensuring all inquiries are directed appropriately.

3. Documentation Readiness:

3.1. Compile Inspection Readiness Documentation: Assemble a comprehensive folder containing readily accessible documentation for the inspector. This should include SOPs, training records, internal audit reports, and any relevant quality agreements with suppliers or contract manufacturers. A well-organised presentation demonstrates a commitment to compliance.

3.2. Review Past Inspection Reports: If applicable, review any prior FDA inspection reports to identify recurring observations and ensure corrective actions have been effectively implemented.

4. Employee Training and Awareness:

4.1. Targeted Training: Provide targeted training to relevant personnel on FDA regulations, inspection procedures, and appropriate responses to

inspector inquiries. This empowers employees to actively participate in the inspection process and contribute to a positive outcome.

4.2. Communication of Importance: Reiterate the importance of regulatory compliance and the ramifications of non-compliance. Foster a culture of quality and encourage employees to report any potential deviations from established procedures.

5. Continuous Improvement:

5.1. Utilise Mock Inspection Findings: Analyse the findings from the mock inspections to identify areas requiring improvement. Implement corrective actions and refine internal processes to address these weaknesses.

5.2. Embrace a Culture of Continuous Improvement: Commit to a culture of continuous improvement within the QMS. Regularly review and update procedures, conduct internal audits, and encourage feedback from employees to identify potential areas for enhancement. (Saini et al.,33)

2.3 FDA 483 INSPECTION PROCESS:

FDA 483 Notifications issued by the FDA (Food and Drug Administration) plays a vital role in ensuring the safety and efficacy of products we consume. Inspections are a key tool for the FDA to verify compliance with regulations. During these inspections, if an investigator observes conditions that raise concerns, they may issue an FDA Form 483, commonly known as an FDA 483 notification.

Let's delve into how inspectors handle this process.

- **Groundwork for Inspection**: Inspections are not random events. The FDA strategically plans them based on risk factors associated with a

facility or product. This might involve past compliance issues, new product launches, or targeting specific industries.

- **The Inspection**: A team of FDA investigators arrives at the facility and presents their credentials. The inspection follows a predetermined course, focusing on areas like manufacturing processes, quality control procedures, and recordkeeping. Investigators meticulously review documents, interview personnel, and physically observe operations.
- **Identifying Potential Violations**: The inspector's keen eye is trained to spot potential violations of the Food, Drug, and Cosmetic (FD&C) Act and related regulations. This could encompass anything from improper storage conditions to inadequate labelling practices or deviations from established protocols.
- **The Form 483 Takes Shape**: If the inspector identifies conditions that, in their judgment, may constitute violations, they begin drafting the FDA 483. This form serves as a factual record of the observed deficiencies. Each observation is documented clearly, specifically, and significantly to ensure a proper understanding by the company.
- **Closing the Inspection**: Nearing the end of the inspection, the investigator(s) will meet with the facility's management to discuss their observations. The draft Form 483 is presented, and each observation is explained in detail. This open communication allows for initial clarification and ensures transparency.
- **The Formal Notification**: Following the inspection, the FDA finalizes the Form 483. This official notification is issued to the company's management, typically within a few days. It details the specific observations of concern and doesn't determine a final violation. However, it serves as a wake-up call for the company to address the identified issues.
- **Beyond the Form 483**: While the Form 483 is a crucial piece, it's important to remember it might not capture every single observation. The inspector may also compile a more comprehensive report called the Establishment Inspection Report (EIR) that goes into further detail. This

report, along with the 483 and any collected evidence, forms the basis for further FDA action.

- **The Road Ahead**: The company has 15 days to respond to the FDA 483 in writing, outlining their corrective action plan. This plan should demonstrate how they intend to address each observation and prevent future occurrences. Taking prompt and effective action is vital to maintain compliance and avoid potential escalation, such as a Warning Letter from the FDA. (Saini et al.,33)

2.3.1 RESPONDING TO FORM 483:

Responding to a Form 483 with alacrity and efficacy is paramount to evincing a commitment to regulatory compliance and mitigating the potential for further enforcement action. The following outlines a structured approach to crafting a response to an FDA 483:

I. A timeline for response activities should be established: A response to the form 483 observations should be within 15 working days.
II. Meticulous Analysis of Observations: A thorough examination of each observation outlined within the Form 483 is imperative to grasp the precise non-conformances identified by the investigator.
III. Identification of main cause: It is important to identify a main cause when issue of form 483 occurs. There are many techniques to identify the root cause.
IV. Cross-functional Response Team Formation: The establishment of a team comprising representatives from quality assurance, production, and regulatory affairs is recommended to facilitate the development of a comprehensive response.
V. Corrective Action Plan (CAP) Development: For each observation, a detailed CAP should be formulated, outlining the root cause of the non-compliance, the corrective actions to be undertaken, and the preventative measures to be implemented to obviate recurrence. Issue of corrective

action plans (CAP) should specify:

a. Description of the issue
b. Main cause analysis
c. Corrective action plans to prevent occurrence/recurrence
d. Assignment of CAP owner

VI. Timely Response: A written response to the FDA must be submitted within a timeframe of 15 working days upon receipt of the Form 483.

VII. Realistic Timelines: The CAP should incorporate realistic timelines for the execution of corrective and preventative actions.

VIII. Documentation: Furthermore, meticulous documentation of all response efforts, encompassing the CAP, the investigation into observations, and the implementation of corrective actions, is essential. (Mujeeb et al.,84)

2.4 HOW TO AVOID GETTING FORM 483:

A Form 483 issued by the Food and Drug Administration (FDA) signifies observations of non- compliance with regulations governing food, drugs, medical devices, and cosmetics. This was noted in 160 separate form instances. While not a formal enforcement action, it indicates potential violations that could lead to product recalls, import detentions, or even criminal prosecution hence it necessitates a prompt and corrective response to ensure compliance and continued product safety. To minimise the likelihood of receiving a Form 483, a comprehensive and proactive approach is essential. The strategies to potentially achieve this are:

I. Cultivating a Culture of Compliance:

- Embed a culture of quality and compliance within the organisation. Senior management should actively demonstrate their commitment to regulatory adherence through visible leadership, resource allocation, and participation in compliance initiatives.
- Implement a robust training programme to ensure all employees

understand the relevant regulations, Standard Operating Procedures (SOPs), and best practices. This fosters a shared understanding of compliance expectations.

II. Establishing a Robust Quality Management System (QMS):

- Develop clear, concise, and up-to-date SOPs for all critical processes. These SOPs should be readily accessible to staff and consistently followed.
- Implement a documented system for managing all quality and regulatory documents. This ensures versions are controlled, readily available, and revisions are tracked and communicated effectively.
- Conduct regular internal audits to identify and address potential deviations from SOPs and regulatory requirements. This proactive approach allows for corrective actions to be taken before an FDA inspection.

III. Maintaining Data Integrity:

- Maintain meticulous and accurate records of all activities relevant to product quality and safety. This includes raw data, batch records, and deviation reports.
- Implement robust data security measures to prevent unauthorized access, modification, or deletion of critical information.

IV. Effective Risk Management:

- Implement a Hazard Analysis and Critical Control Points (HACCP) plan to identify, assess, and control potential hazards throughout the production process
- Conduct regular risk assessments for other product types to identify potential vulnerabilities and establish appropriate controls.

V. Preparation for Inspections:

- Conduct a mock interview to simulate an FDA inspection to identify areas for improvement and enhance employee preparedness.
- Maintain readily accessible documentation for the inspector, such as SOPs, training records, and internal audit reports.

Additionally, you can seek guidance from regulatory consultants or professional bodies familiar with FDA regulations and stay updated on evolving regulations and best practices through relevant publications and industry conferences. Through a well-defined and consistently implemented quality management system, a culture of compliance can be fostered, ultimately safeguarding product quality and public health. (Mujeeb et al.,84)

CHAPTER 3:- AIM AND OBJECTIVES:

AIM:

The aim of this review is to evaluate the trends and observations documented in FDA Form 483 notifications issued for drugs, medical devices, and biologics over the past five years (2019-2023). This evaluation will identify areas where manufacturers and researchers can improve compliance with FDA regulations to ensure the safety and effectiveness of these products.

3.1 OBJECTIVES:

1. To analyze trends in US-FDA inspectional observations in pharmaceutical industry for drugs, medical devices, and biologics over the past five years and focuses on identifying the overarching patterns within the data across different product categories.
2. To identify and divide observations in focus subgroups and to classify most frequent CFR code violations.
3. To assess the effectiveness of current quality system practices in the pharmaceutical industry based on the identified trends in FDA observations.
4. To develop a set of recommendations for improving pharmaceutical industry compliance based on the findings of the analysis.

CHAPTER 4:- METHODOLOGY:

This research investigates trends in these 483 inspectional observations made by the US Food and Drug Administration (FDA) over the duration of five years from 2019 to 2023. Utilizing publicly available data from the FDA website, the study primarily focuses on observations related to drugs, medical devices, and biologics. Analysis is done using Microsoft Excel using charts and graphs.

4.1 CATEGORICAL AREAS OF FOCUS FOR OUR STUDY WITHIN THE DATA INCLUDE:

- Documentation Practices: Evaluating the effectiveness of documentation systems in ensuring adherence to regulations.
- Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP): Assessing compliance with established protocols for manufacturing and laboratory procedures.
- Contamination and Sanitation: Analysing trends in observations related to contamination control and sanitation practices.
- Quality Assurance (QA) and Quality Control (QC): Investigating the effectiveness of quality control measures and quality management systems.
- Personnel: Evaluating observations regarding personnel qualifications and training.
- Donor Factors (for biologics): Analysing trends in observations specific to donor screening and eligibility for biologics.
- Labelling: Assessing compliance with labelling regulations for accurate product information.
- Clinical Investigations: Investigating trends in observations related to the conduct of clinical trials.
- Company Management: Evaluating observations regarding management oversight and accountability for quality system.

CHAPTER 5:- RESULTS & DISCUSSION:

5.1 483 NOTIFICATIONS ISSUED FROM THE YEAR 2019-2023

This review analyses the issuance of Form 483 notifications by the Food and Drug Administration (FDA) for medical devices, drugs, and biologics from 2019 to 2023. During the period of our analysis from 2019 to 2023, it was found that medical devices had the highest frequency of inspections at 9058 which was followed by biologics at 8393 and the drugs products at 7890.

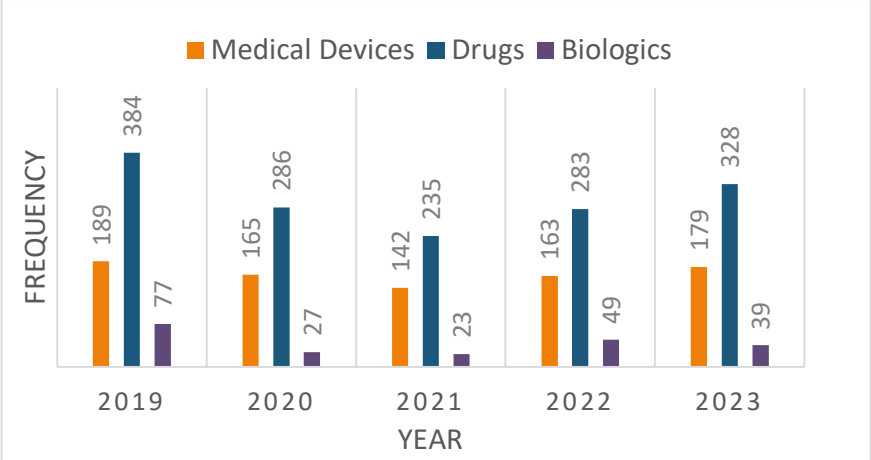

Figure 4.1: Total Number of 483 Notifications issued from 2019-2023 (All three products)

The data presented in Figure 4.1 illustrates that the overall frequency of notifications issued. It was observed that USFDA 483 notifications for Drug Products consistently surpassed those for medical devices and biologics throughout the specified period even though drug products had the least number of inspections among the product category.

Examining the data by product category, the number of notifications observed were:

- Drugs Products: Lowest was of **235 in 2021** to a highest of **384 in 2019**

and **of 328 in 2023**.

- Medical device: Highest Frequency was **189 in 2019** with gradual decline up to **142 in 2021** which was lowest and increased to **179 in 2023**.
- Biologics: Exhibited a decline from **77 in 2019** to **23 in 2021**, followed by a rise to **39 in 2023.**

5.1.1 MEDICAL DEVICES:

An analysis of the provided data in Figure 4.2 reveals a five-year trend (2019-2023) in 483 notifications for medical devices across designated categories.

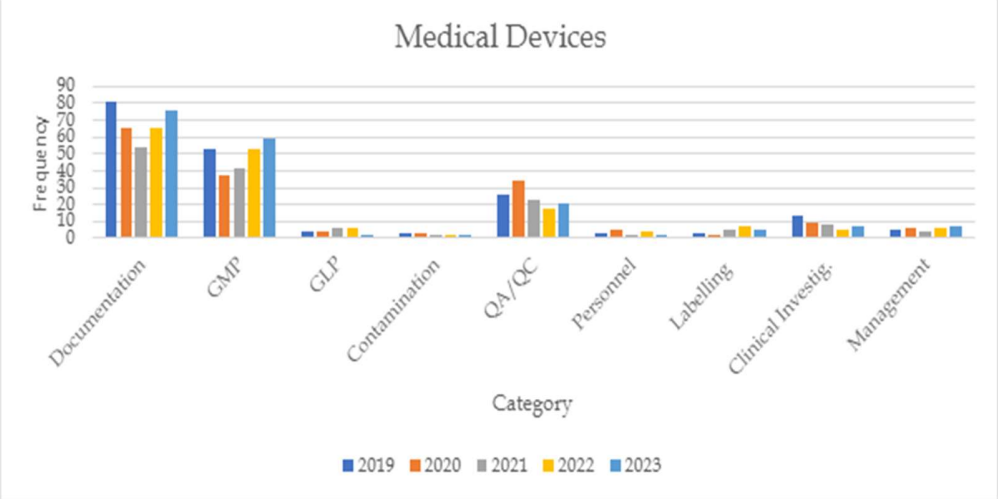

Figure 4.2: Categorical frequencies for Medical Device Products

- Documentation observed a peak of 81 notifications in 2019 and a minimum of 53 in 2021. Notably, a substantial increase of 22 notifications occurred between 2022 and 2023.
- GMP observed a maximum of 59 in 2023 and a minimum of 37 in 2020. It is noteworthy that GMP notifications have exhibited increase in notifications from 2021 to 2023.
- Average of 2 and 6 notifications annually was observed in Good Laboratory Practices in the five years.

In 2019, Documentation notifications outnumbered GMP notifications by a difference of 22. This gap has narrowed over time, reaching just 16 by 2023.

Analysis of Figure 4.3 reveals three key areas necessitating close examination.

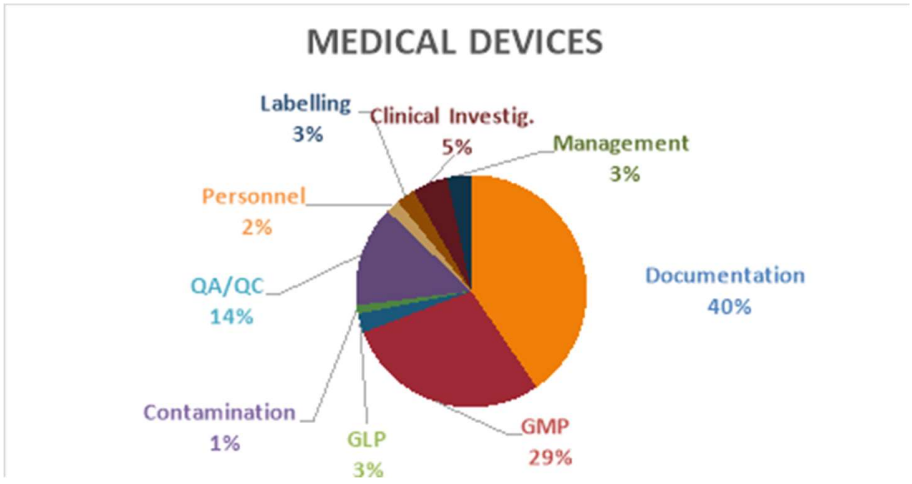

Figure 4.3: Frequency Chart for Medical Device Products

- The most prevalent concern is Documentation with 339 notifications. Specific observations include: In-process inspections, tests, or other verification activities and approvals were not documented, Distribution records were not maintained, the importer failed to submit a report to FDA-on-FDA form 3500A, with a copy to the manufacturer, within 30 days after receiving information that one of its marketed devices may have caused or contributed to adverse effects.
- Second highest was Good Manufacturing Practice (GMP) with 241 notifications which highlight potential systemic issues within the manufacturing process. Specific observations include: Procedures for acceptance of incoming product, procedures to control environmental conditions as well as procedures for receiving, reviewing, and evaluating complaints by a formally designated unit had not been adequately established.

- Finally, Quality Assurance/Quality Control (QA/QC) was third with 118 notifications indicate shortcomings in the processes used by manufacturers to guarantee product quality. Specific observations include: Quality audits were not performed at defined intervals and at sufficient frequency to determine whether the quality system activities and results comply with quality system procedures, process whose results cannot be fully verified by subsequent inspection and test had not been adequately validated according to established procedures.

5.1.2 BIOLOGICS:

Figure 4.4 presents a stratified analysis of 483 notifications issued for biologics during the years 2019- 2023.

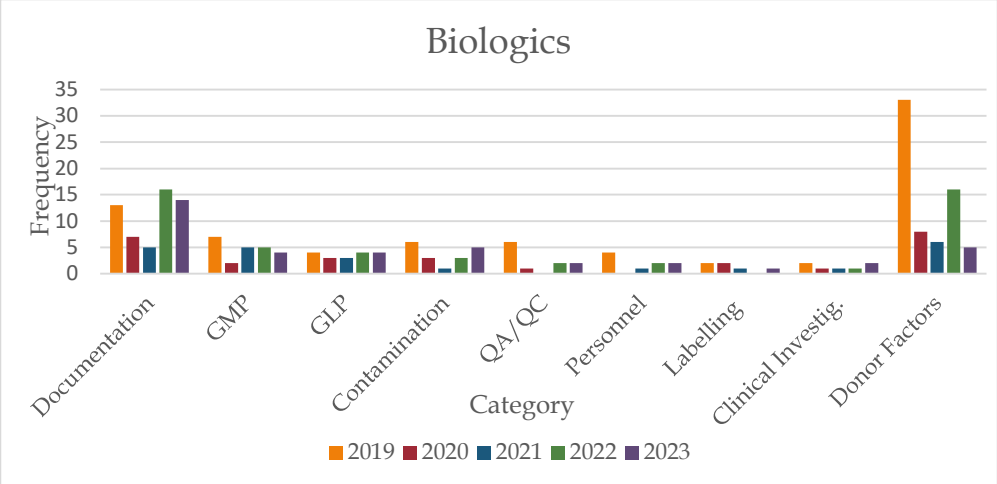

Figure 4.4: Categorical frequencies for Biologic Products

- The notification related to the donor of the biologic products observed highest notifications in 2019 at 33, followed by a sustained decline over the subsequent two years then a rise in 2022 then significantly declining in 2023.
- Documentation observed the highest number of notifications recorded in 2022 at 16 notifications and the lowest of 5 in 2021.

- Good Manufacturing Practice (GMP) notifications were generally lower than those in 'Documentation', ranging from a maximum of 7 in 2019 to a minimum of 2 in 2020.
- The 'Good Laboratory Practice' (GLP) had notifications averaging between 3 and 4 per year in those five years.
- Contamination category, reached a high of 6 notifications in both 2019 and 2023, while dipping to a low of 1 in 2021.

Analyzing the findings from all categories in Figure 4.5, we can identify the three most prevalent areas of concern for 483 inspections of biological products.

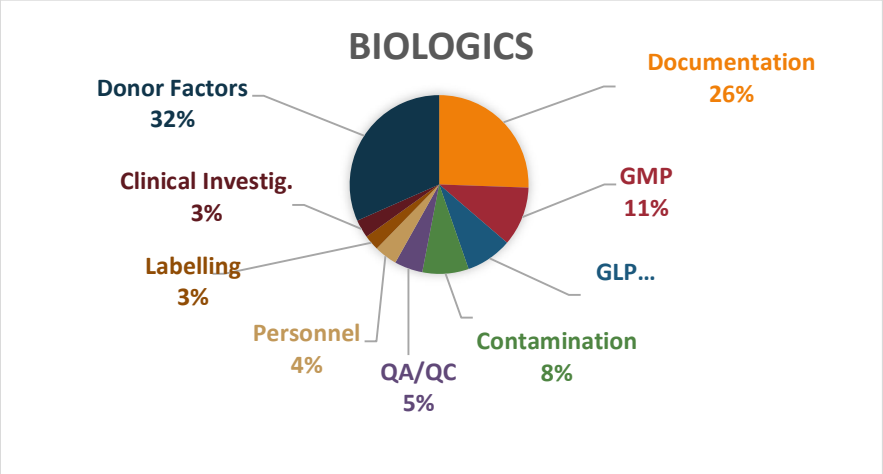

Figure 4.5: Frequency Chart for Biologic Products

➢ The category with highest frequency was the notification related to the donor of the biologic products with 68 notifications. This indicates deficiencies in procedures related to blood or tissue donation, encompassing screening, collection, or storage practices, communication with donor and acquiring proper consent. It included failure to defer a donor who tested reactive by a screening test for evidence of infection and failure to determine the suitability of a donation of blood and blood components based on risk factors or evidence of relevant transfusion-transmitted infections.

- The second highest frequency was Documentation comprising of 55 notifications, specifically failure to maintain donor, processing, storage and distribution, compatibility testing and quality control records, written reports of investigations of adverse reactions, including conclusions and follow up were not prepared and maintained. Biological product deviations were not reported within the 45-calendar day timeframe.
- Finally, "GMP" (Good Manufacturing Practice), with 23 notifications is at third. Specifically, it is observed that standard operating procedures for collection, processing, compatibility testing, storage and distribution of blood and blood components were not established, maintained and followed. Also, failure to store and maintain the Red Blood Cells between 1 and 6^0C immediately after processing and Liquid Plasma at a temperature of 1 to 6^0C within 4 hours after filling the final container as specified in the directions for use of the processing system.

5.1.3 DRUGS:

Figure 4.6 facilitates an examination of trends in 483 notifications for drugs across various categories, spanning the five-year period.

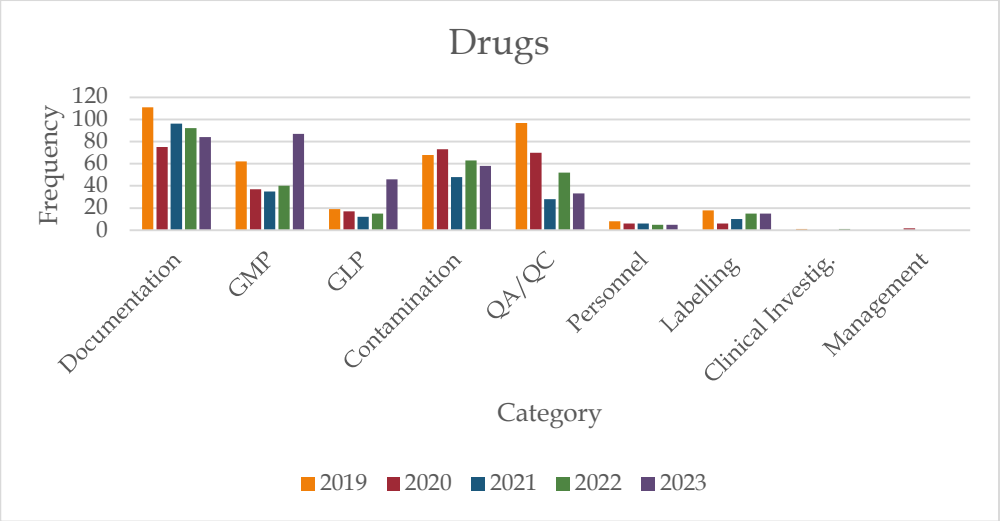

Figure 4.6: Categorical frequencies for Drug Products

- Documentation notifications had a peak of 111 in 2019 and a minimum of 75 in 2020. The frequency peaked again at 96 in 2021 then declining to 84 in 2023.
- Good Manufacturing Practice (GMP) observed high number at 62 in 2019, declining in 2020 then exhibited a significant upward trend, rising from 37 in 2020 to 87 in 2023.
- Notifications for the Good Laboratory Practice (GLP) had range from 12 to 19 annually throughout the five years.
- Contamination and Quality Assurance/Quality Control (QA/QC) categories mirrored each other, recording a high of 97 notifications (QA/QC) in 2019 and 68 notifications (contamination) in the same year, followed by a low of 28 (QA/QC) in 2021. However, QA/QC category notifications did increase to 52 in 2023.

A five-year analysis of 483 inspections for drug products revealed three most recurring areas of concern, as highlighted in Figure 4.7.

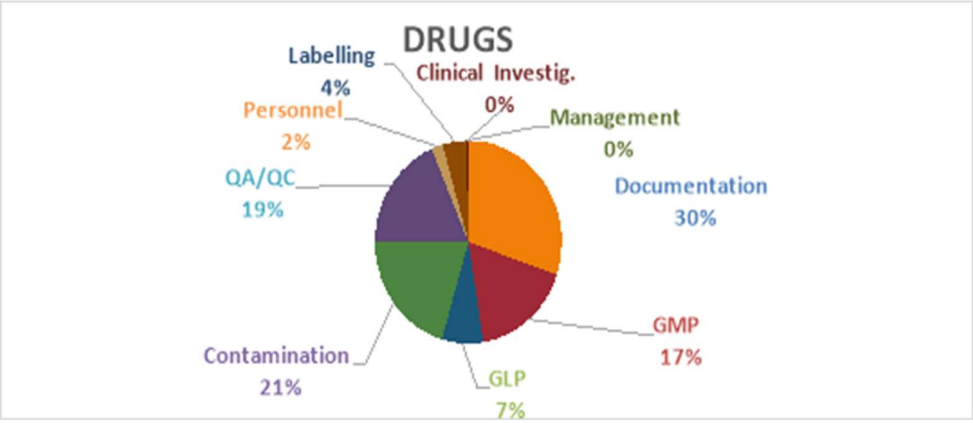

Figure 4.7: Frequency Chart for Drug Products

- The category with the most frequency, accounting for 458 observations, was Documentation. For drug products the specific observations were that batch production and control records did not include the specific identification of each batch of component and in-process material used for each batch of drug product, Laboratory records are deficient and did not

include all calculations performed during testing, Master production and control records lacked a description of the drug product containers, closures and packaging materials. a specimen or copy of each label and the signatures and dates entered by the person or persons responsible for the approval of labeling.

- The second most frequent with 310 observations was of Contamination, with inconsistencies in following sanitation procedures, having inadequate air filtration and plumbing systems and deficiency in separate or defined areas to prevent contamination or mix-ups raise concerns about the potential presence of foreign materials or microbes within the drug products.
- Third frequent was Quality Assurance/Quality Control (QA/QC) with 280 notifications. It specifically observed inconsistencies in the in-process specifications with drug product final specifications derived from previous acceptable process average and process variability estimates. Moreover, the quality control unit lacked responsibility for approving or rejecting drug products

Figure 4.8 analyses the trends in FDA 483 notification frequency for a combined dataset of drugs, biologics, and medical devices from 2019 to 2023. Overall, there is a downward trend in the total number of notifications across all categories during this period (2019-2023).

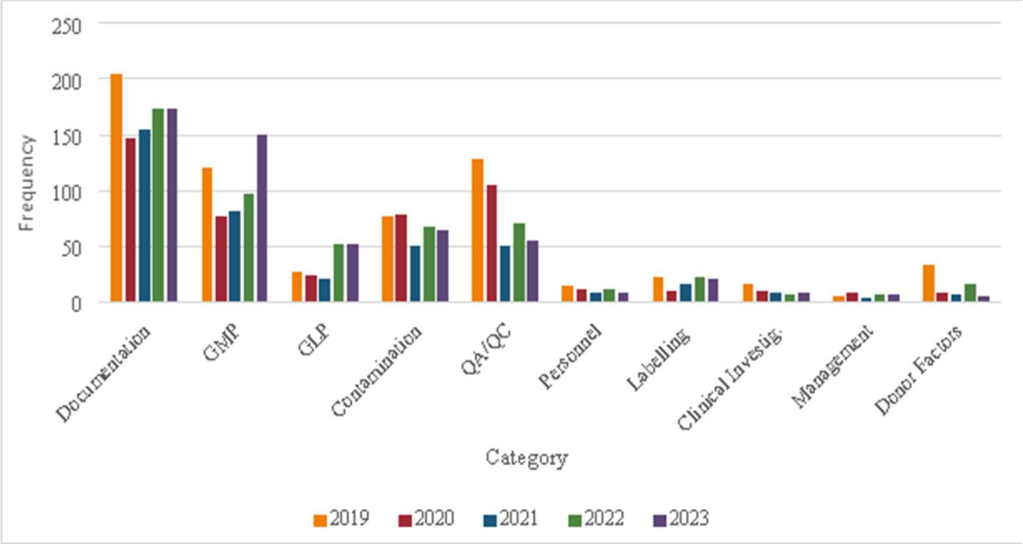

Figure 4.8: Combined Categorical frequencies for All Three Products [2019-2023]

Looking at specific categories,

- Documentation shows an initial drop from 205 notifications in 2019 to 147 in 2020 147 followed by a gradual rise in subsequent years, reaching 173 in 2023, but not surpassing the 2019 level.
- The Good Manufacturing Practice (GMP) exhibits a decline from 121 in 2019

  to 76 in 2020 but has since seen a reversal, with 2023 recording the highest number of 150 within the analyzed timeframe.
- Good Laboratory Practice (GLP) observed a decrease over time, with 27 notifications in 2019 to 24 in 2023.
- Contamination showed initial decrease from 77 in 2019 to 50 in 2021 but then increased in 2022 and 2023, reaching 65 notifications in 2023.
- Quality Assurance/Quality Control (QA/QC) observed a substantial decline over the five years, with the number of notifications dropping from 128 in 2019 to just 55 in 2023. Personnel category shows a steady downward trend, with notifications decreasing from 15 in 2019 to 9 in 2023.

- Labeling shows a minor increase from 2019 (23) to 2022 (22) followed by a slight decrease in 2023 (21).
- Clinical Investigation exhibits a consistent decline, with 16 in 2019 to 9 in 2023. Management observed an upward trend, with notifications increasing from 5 in 2019 to 7 in 2023. Finally, the Donor Factors shows a decrease from 2019 (33) to 2023 (5).

This analysis of notification trends across various categories within the combined dataset revealed mixed progress. The Documentation category initially saw a decline and then subsequently increased but not to 2019 levels. This suggests a potential systemic issue with manufacturers' ability to adequately document processes and procedures. This raises concerns about transparency and these deficiencies in record-keeping practices may potentially lead to compromising product traceability and regulatory compliance. Improvements can be brought about by implement robust documentation procedures within manufacturing facilities, conducting regular audits to ensure stricter adherence to documentation protocols, and providing training for personnel on documentation practices.

Conversely, GMP violations displayed a significant drop followed by a concerning rise, surpassing initial observations. Investing in quality improvement initiatives within their manufacturing facilities, strengthen internal auditing and inspection protocols and train personnel on SOP (Standard Operating Procedure) compliance to help ensure consistent adherence to GMP guidelines.

GLP notifications maintained a slight downward trend, while Contamination concerns fluctuated but ultimately increased in 2023. These can be reduced by conducting a thorough review of sanitation protocols and implementing a preventive maintenance program for air filtration and plumbing systems, designating separate and clearly defined areas to minimize the risk of contamination or mix- ups and invest in ongoing personnel training on aseptic techniques and proper hygiene practices.

Notably, QA/QC notifications exhibited a substantial and sustained decrease, potentially indicating improved quality control processes. Implementing a culture of continuous improvement within the QA/QC departments, conducting independent audits of QA/QC practices to identify and address any weaknesses and clearly define the responsibilities of the quality control unit, including the authority to approve or reject procedures and specifications impacting drug identity, strength, quality, and purity.

Personnel and Labeling categories displayed minor fluctuations, while Clinical Investigations showed a consistent decline and Management observations saw a slight upward trend, developing and implementing clear procedures for managing clinical investigations and ensuring effective oversight from management is essential. Donor Factors, relevant only to biologics, witnessed a significant decrease. This could be further improved by stricter donor screening protocols, improved communication with donors regarding risks and consent procedures, and enhanced training for personnel involved in collection and storage practices.

These findings suggest areas requiring continued focus, such as sustained improvement in Documentation and GMP adherence, alongside vigilance regarding potential increases in Contamination.

5.2 21CFR CITATIONS:

An analysis of citations or reference numbers within the 483 notifications issued [2019-2023] by FDA as per the product category revealed the following trends.

5.2.1 MEDICAL DEVICES:

Table 4.1: Frequency of 21CFR citations for medical devices

	2019	2020	2021	2022	2023
21 CFR 803	14	5	9	12	19
21 CFR 806	6	10	4	6	6
21 CFR 807	1	0	0	0	0
21 CFR 809	0	1	0	1	0
21 CFR 812	25	22	16	12	16
21 CFR 820	143	127	113	132	136

An analysis of medical device 483 citations between 2019 and 2023 as detailed in Table 4.1 reveals variations in the frequency of citations associated with Chapter 1(Subchapter H) of Title 21 of the Code of Federal Regulations (CFR).

21 CFR Part 820, titled "Quality system regulation," consistently exhibited the highest number of inspections across the specified timeframe. This finding suggests that ensuring robust quality management systems remains a critical area of concern for regulatory bodies This was followed by 21 CFR Part 812, concerning "Investigational device Exemptions." Investigational devices, by their very nature, carry inherent risks as they are used in research settings before full approval. This heightened scrutiny ensures that potential risks associated with these devices are adequately identified, mitigated, and monitored during clinical trials.

Conversely, 21 CFR Part 807 pertaining to "establishment registration and device listing for manufacturers and initial importers of devices" and 21 CFR Part 809 titled “in vitro diagnostic products for human use" demonstrates significantly lower inspection rates. Potentially, these areas may be deemed less risky by regulatory bodies, or that these regulations are generally well-understood and adhered to by manufacturers, leading to fewer compliance issues. These findings

highlight the ongoing emphasis on quality management systems and the heightened scrutiny applied to investigational devices within the regulatory landscape for medical devices.

5.2.2 BIOLOGIC PRODUCTS:

Table 4.2: Frequency of 21CFR citations for biologic products

	2019	2020	2021	2022	2023
21 CFR 600	7	2	2	5	5
21 CFR 606	26	13	12	23	22
21 CFR 610	10	2	0	3	4
21 CFR 630	23	9	7	14	5
21 CFR 640	11	1	2	3	3

Table 4.2 shows the 21 CFR citation frequency of the biologic products for the years 2019 through 2023. Chapter 1, Subchapter F has 21 CFR citations associated with biologic products.

21 CFR 606 "current good manufacturing practice for blood and blood Components," indicates the highest number of inspections across the specified timeframe which underscores the paramount importance placed on stringent quality control measures for blood and blood components, likely due to the inherent risks associated with these products.

This is followed by 21 CFR 600 “biological products: general”. This focus on general regulations for biological products ensures adherence to foundational safety and quality standards. The lowest frequency is displayed by 21 CFR 610 "general biological products standards". This shows that the regulations outlined

in Part 610 are well-established and consistently followed by manufacturers, resulting in fewer compliance issues.

5.2.3 DRUG PRODUCTS:

Table 4.3: Frequency of 21CFR citations for drug products.

	2019	2020	2021	2022	2023
21 CFR 211	287	226	184	231	239
21 CFR 212	32	19	19	7	26
21 CFR 310	2	2	0	1	2
21 CFR 314	15	8	10	12	10
21 CFR 361	6	0	0	0	0
FDCA 501	34	28	16	26	42
FDCA 503	3	2	4	3	3
FDCA 505	3	1	1	3	6
FDCA 760	2	0	1	0	0

Table 4.3 displays the 21 CFR citation frequency of the for Drugs products from 2019 to 2023. Citations for Drugs are associated with 21 CFR Chapter 1, Subchapters C and D.

The data reveals that 21 CFR Part 211, titled "current good manufacturing practice for finished pharmaceuticals," consistently garnered the highest number of citations across the entire period. This finding underscores the paramount importance placed on enforcing stringent quality control measures throughout the manufacturing process of finished pharmaceutical drugs.

Conversely, 21 CFR Part 361, concerning "prescription drugs for human use generally recognized as safe and effective and not misbranded: drugs Used in research," exhibits the lowest citation frequency. This observation might be explained by the specific nature of these drugs. As they are intended for research, they may be subject to less stringent regulations compared to marketed drugs.

FDCA (United States Federal Food, Drug, and Cosmetic Act) citations were also observed for drug products. FDCA 501 “Adulterated medications and devices” showed the highest number of citations. This finding suggests that ensuring the purity and safety of drugs remains a critical focus for regulatory bodies, with adulterated medications posing a significant public health concern. The data highlights the emphasis on enforcing good manufacturing practices for finished pharmaceuticals and the critical public health concern posed by adulterated medications, necessitating continued vigilance from regulatory bodies.

CHAPTER 6:- CONCLUSION

In conclusion the analysis of FDA 483 notification trends for drugs, biologics, and medical devices from 2019 to 2023 reveals a mixed picture. While there is a generally positive trend of decreasing total notifications, a closer look at specific categories highlights areas requiring continued focus and improvement efforts. The data for issuance of Form 483 notifications highlight certain categories across the three products.

Consistently high frequency of notifications for all three products was observed in the Documentation category. This suggests a potential systemic issue with manufacturers' ability to adequately document processes and procedures. This raises concerns about transparency and these deficiencies in record-keeping practices may potentially lead to compromising product traceability and regulatory compliance. Implementing standardized templates for master production and control records, exploring electronic data capture systems could streamline record-keeping and facilitate data analysis, implement a comprehensive documentation management system to ensure accurate, complete, and up-to-date records and establishing clear guidelines for timely submission of required reports may lead to decreased 483 issuances.

Good Manufacturing Practice (GMP) was the second most common category for 483 notifications which highlights potential shortcomings in manufacturing processes and procedures. Manufacturers should re-evaluate their production practices to identify and address any deviations from GMP guidelines. Quality Assurance/Quality Control (QA/QC) category can be improved by review and potentially change in inspection and testing protocols to ensure product quality.

The Donor Factors category specifically for biologics indicates a need for a comprehensive review and potential tightening of procedures related to blood or

tissue donation. Clinical Investigations and Management category while the current low number of notifications is positive, continued vigilance is essential. Contamination issues, including inadequate sanitation procedures and lack of dedicated workspaces, raise serious concerns about product safety and potential contamination risks.

The identified positive trends are the substantial and sustained decrease in QA/QC category notifications. This potentially indicates improvements in quality control processes, a crucial aspect of ensuring product safety. Additionally, the consistent decline in Clinical Investigation observations and the significant decrease in Donor Factors (relevant only to biologics) are encouraging signs.
However, the initial decline followed by a rise in the Documentation category suggests a need for more robust documentation practices to ensure consistent adherence to regulations. Similarly, the slight upward trend in Management observations highlights the importance of continual improvement in management oversight and quality management systems.

Final recommendations would be to have a comprehensive review of GMP compliance programs is recommended to identify and address any root causes leading to the rise in observations. Implementing stricter contamination control protocols and conducting regular audits to ensure their effectiveness are crucial steps. Developing and implementing standardized documentation procedures and regular review and improvement of quality management systems, along with fostering a culture of quality within the organization, are essential.

Understanding the root causes behind issuance of specific notification would help manufacturers to implement more targeted solutions. Conducting cause analysis for a representative sample of notifications could reveal underlying systemic issues requiring corrective action. Comparing notification trends with industry benchmarks or those of regulatory bodies could provide valuable insights into areas where the current practices fall short.

Moreover, developing a culture of continuous improvement within the organization., regularly review inspection findings and implement corrective and preventive actions (CAPAs) to address identified deficiencies and implementing a systematic quality improvement program for all aspects of manufacturing would foster a culture of continuous improvement and potentially reduce future notifications.

CHAPTER 7:- SUMMARY

This study examines trends in inspectional observations documented on FDA Form 483 over the past five years (2019-2023) with a focus on human drugs, medical devices, and biologics. The FDA's Office of Regulatory Affairs (ORA) plays a vital role in ensuring public health by conducting inspections of pharmaceutical industries and identifying potential violations through Form 483. These observations serve as a crucial tool for the FDA to communicate deviations from regulatory standards and potential public health risks to manufacturers.

This research aims to achieve several objectives. First, it seeks to identify overarching patterns in 483 observations across different product categories (drugs, medical devices, biologics). Second, it delves deeper into specific regulations by analyzing the most frequent CFR code violations within designated focus areas like documentation practices, Good Manufacturing Practices (GMP), and Good Laboratory Practices (GLP), etc. Third, the study intends to assess the effectiveness of current quality system practices in the pharmaceutical industry based on identified trends. By bridging the gap between external observations and internal practices, the research will evaluate how well current quality systems address areas of frequent non-compliance.

The methodology involves analyzing publicly available data on USFDA website related to 483 notifications for last five-year period. All observations were categorized in eight subgroups namely documentation practices, GMP/GLP compliance, contamination control, quality control/Quality assurance, personnel qualifications, labelling regulations, clinical trial conduct and management oversight. One additional subgroup was created for biologics namely donor factors. Data analysis will be conducted using Microsoft Excel with the aid of charts and graphs.

A analysis of FDA 483 notifications data from 2019 to 2023 revealed a general

decrease in observations across medical devices, drugs, and biologics. However, specific concerns remain within each category. For medical devices, documentation and Good Manufacturing Practices require the most attention. Documentation, Contamination, and Quality Assurance/Quality Control (QA/QC) were the most frequent observations for drugs, with QA/QC violations showing a positive downward trend. For Biologics, issue related to donors, indicates a need for a comprehensive review and potential tightening of procedures related to blood or tissue donation.

An analysis of CFR citations linked the most frequent citations in medical devices to Quality System Regulation and investigational devices, while biologics citations focused on stringent quality control for blood products. For drugs, the emphasis remains on enforcing good manufacturing practices throughout production, with a high number of citations for adulterated medications highlighting the need for vigilance in the drug supply chain. Overall, the findings call for sustained focus on documentation and GMP adherence across all product categories, alongside continued efforts to ensure robust quality control processes.

In conclusion, to ensure a sustained decrease in 483 notifications, a culture of continuous improvement is vital. Manufacturers must delve deeper by conducting root cause analyses to pinpoint and rectify underlying problems. Benchmarking against industry standards provides valuable insights into areas needing improvement. Implementing stricter contamination control protocols alongside robust documentation procedures and electronic data capture systems are crucial steps. Furthermore, fostering a quality-centric environment requires regular review of inspection findings, implementing corrective actions, and establishing a systematic quality improvement program encompassing all facets of manufacturing. This comprehensive approach will solidify a focus on quality and minimize the likelihood of future notifications.

CHAPTER 8:- REFERENCES

1. Dr. Mujeeb Shaik, Tabassum, Vidya Rachakonda, Manashwini "Findings and Regulatory Inspections of USFDA Form 483." *Int. J. Pharm. Sci. Rev. Res* 61(2) (2020): 83-87.

2. Saini Chandan, Saini Chandan, Miglani Ashish, Musyuni Pankaj, Aggarwal Geeta. "Review of form 483s and warning letters to pharmaceutical manufacturers issued by USFDA." Journal of Generic Medicines 18.1 (2022): 32-41.

3. Wang Liqing, Zheng Hang, Ren Xiaohong, Sun He "Trend analysis of FDA warning letters issued to medical products about violations to current good manufacturing practices (cGMP) between 2007 and 2014." Therapeutic Innovation & Regulatory Science 50.3 (2016): 312-318.

4. Alam, Abm Mahfuz Ul. Analyzing FDA Form 483 Data of 2023: Identifying Trends and Areas of Concern in Regulatory Compliance (2024): 1. 1-9.

5. Jyothi, M. S., V. Balamuralidhara, and R. Mahalakshmi. "Form 483, Fda warning letter and retrospective study of warning letter issued by us Fda in fiscal year 2019-2020". Journal of International Research in Medical and Pharmaceutical Sciences, vol. 16, no. 1, Apr. 2021, pp. 26-33, https://ikprress.org/index.php/JIRMEPS/article/view/6224.

6. US Food and Drug Administration. Information observation Data Sets. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection- references/inspection-observations. [Accessed 08 May 2024]

7. FDA Code of Federal Regulation Title 21. https://www.ecfr.gov/current/title-21 [Accessed 08 May 2024]

8. FDA Code of Federal Regulations (CFR) Title 21, Chapter 1, Subchapter H, C, D, F. https://www.ecfr.gov/current/title-21 [Accessed 08 May 2024]

9. FDA Form 483 Frequently Asked Questions. Available: https://www.fda.gov/inspections- compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently- asked-questions[Accessed 08 May 2024]

10. Investigations Operations Manual (2021 Version) [Internet]. U.S. Food and Drug Administration; 2021. Available: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual.[Accessed 08 May 2024]

11. The Emergency Guide to FDA Warning Letters & FDA 483 [Internet]. Thefdagroup.com; 2021. Available: https://www.thefdagroup.com/the-emergency-guide-to-fda-warning-letters-fda-483#:~:text=Receiving%20an%20FDA%20Warning%20Letter,regulators%20within%2015%20busi ness%20days [Accessed 08 May 2024

12. FDA Dashboards - Home [Internet]. Datadashboard.fda.gov; 2021. Available: https://datadashboard.fda.gov/ora/index.htm [Accessed 08 May 2024].

13. DiGIulio D. FDA's Pre-Approval inspection (PAI) program and how to prepare for a successful outcome, https://www.fda.gov/media/94064/download (2015, accessed 8 May 2024).

14. Ohanian P. Understanding the 4 types of FDA inspections. Halloran Consulting Group, https://www.meddeviceon line.com/doc/understanding-the-types-of-fda-inspection-0001 (Accessed 8 May 2024).

15. Lauer, Madelyn, "FDA Device Regulation." *Missouri medicine* vol. 114,4 (2017): 283-288.

16. Rägo, Lembit, "Regulatory framework for access to safe, effective quality medicines." *Antiviral therapy* vol. 19 Suppl 3 (2014): 69-77. doi:10.3851/IMP2902.

17. Inspectional Observations and Citations. Available https://www.fda.gov/inspections-compliance- enforcement-and-criminal-investigations/inspection-references/inspectional-observations-and- citations. [Accessed 7 May, 2024]

18. Inspection Guides https://www.fda.gov/inspections-compliance-enforcement-and-criminal- investigations/inspection-references/inspection-observations [Accessed 8 May, 2024]

THESIS.docx

ORIGINALITY REPORT

7%	6%	3%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	ecfr.federalregister.gov Internet Source	2%
2	globalresearchonline.net Internet Source	2%
3	Antoine Al-Achi, Mali Ram Gupta, William Craig Stagner. "Integrated Pharmaceutics", Wiley, 2022 Publication	1%
4	etheses.lse.ac.uk Internet Source	1%
5	public4.pagefreezer.com Internet Source	1%
6	elibrary.law.psu.edu Internet Source	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		