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GMP Compliance on Ophthalmics

Analysis of EMA and FDA inspections deviations

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Declaro que o presente documento é um trabalho original da minha autoria e que cumpre todos os requisitos do Código de Conduta e Boas Práticas da Universidade de Lisboa.

Preface

The work presented in this thesis was perfomed at the company *Dávi II Farmacêutica- Produção e Desenvolvimento* (Lisbon, Portugal), during the period March-September 2021, under the supervision of Dr. Rui Loureiro. The thesis was co-supervised at Instituto Superior Técnico by Prof. José Cardoso Menezes.

Resumo

A indústria farmacêutica é uma das indústrias mais reguladas no mundo. As entidades reguladoras, como a Agência Europeia de Medicamentos (EMA) e a Federal Drug Administration (FDA), realizam inspeções regulares para avaliar se o processo de fabrico e a unidade fabril cumprem os requisitos legais. Como os requisitos das preparações oftálmicas são particularmente mais exigentes, que outras formas de farmacêuticas, o seu processo de fabrico é mais complexo e, por conseguinte, apresenta um maior risco de desvios.

Para identificar os desafios do setor, relativamente ao cumprimento da regulamentação das entidades reguladoras Europeia e Americana, foram recolhidos dados da base de dados pública da FDA e através do pedido pelo *Freedom of Information Act* (FOIA) e pelo relatório de boas práticas de fabrico da EMA. Posteriormente, foi analisada, sistematizada por categorias, e verificada.

O desvio mais comum encontrado está associado à categoria Procedimentos nas inspeções da EMA (31,1%) e da FDA (42%). Numa análise mais aprofundada dos dados das inspeções da FDA, os procedimentos foram a causa principal de desvio, dado que na maioria das vezes os procedimentos não se encontravam escritos (33%) e aqueles que estavam não foram seguidos (18%). A categoria Registos, correspondente a 30% de todos os desvios nas inspeções da FDA, é a segunda categoria mais prevalente, devido à falta de investigações (79%).

A análise sistemática identifica os principais desvios encontrados nas inspeções oftálmicas. Desta forma, os produtores de produtos oftalmológicos podem estar mais atentos a estes aspetos e melhor preparados no caso de uma inspeção.

Palavras-chave: Inspeções; Desvios; EMA; FDA; Procedimentos; Registos.

Abstract

The pharmaceutical industry is one of the most regulated industries worldwide. Regulatory authorities like the European Medicines Agency (EMA) and Federal Drug Administration (FDA) conduct regular inspections to assess sites and manufacturing process compliance with regulations. As ophthalmic preparations are particularly demanding as far as requirements are compared with other dosage forms, their manufacturing process is more complex and, therefore, shows a higher risk for deviations.

To identify the industry's hurdles, as far as compliance with regulatory authorities in Europe and the United States, data was gathered from the FDA public database and from the request made by the Freedom of Information Act (FOIA) and EMA's Good Manufacturing Practice report. Subsequently, it was analyzed, systematized by categories, and verified.

The most common deficiency was related to the Procedures category in EMA's (31,1%) and the FDA's inspections (42%). In a more in-depth analysis of the FDA's inspections data, this mostly happened because there were no written Procedures 33% of the time, and 18% of those written were not followed. The Records category, 30% of all deviations in the FDA's inspections, is the second-highest from which 79% are of investigations not followed through.

The systematic analysis enabled the identification of the main issues around Ophthalmic inspections. This way, Ophthalmic manufacturers can be more attentive to these aspects and be better prepared in the event of an inspection.

Keywords: Inspections; Deviations; EMA; FDA; Procedures; Records.

Acknowledgments

Behind our achievements, we usually associate luck. Although luck may have a small part in them, they are mostly the result of a huge amount of work and determination. The support and assistance of some of the people mentioned below are what kept me going and focused on the finishing line.

First and foremost, I would like to thank the Food and Drug Administration (FDA) for providing me the data I needed to fulfill the purpose of this master thesis.

I want to thank my supervisor, Professor Rui Loureiro, for his dedication and guidance throughout each step of the way. You inspired my interest in this thesis, and I never felt like this was a burden because of it. Your expertise was invaluable in its development, as was your feedback. It encouraged me to sharpen my thinking and brought my work to a higher level. I am extremely thankful to have you as my supervisor.

Last but not least, I would like to thank my parents and family for their wise counsel, a sympathetic ear, encouragement, and for believing in me. You are always there for me, and I am extremely grateful for you. Finally, I could not have completed this dissertation without the support of my friends and my loving boyfriend. Thank you for proofreading all of my work.

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List of Acronyms

ADME- Absorption, Distribution, Metabolism, and Excretion

API- Active Pharmaceutical Ingredient

CAPA- Corrective Actions and Preventive Actions

CFR- Code of Federal Regulations

cGMP- Current Good Manufacturing Practices

CHMP- Committee for Medicinal Products for Human Use

CMO- Contract Manufacturing Organization

CVMP- Committee for Medicinal Products for Veterinary Use ().

EEA- European Economic Area

EMA- European Medicines Agency

EU- European Union

FEI- FDA Establishment Identifier

FDA- Food and Drug Administration

FOIA- Freedom of Information Act

GMP- Good Manufacturing Practices

MA- Marketing Authorization

MAH- Marketing Authorization Holder

NAI- No Action Indicated

NCA- National Competent Authorities

OAI- Official Action Indicated

R&D- Research and Development

US- United States of America

VAI- Voluntary Action Indicated

WHO- World Health Organization

WFI- Water for Injection

Glossary

Instillation- is the act of pouring or injecting a substance, in this case, eye drops, drop by drop.[1]

Ophthalmic drops (eye drops) are sterile aqueous or oily solutions, suspensions, or emulsions intended for instillation into the conjunctival sac.[2]

Ophthalmic emulsions are generally dispersions of oily droplets in an aqueous phase. There should be no evidence of breaking or coalescence.[2]

Ophthalmic suspensions- contain solid particles dispersed in a liquid vehicle and must be homogeneous when shaken gently and remain sufficiently dispersed to enable the correct dose to be removed from the container. A sediment may occur, but this should disperse readily when the container is shaken, and the size of the dispersed particles should be controlled. The active ingredient and any other suspended material must be reduced to a particle size small enough to prevent irritation and damage to the cornea.[2]

Ophthalmic ointments are sterile, homogeneous, semi-solid preparations intended for application to the conjunctiva or the eyelids.[2]

1. Introduction

Ophthalmic preparations present a particular challenge to developers and manufacturers due to the targeted organ and their manufacturing process complexity and requirements. Regulatory agencies are incredibly attentive when dealing with this kind of pharmaceutical dosage form, manufacturing process, and facilities.

1.1 Contextualization

The International Pharmacopoeia defines ophthalmic preparations as “sterile, liquid, semi-solid, or solid preparations that can contain one or more active pharmaceutical ingredient(s) (API) meant for the application on the conjunctiva, the conjunctival sac, or the eyelids”.[3]

The excipients or base used on the preparation of ophthalmic preparations must not adversely affect the stability of the final product or the availability of the API. Product development studies are done to prove that the chosen excipients or base do not react as expected.[3] The same also applies to the primary packaging materials; they should not react with the formulation and components.

Ophthalmic preparations can be single or multidose. Multidose preparations, whose API does not have antimicrobial activity, may include an appropriate antimicrobial agent to prevent microbiological activity. During the product’s period of use, the antimicrobial activity should endure its effectiveness.[3]

As previously mentioned, these products are required to be sterile. They also have other requirements, like isotonicity and restrictive pH range, that should be considered.[4] Therefore, their manufacturing process is more demanding than the other drug products.

All manufacturing processes consist of two parts: Research and Development (R&D) and Production. They must all follow the requirements of Good Manufacturing Practices (GMP). These regulations establish the minimum standards for the manufacture, processing, and packing of a drug product.[5]

The R&D process consists of seven steps, as indicated in Figure 1.1.

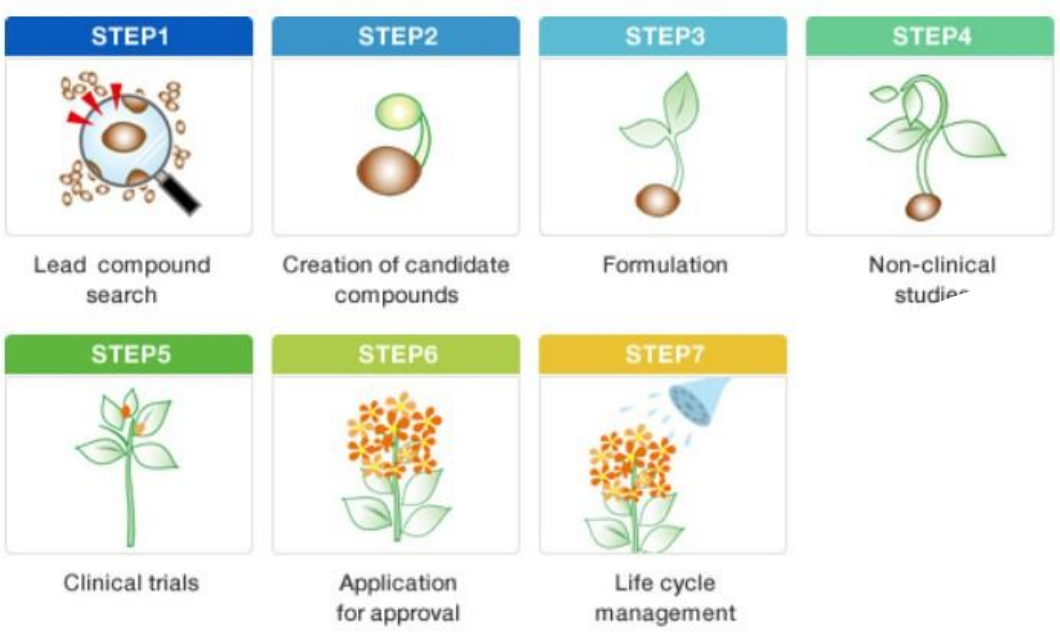

Figure 1.1- The Ophthalmic Production Process Part I: R&D [6]

The first step in the R&D process is searching for a lead compound that could end up in a new drug. A lead compound has a chemical component that demonstrates good biological activity and shows preferential pharmaceutical properties. The pursuit for potential lead compounds consists, firstly, of sorting through natural ingredients from plants and microorganisms and then artificially synthesized compounds. The process of testing millions of possible compounds is a time-consuming job. For this reason, companies focus on shortening the screening process by using network-based drug discovery processes or by partnerships between other pharmaceutical companies or universities.[6]

The finding of a lead compound does not necessarily mean the development of a new drug product.

The creation of candidate components, step 2, includes repeated chemical modification and evaluation throughout the process to achieve the highest level of safety and efficacy possible. A multidisciplinary team is assembled to enhance research productivity. The result of their collaborative screening work leads to the conduct of several pharmacological and toxicity studies on the derivatives of the lead compound to determine its safety and efficacy. Given the results of these tests, some compounds can proceed to the Third Phase of the development process.[6]

The compound that makes it to this stage is known as the Active Pharmaceutical Ingredient (API). The API is mixed with additional substances called excipients to maximize the performance of the API. As previously mentioned, these cannot adversely affect the final product's stability or the availability of the API. After mixing ratios of excipients and optimal dosage form of the final product are established, the compound is suitable for clinical use. Stability and formulation performance tests are also conducted for the development of safer and efficacious drugs.[6]

The following step, step 4, exists to determine if the desired expectations are met or if any other safety concerns arise. In this step, the finished product undergoes non-clinical studies on animals or in-vivo models that evaluate the effects on human physiology. These tests involve pharmacokinetic

studies, also known as ADME studies, whose purpose is to examine the compound's performance under physiological conditions.[6]

A positive outcome on the non-clinical studies leads to the next stage of the manufacturing process, full-scale clinical studies (step 5). These studies, divided into three phases, examine the effects of the drug product on the human body. In Phase I of the clinical trials, the compound is administrated to a small number of healthy individuals. Phase II aims to analyze and characterize the safety and performance of the product. This Phase is helpful when it comes to pinpointing the appropriate dosage and administration methods. It is conducted in a small group of people that suffer from a particular disease at different stages for which the product is being developed. Finally, in Phase III, the product is administered to a large number of patients to establish a comparison between the product in the study and alternative available treatments or placebo. Some clinical trials are performed at local and international sites.[6]

After proving its safety and effectiveness, the product must obtain market authorization to be commercialized, step 6. As such, the drug must be approved by the regulatory agencies where the product is being manufactured and commercialized.[6] The two most important regulatory agencies discussed throughout this thesis are EMA and FDA. These agencies choose several experts in the field to analyze the application and results from the clinical trials. If the product is approved, then it is ready to be commercialized.

The newly approved drug will continue to be monitored, given that patients react differently to its properties. As such, it is the pharmaceutical companies' responsibility to monitor every drug that enters the market for adverse effects or even unanticipated positive effects that go unnoticed throughout the clinical trials. This monitoring program is known as the Life Cycle Management (LCM), whose purpose is to ensure that the product remains safe and effective from an ethical, medical, regulatory, and commercial point of view. Pharmacovigilance, one of the main functional groups of the LCM, is responsible for the detection, assessment, understanding, and prevention of adverse reactions and any other problems that can emerge associated with a medicine or vaccine.[6–8]

The second part of the manufacturing process is the production itself. This manufacturing process, represented in Figure 1.2, splits into five steps. This manufacturing process has more steps and has a greater impact if specifications are not met.[9]

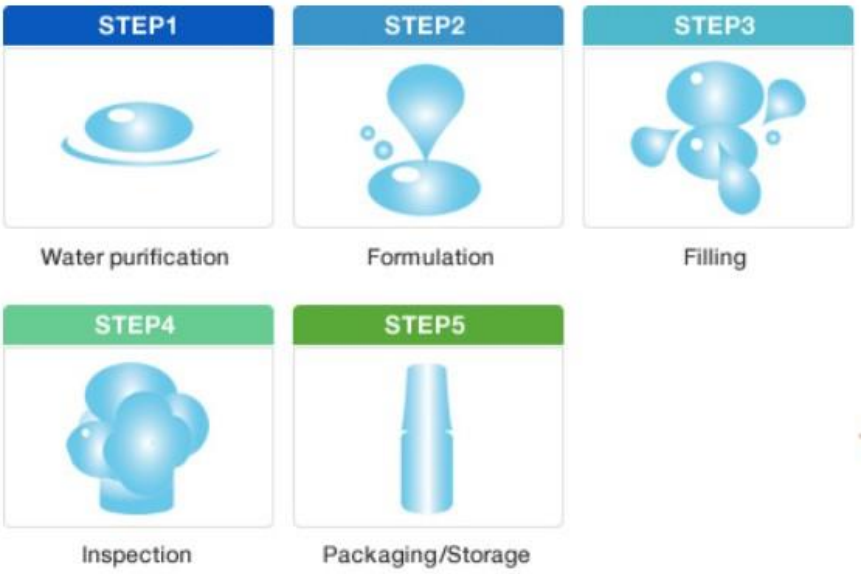

Figure 1.2- The Ophthalmic Production Process Part 2: Production [9]

The first step has been revealed as one of the most critical steps in the production process as it is the most significant component in the final product. The water used in the production of sterile products is known as Water for Injection (WFI). The International Pharmacopeia describes this water as clear and colorless liquid and odorless.[2,9] It is obtained by distillation or reverse osmosis of purified or potable water. [2,10]

Raw materials are subjected to quality control testing and documentation review upon arrival at the firm. When approved, they undergo an air shower to remove undesired particles and are left in quarantine. In this step, they are carefully weighed and loaded into the formulation tanks. As previously said, the water used throughout the process is purified water. It is charged to the formulation tanks after passing through airtight and septic pipes. Even though this process is computer-controlled, it should be supervised by the operators or managers to safeguard the quality of the final product. [9]

The resulting solution from the formulation process is subject to sterile microfiltration. Then, via airtight aseptic pipes, this solution is set to the filling machine. The machine most commonly used in this field is the Blow/Fill/Seal (B/F/S) since it can continuously form, fill, and seal while maintaining a sterile environment. Step 3 is known as the step most susceptible to microbiological contamination. For this reason, the filling area must maintain a comparable degree of air quality as the standards required in the other operating rooms.[9]

The equipment used for filling depends on whether the product is single-dose or multidose. If the product is a single dose, the equipment used is a Blow/Fill/Seal machine (B/F/S), while multidose products use an aseptic bottle filling machine. The air quality in this area should be the same as the operating rooms as this step is the most prone in terms of microbiological contamination. The resulting solution from step 2 is subjected to sterile microfiltration and pumped through airtight septic pipes to the designated equipment.

In step 5, if the final products meet specifications, then they are labeled according to their serial numbers and expiration dates and, finally, placed in small boxes. These are packed in larger cardboard boxes and stored in climate-controlled rooms. Additional testing is conducted on sample products to assure the quality of the manufactured goods. These tests aim to determine the sterility and chemical quality of the finished product. The results from these studies will determine if the products are finally ready for shipment. For this to happen, asepsis, physical chemistry, water quality, environmental monitoring, and other specific requirements must be considered satisfactory.

According to the International Pharmacopeia, there are several types of ophthalmic preparations, and requirements should be met. Generally speaking, all preparations must comply with the general requirements presented in the first column of Table 1.1. The other columns show which requirements need special consideration for specific Ophthalmic preparations, including Ophthalmic drops, emulsions, suspensions, and ointments. [3]

Table 1.1- Requirements for specific types of ophthalmic preparations

	Ophthalmics (general)	**Drops**	**Ointments**	**Emulsions**	**Suspensions**
Visual Inspection	X	X			X
Sterility	X				
Particle Size	X				
Containers	X	X	X		
Labeling	X				
Storage	X				
Organoleptic inspection			X		
Uniform consistency			X		

Inspections are conducted regularly to assess if the manufacturing process is compliant with regulations. Several types of inspections and regulatory agencies will be discussed further on, mainly focused on the European Medicines Agency (EMA) and Federal Drug Administration (FDA).

As the manufacturing process is more complex than the other drug products, there is an increased risk of presenting deviations during inspections. The deviations found during inspections were analyzed according to their frequency, type, location, and company.

1.2 Objectives

Inspections are a regular part of the pharmaceutical industry. Depending on the regulatory authority conducting the inspection, different outcomes can arise from the observations, such as the inspection's classification and its consequences. The data gathered during the inspection process is registered and later put in a database. This data makes it possible to monitor differences between different ophthalmic manufacturers, countries, regulatory agencies, and deviation trends.

The purpose of this master thesis is to study quality issues reported during inspections by regulatory authorities, EMA, and FDA. This thesis allowed us to identify the industry's hurdles regarding compliance with regulatory authorities in Europe and the United States.

To accomplish this, data of inspections carried out (in ophthalmic manufacturers) by the EMA and FDA, both published and non-published data, was gathered, analyzed, systematized, and verified. It was possible to identify the most commonly found deficiencies and which of them were major, minor, and critical. This analysis helps manufacturers prevent these issues and be prepared in the event of an inspection.

1.3 Methodology

First and foremost, it was necessary to gather data from inspections conducted by EMA and FDA.

The FDA has an available public Inspection Classification Database where information is disclosed about inspections' classification, manufacturers, company location, etc.

Unlike FDA, EMA does not have a public database. There is a public GMP database, but it only discloses the current status of the manufacturer that shows if the manufacturer's GMP license is suspended or revoked. The EMEA Inspections Sector registers all GMP deficiencies on a GMP database, using Microsoft Access GMP Database.[11]

As for the FDA data, the public database only allowed us to narrow down to two companies known for manufacturing only ophthalmic products. Through the CFR infringed, it was possible to exclude infringements of other deviations beyond GMP deviations. Given that the sample of data was not significant, I contacted the FDA Inspection Classification to request information on inspections carried out in Ophthalmic companies or Contract Manufacturing Organizations (CMOs) that manufactured Ophthalmics. I hoped that by having more data on Ophthalmic manufacturing firms, I would have more comprehensive information. They replied, saying that the information I required wasn't available online and that I could submit the Freedom of Information Act (FOIA) requesting it.

I ended up submitting a FOIA, number FDA2174286. The request was approved, and the data was sent. The Acknowledgment Letter of the FOIA submission can be found in Annex A. The FDA's response to the FOIA application can be found in Annex B.

This master thesis is based on the data that FDA disclosed on their database and the data that was received from the FDA. Also, it is based on the EMA's data report called *"Good Manufacturing Practice: An analysis of regulatory inspection findings in the centralised procedure."* The data analyzed and systematized in categories was based on the available online data and the data requested and supplied by the FDA. Nevertheless, more data may exist than the ones included in this analysis as it was possible to find several Warning Letters and Observations Forms of inspections carried out in Ophthalmic manufacturers with GMP deviations not present in the Excel file provided.

2. Inspections

The pharmaceutical industry is one of the most regulated industries worldwide. Each country has a National Competent Authority (NCA), and geopolitical entities have supernational agencies (*e.g.,* EMA). Its purpose is to verify the company's compliance with current and local legislation and regulations regarding its development, manufacturing process, licensing, registration, manufacturing, marketing, labeling of pharmaceutical products, and post-marketing surveillance. They are also responsible for issuing guidelines for pharmaceutical companies. Besides that, their main challenges are safeguarding the drug product's safety, quality, and efficacy. This thesis mainly focuses on the US Regulatory Authority, Food and Drug Administration (FDA), and European Medicines Agency (EMA). Other major Regulatory Agencies are presented in Annex C.[12]

The Regulatory Authorities make either announced or unannounced assessments at the facility's location. This assessment is called an inspection. As the name says, inspections are carried out by inspectors. There are different types of inspections: general GMP inspection, routine inspections, product-related inspection, or a for-cause/targeted inspection. In the industry, inspections are regularly part of the business. For example, it is requested to have a pre-approval inspection of the manufacturing site to guarantee that there are systems in place that ensure the safety and quality of the product as soon as it enters the market. In this regard, inspections can focus either on the product itself or in a broader scope (product, line, site, or function). It is also possible that they are focused on a particular function that the Agency looks into, like IT systems, data privacy, etc.

2.1 Beginning the Inspection

As previously mentioned, inspections can be announced or unannounced. Either way, the beginning of an inspection starts this way:

In case of an FDA inspection, the inspection is initiated as soon as the inspector arrives at the company. The inspector presents their credentials and the original, duly signed copy of the Notice of Inspection (FDA Form 482).[13,14] You can find an example of this Form in Annex D.

Unlike FDA inspections, EU inspections start with an open and verbal discussion regarding the objective of the inspection, expectations, documents that they will need, and people to be interviewed throughout the inspection process. There is no formal documentation to be handed in at the beginning of the inspection.[13]

2.2 Document Requests

Inspectors may request access to documents. These should have the "confidential" stamp on, and subject identifiers should be removed from the copies provided as much as possible. The company assigns an employee the responsibility to stay with the inspectors and keep track of their requests, questions, and comments.

The Document requests can be made verbally (FDA inspections) or in writing, maintaining a record of the requested documents versus received (EU inspections). This record is given to the designated employee, who is responsible for assisting the inspection process.[13]

2.3 Site tour

Inspections carried out by FDA or EEA Member States on behalf of EMA require a site tour. The investigator will assess and verify if all resources, personnel, and the entire facility site meet the requirements.[13]

The inspectors may request additional documents or procedures. As part of the inspection preparation, general rules should be followed by staff members. They should be prepared and trained to:[13]

- "Be concise and answer only the questions that are asked;
- Do not volunteer information outside of what is asked;
- Do not guess or speculate;
- Do not refuse information requests or argue with inspectors."

2.4 Inspection Close-out meetings

2.4.1 Food and Drug Administration (FDA)

Before the inspection process is completed, inspectors meet with the firm's management team for a close-out meeting. In this meeting, they discuss the observations (if any) that were made during the inspection. They leave a written report whenever there are deviations, known as "Inspectional Observations," Form- 483. This Form is issued and objectively lists the observations found during the inspection, whether related to the product itself or the manufacturing process. It also states whether the observations made in a prior inspection have not been resolved or whether they are recurrent.[13,14] An example of the FDA- 483 Form can be found in Annex E. The Form attached is relevant to Ophthalmic preparations.

2.4.2 European Medicines Agency (EMA)

In the close-out meeting, held at the end of every inspection, the inspector presents the deficiencies and failures found during the inspection process to the firm's representatives. The meeting's agenda is to discuss the deficiencies encountered during the inspection process and their importance. Deadlines are also established for the implementation of a Corrective Action and Preventive Action (CAPA) program. [11]

First, a draft of the report or a post-inspection letter is sent to the manufacturer. This draft addresses the deficiencies found. Then, when the process is complete, a final report is sent to EMA incorporating

the manufacture's response to the draft and respective chapters and paragraphs of the EU GMP guide regarding every deviation found.[11,15]

2.5 Types of Inspections

2.5.1 General GMP Inspection

A GMP general inspection is intended to verify that the manufacturer is compliant with GMP standards. These aim to ensure that the entire manufacturing process is following relevant marketing authorization, described in Articles 5 of Directive 2003/94/EC and 91/412/EC.[11]

2.5.2 Routine Inspections

Routine inspections are performed regularly and scheduled by the Regulatory Authority at the Marketing Authorization Holder (MAH) or, if the MAH does not manufacture the product, Contract Manufacturing Organization (CMO), typically every 2 to 4 years. Usually, these types of inspections are announced in advance. Some Regulatory Authorities, like FDA, generally arrive unannounced, even in these types of inspections.

2.5.3 Targeted Inspections

Unlike routine inspections, a for-cause inspection, also known as targeted inspections, is likely unannounced. These inspections are initiated in response to a particular matter that the Regulatory Authority notices or is warned by several sources. Their purpose is to determine whether an issue exists.

The following items demonstrate what would eventually trigger a for-cause inspection:

- A health concern of use particular class of products- active ingredients or excipients;
- Poor GMP compliance;
- Poor compliance company profile;
- A new interpretation of an existing regulation;
- A change to the GMP or cGMP;
- Disgruntled staff complaint;
- Product's Recall;
- A follow-up to a recent inspection.

2.6 Inspection Classification

Throughout the inspection process, inspectors make several observations. In the end, they evaluate them and determine which ones are to be reported. Note that all of these observations must be recorded and backed up by factual evidence.

At the close-out meeting, inspectors inform that additional observations may be made in the written inspection report. The final report is handed to the manufacture within a specified timeframe, generally after the close-out of the inspection. Some agencies, namely FDA, provide the detailed inspection report at the inspection close-out.

In the event of deviations, a CAPA program should be initiated. This program intends to identify, acknowledge, and investigate a given deviation and then implement actions to correct and prevent the deviation from happening again. These actions are later validated, and the program is complete. The actions implemented must be communicated to the Regulatory Agencies to let them know what measures were taken and whether these measures solve the deviations found in the inspection.

2.6.1 EMA's Inspection Classification

Deviations found during inspections are classified according to the EMA's guidelines as per Table 2.1:

Table 2.1- EMA's grading of inspection findings [11,16]

Grade	Description
Minor Findings / Other / Recommendations	Conditions, practices, or processes that would not be expected to adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data.[16] **Possible consequences:** Observations classified as minor indicate the need for improvement of conditions, practices, and processes.[16] **Remark:** Many minor observations might indicate a bad quality, and the sum might be equal to a major finding with its consequences.[16] **Comments:** The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.[16] Deficiencies which cannot be classified as critical or major, possibly because of lack of information, but which nevertheless indicate departures from GMP. They are not necessarily of minor nature and are essentially unclassified.[11]
Major Findings	Conditions, practices, or processes that might adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GMP principles.[16] **Possible consequences:** data may be rejected and/or legal action required.[16] **Remark:** Observations classified as major, may include a pattern of deviations and/or numerous minor observations.[16] A non-critical deficiency which has produced or may produce a product, which does not comply with its marketing authorization;[11] A non-critical deficiency which indicates a major deviation from EU GMP;[11] (within EU) A non-critical deficiency which indicates a major deviation from the terms of the manufacturing authorization;[11] A non-critical deficiency which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfill his legal duties;[11] A combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.[11]

Critical Findings	Conditions, practices, or processes that adversely affect the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.[16] **Possible consequences:** rejection of data and/or legal action required.[16] **Remark:** Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data, and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.[16] A critical GMP failure occurs when a practice could give rise to a product which could or would be harmful to the patient or animal, or which has produced a harmful product. A combination of major deficiencies, which indicates a serious system failure, may also be classified as a critical deficiency.[11]

2.6.2 FDA's Inspection Classification

As previously discussed, the close-out meeting is meant to discuss the observations that have been made throughout the investigation process. The inspection is classified as No Action Indicated (NAI) when no deficiencies were found. [14,17]

In case deviations are found, they need to determine if they are minor or major violations. If they are faced with minor violations, the inspection is classified as Voluntary Action Indicated (VAI), and a '483 Observation Forms is issued. This Form lists the deficiencies found in the system or processes. It is the lowest grade of the FDA's grading system. The manufacture has 90 days to submit, be approved, and implement a CAPA program. [14,17]

Serious violations trigger an Official Action Indicated (OAI) rating, issuing a Warning Letter/Untitled Letter. Warning Letters, also known as Untitled Letters, are issued for serious violations with regulatory implications. Like the previous grading, the manufacturer has 90 days to submit, be approved, and implement a CAPA program. [14,17]

If by any chance a CAPA program is not submitted or approved, or implemented within 90 days or the stipulated timeframe, VAI classifications scale-up to OAI and OAI can turn into a Consent Decree.

A Consent Decree is an agreement approved by the Federal Court between the company and the Regulatory Agency, the FDA. Its purpose is to bring the case to a close. In exchange, the company has to pay a fine or promptly implement actions that satisfy the FDA. During this time, the company is obliged to cancel or stop the production of non-essential or multi-source products and must appoint a third party company who will take over testing, release functions, and other responsibilities.[18]

In Annex F there's an example of a Warning letter sent to Akorn, Inc., relevant to Ophthalmic preparations.

Table 2.2 describes FDA inspection grading, while Figure 2.1 illustrates the process described earlier.

Table 2.2- FDA's grading of inspection findings

Inspection Classification	**Description** [19]
No Action Indicated (NAI)	No objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action).
Voluntary Action Indicated (VAI)	Objectionable conditions or practices were found, but the Agency is not prepared to take or recommend any administrative or regulatory action.
Official Action Indicated (OAI)	Regulatory and/or administrative actions will be recommended.

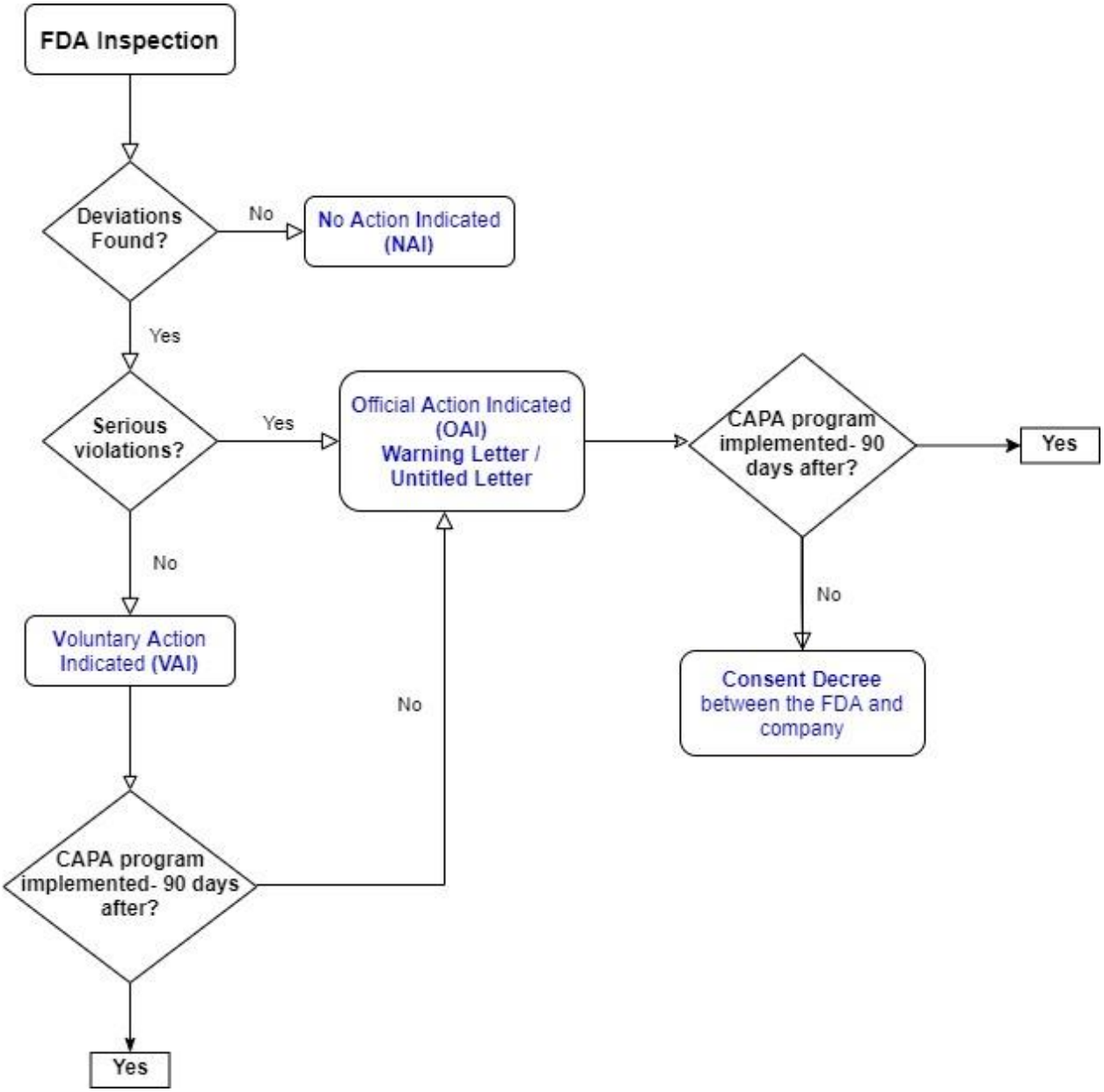

Figure 2.1- FDA's Inspection process

2.7 Overview

The following table, Table 2.3, gives an overview of the differences between the Regulatory Authorities inspections.

Table 2.3- Overview of the general aspects of inspections carried out by different Regulatory Authorities

Regulatory Authorities	Inspections	Duration	Beginning of Inspections	Document Requests	Site Tour	Classification
FDA	Usually **unannounced,** regardless of what type of inspection	**No timeframe** for the conclusion of the inspections	Inspectors present their **Credentials** and **Notice of Inspection- Form 482**	**Yes** Request them **Verbally**	**Yes**	• **No Action Indicated (NAI)** • **Voluntary Action Indicated (VAI)** • **Official Action Indicated (OAI)**
EMA	Typically, they are **announced** in advance. However, and although rare, inspections can also be unannounced. Provides an agenda.	**Stipulated timeframe-** however, extra inspection days may be needed if issues are encountered that should be further investigated.	**Open Verbal Discussion** **No formal Documentation**	**Yes** Keep a **Written Record** (Requested versus Received)	**Yes**	• **Critical Findings** • **Major Findings** • **Minor Findings / Other / Recommendations**
Globally	In contrast with the FDA and EMA, inspections carried out in the rest of the world have a more **local focus**, given that their **Regulatory Authorities have different levels of maturity and experience.**					

3. European Medicines Agency (EMA)

The European Medicines Agency (EMA) is the Regulatory Authority in charge of the scientific evaluation, supervision, and safety monitoring of drug products in the EU.

Pharmaceutical companies must apply to be able to market and distribute drug products. In the EU, a centralized procedure allows the companies to submit a single application, evaluation, and authorization to be granted marketing authorization in all EU countries and European Economic Area (EEA). The company that has been granted marketing authorization is known as Marketing-Authorization Holder (MAH). EMA is the regulatory authority responsible for all drug products' application reviewal governed by the centralized procedure, as not all are suitable for this application.[20–22]

The centralized procedure assures that all drug products sold in the EU or the EEA Member States are the same. It also allows permanent centralized safety monitoring as well as product information available in all EU languages.[20]

Depending on whether the drug product is intended for Human use or Veterinary User, EMA will gather a scientific committee that will be responsible for the evaluation and recommendation if the marketing authorization application should be granted or not. These scientific committees are Committee for Medicinal Products for Human Use (CHMP) And Committee for Medicinal Products for Veterinary Use (CVMP).[11,20]

As EMA does not have the authority to allow marketing authorization in the EU countries, a recommendation is sent to the European Commission. This entity has a legal binding force to grant drug products authorization. It is based on EMA's feedback that a decision will take place. If the EMA's recommendation is positive, the European Commission has 67 days to enact its decision.[20]

In the EU, every company is inspected by the NCA and NCA of the countries they intend to export. The NCA is responsible for the authorization and drug reimbursement program at a country level.

If the NCA is part of the EEA Member States, they can carry out inspections on behalf of the EMA. For example, Portugal is a Member State of the EEA. As such, its NCA, Infarmed, can carry out inspections on behalf of EMA. Therefore, every manufacturing process inspected and approved by Infarmed is automatically approved by EMA, which enables Portugal to distribute its products to the other EEA Member States.[11,21]

EudraLex regulates drug product manufacturers in the EEA. EudraLex is a set of Regulations and Directives that govern drug products in the EU, compiled into ten volumes. The difference between Regulations and Directives is that Regulations are legally binding and have to be implemented in every Member State precisely and enter into action on the same date. Directives, however, establish a set of outcomes that must be achieved and need to be transposed into National Laws. Member States can make minor changes as long as the content and purpose of the Directive are not altered. Unlike the Regulations, they do not enter into force immediately. All Member States must transpose the Directive into national law within the timeframe stipulated in the Directive.[20,21,23]

EudraLex Volume 4 lays down the Regulations and Directives governing the drug products in the EU. It consists of three parts:[24]

- **Part I**- Basic Requirements for Medicinal Products;
- **Part II-** Basic Requirements for Active Substances used as Starting Materials;
- **Part III**- GMP related Documents

Directives 2003/94/EC and 91/412/EEC establish principles and guidelines of GMP for human use and veterinary use drug products, respectively. The Guide to Good Manufacturing Practices has detailed guidelines according to the Directives' principles. These are used in the evaluation of manufacturing authorizations as well as a basis for drug manufacture inspection.[24]

Manufacturers are liable to hold relevant authorizations, in line with Article 40 of Directive 2001/83/ECC and Article 44 of Directive 2001/82/EC. Companies can be granted or retain a GMP license when compliant with the EU regulations. The NCA has to conduct regular inspections to verify that all requirements are being met to assess this. If so, companies can keep their GMP licenses.[11,25]

When the company is not compliant with the regulations, its GMP license may be suspended or withdrawn. The suspension or removal conditions may be regarding a single product, production line, or technology used to manufacture multiple products within the same manufacturing facility. If the manufacture is a subcontracted company, *i.e*., a CMO, and its license has been withdrawn or suspended, they should or must inform the MAH, per their contract.

4. Food and Drug Administration (FDA)

In contrast with EMA, the Food and Drug Administration (FDA) has a set of general and permanent rules with a legal biding force, known as the Code of Federal Regulations (CFR). These are published in the Federal Register by the executive departments and agencies of the Federal Government. The 50 Titles represented in the CFR cover broad subject areas liable to Federal Regulation and are updated yearly. Each Title can have individual or several volumes. They are divided into Chapters, Subchapters, Part, Subparts, and Sections, as represented in Figure 4.1.[21,26]

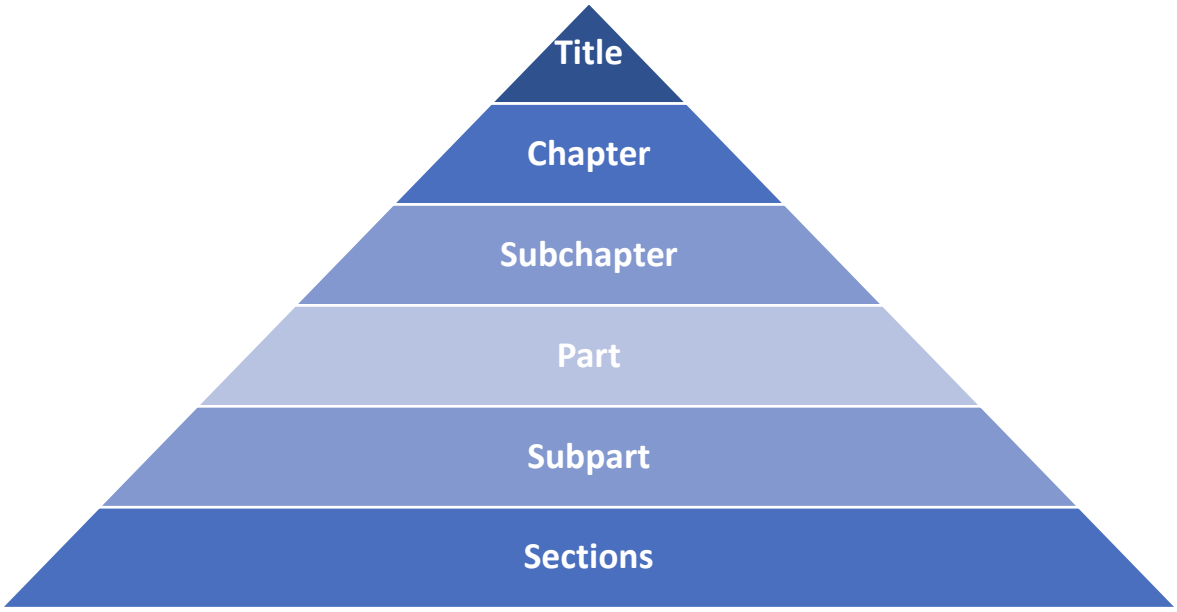

Figure 4.1- Blueprint of how the CFR are organized

The chapter's name is usually the name of the Agency responsible for issuing them. Chapters are divided into Subchapters that concern specific regulatory areas. Subchapters are split into Parts, then into Subparts and Sections. The CFR citations are normally given at section level.[26]

In this case, the cGMP is covered in the:

- **Title:** 21 CFR- Volume 4
- **Chapter I-** Food and Drug Administration
- **Subchapter:** Drugs: General
- **Parts:**
    - Part 210- Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drug; General
    - Part 211- Current Good Manufacturing Practices for Finished Pharmaceuticals

4.1 Guidance for Industry for Sterile Drug Products

FDA has several guidelines aimed for the industry representing its current thinking on a specific topic. One of their Guidances is for the Industry for Sterile Drug Products Produced by Aseptic

Processing. Its purpose is to help manufacturers comply with Regulatory Agency's standards, current Good Manufacturing Practices (cGMP). This document approaches some of the relevant aspects of aseptic processing and is not legally binding, and it is viewed as suggestions or recommendations.[27]

The document is divided into several sections. In each section, there is a text box containing CFR quotes relevant to the topic addressed in that section. Therefore, the CFRs presented in this document are those most directed to this type of processing, mainly focused on 21 CFR section 211. However, ophthalmic production has to comply with the other general cGMP in the CFR sections mentioned above.[27]

The following table, Table 4.1, shows the CFR discussed on the Guidance for Industry for Sterile Drug Products, the subpart they belong to, and the section's name. Some of the CFR cited on the guidance is repeated throughout the document. Therefore means that the same CFR section is applicable in several aspects of the manufacturing process.

Table 4.1- Subpart and Section level that the CFR falls into

Guidance for Industry for Sterile Drug Products' CFR	Subpart [28]	Section [28]
211.3	A- General Provisions	Definitions
211.22	B- Organization and Personnel	Responsibilities of Quality Control Unit
211.25	B- Organization and Personnel	Personnel qualifications
211.28	B- Organization and Personnel	Personnel responsibilities
211.42	C- Buildings and Facilities	Design and construction features
211.46	C- Buildings and Facilities	Ventilation, air filtration, air heating, and cooling
211.56	C- Buildings and Facilities	Sanitation
211.63	D- Equipment	Equipment design, size, and location
211.65	D- Equipment	Equipment construction
211.67	D- Equipment	Equipment cleaning and Maintenance
211.80	E- Control of Components and Drug Product Containers and Closures	General Requirements
211.84	E- Control of Components and Drug Product Containers and Closures	Testing and approval or rejection of components, drug product containers, and closures
211.94	E- Control of Components and Drug Product Containers and Closures	Drug product containers and closures
211.100	F- Production and Process Controls	Written procedures; deviations
211.110	F- Production and Process Controls	Sampling and testing of in-process materials and drug products
211.111	F- Production and Process Controls	Time Limitations on production
211.113	F- Production and Process Controls	Control of microbiological contamination
211.160	I- Laboratory Controls	General Requirements
211.165	I- Laboratory Controls	Testing and release for distribution
211.167	I- Laboratory Controls	Special Testing requirements
211.180	J- Records and Reports	General requirements
211.186	J- Records and Reports	Master production and control records
211.188	J- Records and Reports	Batch production and control records
211.192	J- Records and Reports	Production record review

Considering the CFR infringed and the short description given, each item was categorized. Categories were created in broad terms to be as comprehensive as possible without going too much into detail. The following table, Table 4.2, presents the categories established as well as what they involve. These categories were later applied to EMA's data as well.

Table 4.2- Name and a short description of the newly established categories

Category	Description
Areas of operation	Adequate and defined areas in size, construction, and location
Aseptic processing	Environmental Monitoring System Sanitation Air Supply Cleaning System
Education, Training, and Experience	Training, Education, Experience of Personnel Identification of persons involved
Equipment	Equipment Design, Size, and Location Equipment Identification Cleaning / Sanitizing / Maintenance of Equipment
Maintenance	Buildings
Procedures	Control procedures Validation Laboratory Controls Written documents Standard Operation Procedures
Quality Control	Accept or Reject Specifications or Procedures Adequate Laboratory Facilities Status of the Lot and accept or reject it
Records	Records of investigations, deviations, certificates, testing, complaints, data. Computer control of master formula records
Specifications	In-process materials specifications
Testing	Testing, Sampling, and Samples

4.2 Inspection Classification Database

The FDA's website discloses a database of inspections carried out by the FDA. This database provides a lot of information such as the company's name, project area, inspection end date, country, and inspection classification. In another section, you can access an Excel document that provides a short description and a long description of the observations made in the inspection report and the CFRs infringed.

This information is made available to the public to recognize how the FDA works to protect public health. In addition to this, it aims to encourage companies to be more compliant and, at the same time, raise public awareness of the Agency's enforcement actions and a capability of making more informed choices.[29]

Inspection data can only be made public when the company implements corrective actions, the CAPA program. Not all inspections are made public and presented in this database. Therefore, it should not be used as a method to count the number of inspections carried out by the FDA.[19,29]

The data and classifications presented of inspections carried out should not reflect companies' current state of compliance. They merely demonstrate the compliance status at the time the report was generated.[29]

This database was used to collect data relevant to ophthalmic companies found not compliant with the GMP.

5. Results and Discussion

5.1 European Medicines Agency (EMA)

In 2007, EMA published an analysis of regulatory GMP inspection findings from 1995 to 2005. Its objective was to identify the leading causes of deficiencies to comply with the EU GMP regulations.

Although it is not open access, EMA Inspections Sector also has a database that maintains all GMP deficiencies listed in the final inspection reports. Together with the MHRA, EMA created 40 categories that aim to simplify the deficiencies classification. This way, one deficiency is assigned to a single category. The list of these categories, frequency, and incidence from 1995-2005, can be found in Table 5.1.[11]

Table 5.1- List of categories of deficiencies used in the EMA GMP database [11]

No	Category of GMP deficiency	No	Category of GMP deficiency
1	Analytical validation	21	Housekeeping - cleanliness, tidiness
2	Batch release procedures	22	In-process controls - control and monitoring of production operations
3	Calibration of measuring and test equipment	23	Intermediate and bulk product testing
4	Calibration of reference materials and reagents	24	Investigation of anomalies
5	Cleaning validation	25	Line clearance, segregation and potential for mix-up
6	Complaints and product recall	26	Personnel issues: Duties of key personnel
7	Computerised systems - documentation and control	27	Personnel issues: Hygiene/Clothing
8	Computerised systems - validation	28	Personnel issues: Training
9	Contamination, chemical/physical - potential for	29	Process validation
10	Contamination, microbiological - potential for	30	Production planning and scheduling
11	Design and maintenance of equipment	31	Regulatory issues: Non-compliance with manufacturing authorisation
12	Design and maintenance of premises	32	Regulatory issues: Non-compliance with marketing authorisation
13	Documentation - manufacturing	33	Regulatory issues: Unauthorised activities
14	Documentation - quality system elements/procedures	34	Sampling - procedures and facilities
15	Documentation - specification and testing	35	Self-inspection
16	Environmental control	36	Starting material and packaging component testing
17	Environmental monitoring	37	Status labelling - work in progress, facilities and equipment
18	Equipment qualification	38	Sterility Assurance
19	Finished product testing	39	Supplier and contractor audit and technical agreements
20	Handling and control of packaging components	40	Warehousing and distribution activities

These categories are a little exhaustive and won't enable us to compare with the FDA's data. Given the categories presented in section 4.1, EMA's categories were appointed to the same groups. Table 5.2 discloses the categories attributed to EMA's GMP Database Categories, the number of deficiencies

found during this time, and their incidence. The data presented in the table below correspond to 435 inspections which 255 were pre-approval, 132 routine, 29 variations, and 9 ‘for cause’ inspections. During this time, 9519 deficiencies were accounted for, including 193 critical (2%), 1003 major (11%), and 8323 other deficiencies (87%).[11]

It was found that the numbers of total deficiencies, critical, major, and other deficiencies have been wrongly added as they do not correspond to the values shown in the table that followed in the EMA’s report. The values presented above should be considered the correct number of total deficiencies, critical, major, and others.

Table 5.2- Categories attributed to EMA’s GMP Database, number, and incidence

Category	EMA’s GMP Database Categories [11]	Number[11]	Incidence[11]	Total	Incidence
Areas of operation	-	0	0%	0	0%
Aseptic processing	Environmental Control	192	2,0%	709	7,4%
	Environmental monitoring	323	3,4%		
	Sterility Assurance	194	2,0%		
Education, Training, and Experience	Personnel issues: Duties of key personnel	258	2,7%	729	7,7%
	Personnel issues: Hygiene/Clothing	266	2,8%		
	Personnel issues: Training	205	2,2%		
Equipment	Calibration of measuring and test equipment	202	2,1%	1084	11,4%
	Design and Maintenance of Equipment	594	6,2%		
	Equipment validation	288	3,0%		
Maintenance	Design and Maintenance of premises	634	6,7%	634	6,7%
Procedures	Analytical validation	83	0,9%	2963	31,1%
	Batch release procedures	118	1,2%		
	Calibration of reference materials and reagents	28	0,3%		
	Cleaning validation	173	1,8%		
	Computerised systems - validation	27	0,3%		
	Documentation - quality system elements/procedures	1341	14,1%		
	Handling and control of packaging components	38	0,4%		
	In-process controls - control and monitoring of production operations	153	1,6%		
	Intermediate and bulk product testing	18	0,2%		
	Investigation of anomalies	164	1,7%		

	Process validation	317	3,3%		
	Production planning and scheduling	11	0,1%		
	Sampling - procedures and facilities	297	3,1%		
	Self-inspection	91	1,0%		
	Warehousing and distribution activities	104	1,1%		
Quality Control	-	0	0%	0	0%
Records	Complaints and product recall	47	0,5%	1736	18,2%
	Computerised systems - documentation and control	64	0,7%		
	Documentation – manufacturing	526	5,5%		
	Documentation - specification and testing	432	4,5%		
	Status labeling - work in progress, facilities, and equipment	371	3,9%		
	Supplier and contractor audit and technical agreements	296	3,1%		
Specifications	Contamination, chemical/physical - potential for	256	2,7%	1628	17,1%
	Contamination, microbiological - potential for	463	4,9%		
	Housekeeping - cleanliness, tidiness	243	2,6%		
	Line clearance, segregation and potential for mix-up	238	2,5%		
	Regulatory issues: Non-compliance with manufacturing authorization	18	0,2%		
	Regulatory issues: Non-compliance with marketing authorization	113	1,2%		
	Regulatory issues: Unauthorised activities	176	1,8%		
	Starting material and packaging component testing	121	1,3%		
Testing	Finished product testing	36	0,4%	36	0,04%

The Pareto analysis shows that the procedures and records are the lead categories lead of deficiencies found when grouped this way, Figure 5.1. The procedures category showed an incidence of 31,1%, while the category of the records represented 18,2%. This means that for every three deficiencies, one will be related to procedures. Applying the Pareto principle, we observe that the first four categories represent roughly 80%.

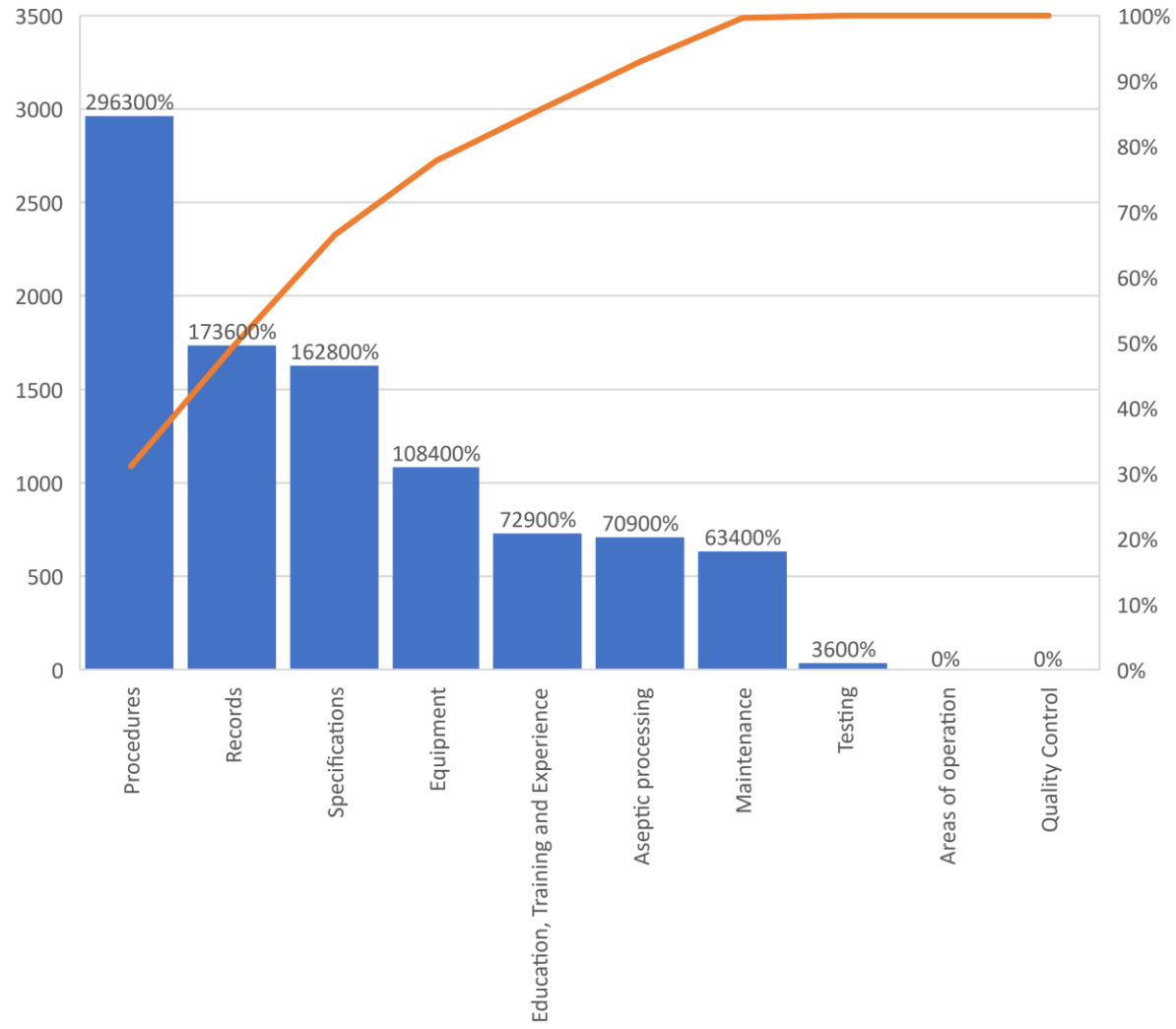

Figure 5.1- Frequency of deficiencies by category

These inspections were carried out by finished drug product manufacturers (316 inspections) and active ingredient manufacturers (119 inspections). Most of these inspections were conducted in a third country, 400 of them. The data collected from all these inspections is summed up in the following table, Table 5.3. [11]

Table 5.3- Deficiencies found in 1995/2005 by different categories (active ingredient vs. finished product, and EEA vs. Third country).[11]

	Active Ingredient	Finished Product	EEA	Third Country
Number of inspections	119	316	35	400
Number of critical deficiencies	34 (1,64%)	159 (2,13%)	55 (7,49%)	138 (1,57%)
Number of major deficiencies	321 (15,53%)	682 (9,15%)	26 (3,54%)	977 (11,12%)
Number of other/minor deficiencies	1712 (82,83%)	6611 (88,71%)	653 (88,96%)	7670 (87,31%)
Total of deficiencies	2067	7452	734	8785
Average deficiencies per inspection	17	23	21	22

When comparing the finished product manufacturers of sterile and non-sterile products, the average number of deficiencies per inspection is similar; see Table 5.4. Nevertheless, their distribution differs as sterile product manufacturers show a higher risk for critical and major deficiencies. One possible explanation is the fact that the manufacturing process is of higher complexity and, therefore, higher risk of deviations.[11]

Table 5.4- Comparison of the deficiencies found in 1995/2005 between manufacturers of sterile vs. non-sterile products[11]

	Non-sterile	Sterile
Number of inspections	186	249
Number of critical deficiencies	33 (0,88%)	160 (2,77%)
Number of major deficiencies	251 (6,72%)	752 (13,00%)
Number of other deficiencies	3451 (92,40%)	4872 (84,23%)
Total deficiencies	3735	5784
Average deficiencies per inspection	20	23

5.1.1 Minor/Other Findings

As previously mentioned, deficiencies were categorized according to the EMA GMP database. Table 5.5 demonstrates the top 20 categories for minor/other deficiencies.

Table 5.5- Ranking of the top 20 minor/other significant GMP deficiencies for 1995/2005 [11]

No	Category of GMP Deficiency
1	Documentation - quality system elements/procedures
2	Design and Maintenance of equipment
3	Design and Maintenance of premises
4	Documentation - manufacturing
5	Documentation - specification and testing
6	Status labeling - work in progress, facilities, and equipment
7	Contamination, microbiological - potential for
8	Environmental monitoring
9	Sampling - procedures and facilities
10	Process validation
11	Supplier and contractor audit and technical agreements
12	Equipment validation
13	Personnel issues: Hygiene/Clothing
14	Housekeeping - cleanliness, tidiness
15	Personnel issues: Duties of key personnel
16	Line clearance, segregation, and potential for the mix-up
17	Contamination, chemical/physical - potential for
18	Calibration of measuring and test equipment
19	Personnel issues: Training
20	Environmental control

These top 20 categories were placed in the same groups as displayed in Table 4.2. Table 5.6 presents the number and incidence per EMA's GMP Database category and the total and incidence of the overall category established.

Table 5.6- Categories attributed to Minor Findings on EMA's GMP Database, number and incidence

Category	EMA's GMP Database Categories [11]	Number[11]	Incidence[11]	Total	Incidence
Areas of operation	-	0	0%	0	0%
Aseptic processing	Environmental control	168	2,0%	459	6,7%
	Environmental monitoring	291	3,5%		
Education, Training, and Experience	Personnel issues: Duties of key personnel	222	2,7%	632	9,2%
	Personnel issues: Hygiene/Clothing	230	2,8%		
	Personnel issues: Training	180	2,2%		
Equipment	Calibration of measuring and test equipment	195	2,3%	747	10,9%
	Design and Maintenance of equipment	552	6,6%		
	Equipment validation	245	2,9%		
Maintenance	Design and maintenance of premises	544	6,5%	544	7,9%
Procedures	Documentation- quality system elements/procedures	1223	14,7%	2022	29,5%
	Process validation	272	3,3%		
	Sampling- procedures and facilities	282	3,4%		
Quality Control	-	0	5,7%	0	0%
Records	Documentation- manufacturing	472	4,6%	1467	21,4%
	Documentation- specification and testing	381	4,2%		
	Status labeling- work in progress, facilities, and equipment	352	3,1%		
	Supplier and contractor audit and technical agreements	262	2,5%		
Specifications	Contamination, microbiological – potential for	206	4,0%	983	14,3%
	Contamination, chemical/physical – potential for	331	2,7%		
	Housekeeping – cleanliness, tidiness	228	2,6%		
	Line clearance, segregation, and potential for the mix-up	218	2,0%		
Testing	-	0	0%	0	0%

When a deficiency is classified as minor or other, it is known that they are considered to be of lower risk, which means that they are not viewed as potentially harmful for patients' and animals' health. Therefore, whenever a deficiency is categorized as lower risk, the probability of being related to

documentation like procedures and records is higher, as shown in Figure 5.2.[11]. The first four categories explain approximately 80% of all minor deviations.

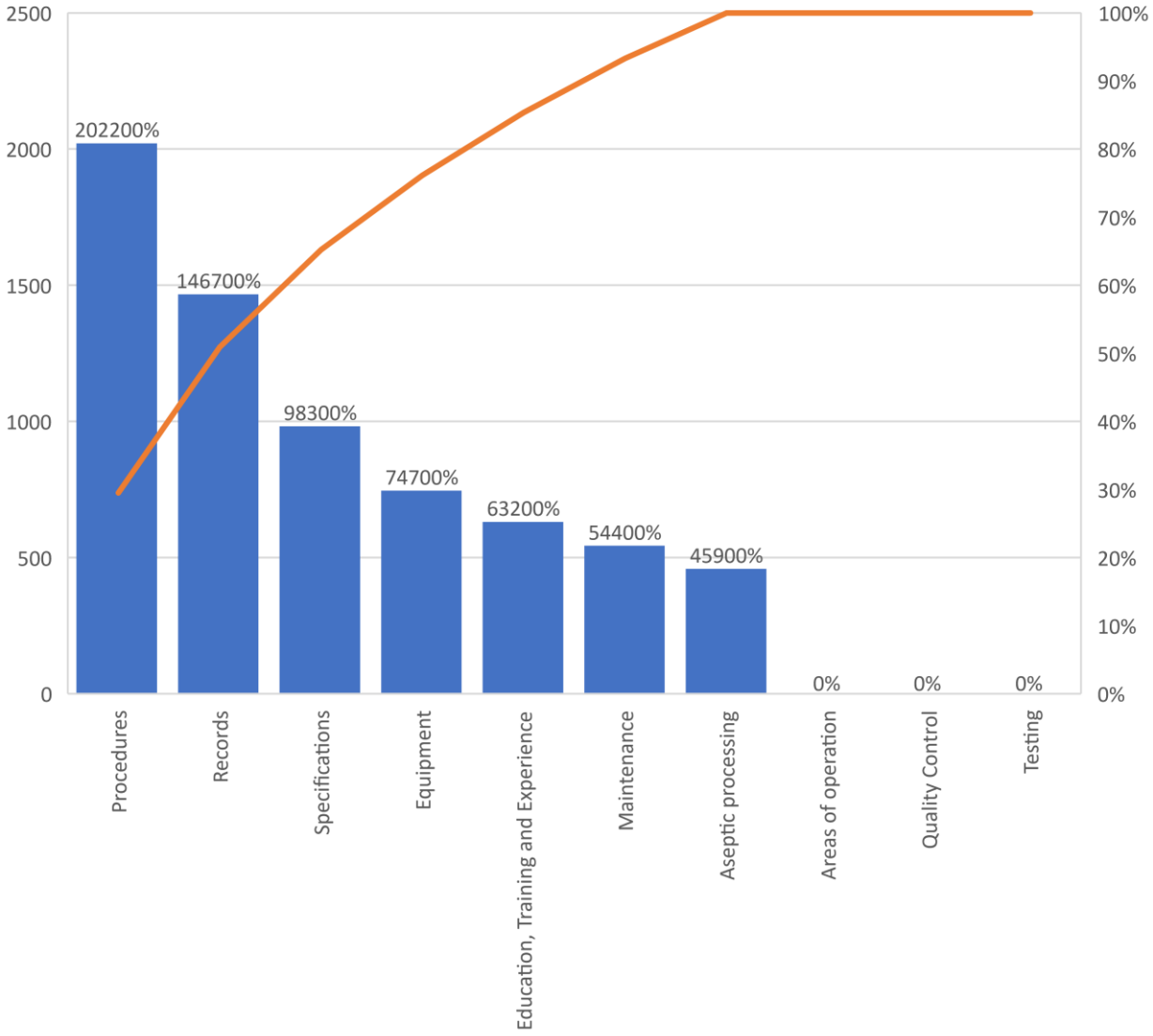

Figure 5.2- Frequency of Minor Findings per category

5.1.2 Major Findings

The following table, Table 5.7, indicates the top 20 major GMP deficiencies categories from 1995 to 2005.

Table 5.7- Ranking of the top 20 major GMP deficiencies from 1995/2005 [11]

No	Category of GMP Deficiency
1	Contamination, microbiological - potential for
2	Documentation - quality system elements/procedures
3	Regulatory issues: Unauthorised activities
4	Design and Maintenance of premises
5	Regulatory issues: Non-compliance with marketing authorisation
6	Sterility Assurance
7	Documentation - manufacturing
8	Documentation - specification and testing
9	Equipment validation
10	Design and Maintenance of equipment
11	Personnel issues: Duties of key personnel
12	Supplier and contractor audit and technical agreements
13	Contamination, chemical/physical - potential for
14	Process validation
15	Environmental monitoring
16	Personnel issues: Hygiene/Clothing
17	Investigation of anomalies
18	In-process controls - control and monitoring of production operations
19	Line clearance, segregation, and potential for the mix-up
20	Personnel issues: Training

Similarly, these top 20 categories were placed in the same groups as displayed in Table 4.2. The number of major deficiencies and incidence is broken down by category; see Table 5.8.

Table 5.8- Categories attributed to Major Findings on EMA's GMP Database, number and incidence

Category	EMA's GMP Database Categories[11]	Number[11]	Incidence[11]	Total	Incidence
Areas of operation	-	0	0%	0	0%
Aseptic processing	Environmental monitoring	25	2,5%	78	8,8%
	Sterility Assurance	53	5,3%		
Education, Training, and Experience	Personnel issues: Duties of key personnel	35	3,5%	77	8,7%
	Personnel issues: Hygiene/Clothing	25	2,5%		
	Personnel issues: Training	17	1,7%		
Equipment	Design and maintenance of equipment	36	3,6%	79	9,0%
	Equipment validation	43	4,3%		
Maintenance	Design and maintenance of premises	59	5,9%	59	6,7%
Procedures	Documentation - quality system elements/procedures	102	10,2%	175	19,8%
	In-process controls - control and monitoring of production operations	18	1,8%		
	Investigation of anomalies	22	2,2%		
	Process validation	33	3,3%		
Quality Control	-	0	5,0%	0	0%
Records	Documentation – manufacturing	50	4,6%	130	14,7%
	Documentation – specification and testing	46	3,4%		
	Supplier and contractor audit and technical agreements	34	3,3%		
Specifications	Contamination, chemical/physical – potential for	33	11,2%	284	32,2%
	Contamination, microbiological – potential for	112	1,8%		
	Line clearance, segregation, and potential for the mix-up	18	5,5%		
	Regulatory issues: Non-compliance with marketing authorisation	55	6,6%		
	Regulatory issues: Unauthorised activities	66	2,5%		
Testing	-	0	0%	0	0%

As the risk of deficiencies that are considered as having potentially harmful consequences increases, categories with a high percentage of critical deficiencies like specifications will equally increase.[11] Figure 5.3 proves this as it shows an increase of deficiencies related to specifications and lowers in records, as opposed to Figure 5.2, from the previous section. Specifications unveil 32,2% of

all deficiencies found in inspections classified as major findings, while the Procedures category has fallen to second place, representing 19,8% of total deficiencies acknowledged. The Specifications, Procedures, Records, and Equipment categories account for about 80% of all major deficiencies.

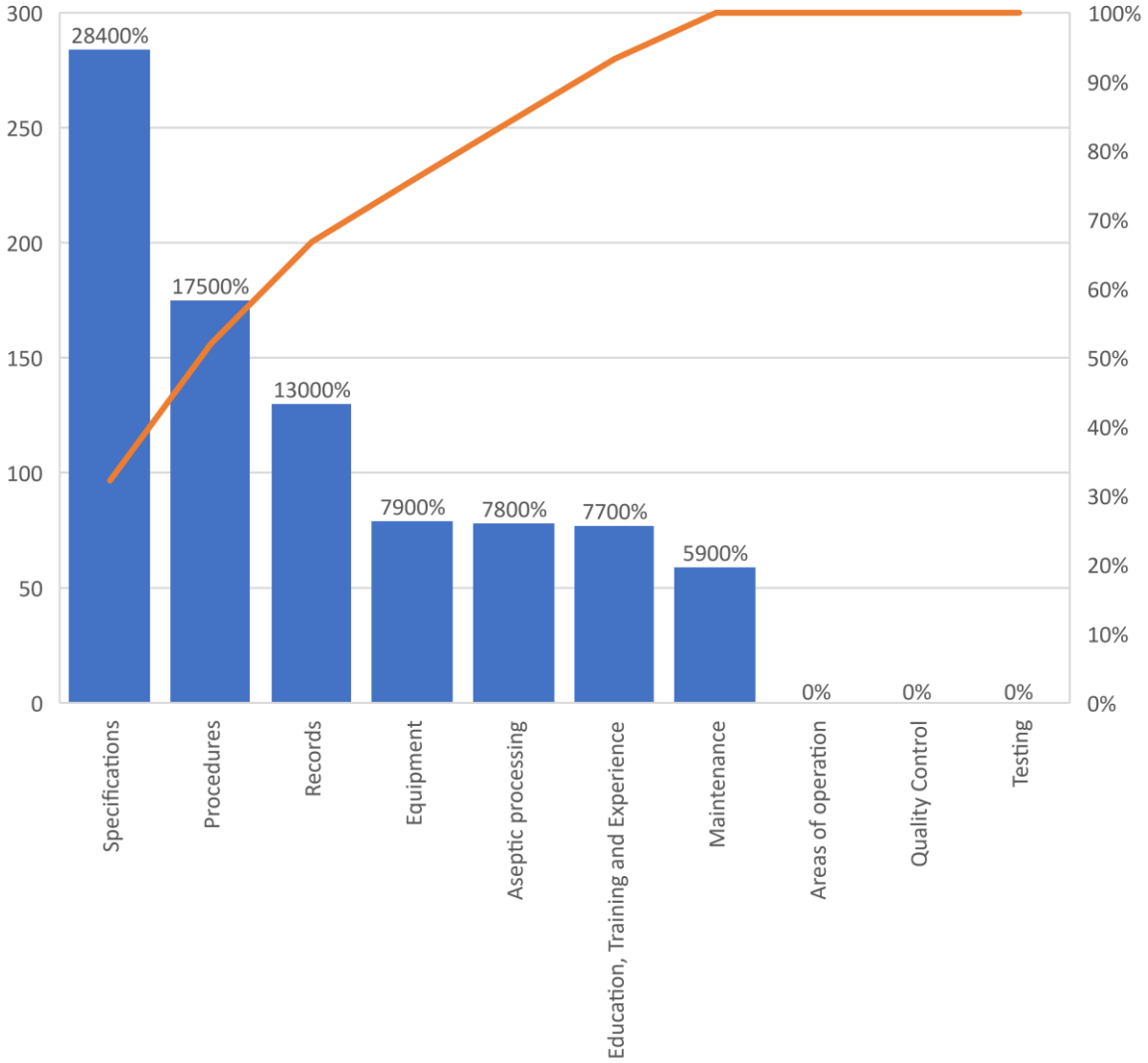

Figure 5.3- Frequency of Major Findings per category

5.1.3 Critical Findings

Finally, Table 5.9 represents the ranking of critical GMP deficiencies over ten years (1995/2005).

Table 5.9- Ranking of critical GMP deficiencies for 1995/2005 [11]

No	Category of GMP Deficiency
1	Design and Maintenance of premises
2	Contamination, microbiological - potential for
3	Contamination, chemical/physical - potential for
4	Documentation - quality system elements/procedures
5	Process validation
6	Housekeeping - cleanliness, tidiness
7	Personnel issues: Hygiene/Clothing
8	Environmental Control
9	Personnel issues: Training
10	Sterility Assurance
11	Environmental monitoring
12	Design and Maintenance of Equipment
13	Batch release procedures
14	Documentation - specification and testing
15	Documentation - manufacturing
16	Status labeling - work in progress, facilities and equipment
17	Handling and control of packaging components
18	In-process controls - control and monitoring of production operations
19	Line clearance, segregation, and potential for the mix-up
20	Computerised systems - documentation and control
21	Investigation of anomalies
22	Sampling - procedures and facilities
23	Cleaning validation
24	Personnel issues: Duties of key personnel
25	Regulatory issues: Non-compliance with manufacturing authorisation
26	Regulatory issues: Non-compliance with marketing authorisation

The categories presented in the previous table were placed in the same groups as the last sections. The data of critical deficiencies, numbers, and incidence, is detailed by category in Table 5.10.

Table 5.10- Category attributed to Critical Findings on EMA's GMP Database, number and incidence

Categories	EMA's GMP Database Categories [11]	Number[11]	Incidence[11]	Total	Incidence
Areas of operation	-	0	0%	0	0%
Aseptic processing	Environmental control	10	5,2%	25	13,0%
	Environmental monitoring	7	3,6%		
	Sterility Assurance	8	4,1%		
Education, Training, and Experience	Personnel issues: Duties of key personnel	1	0,5%	20	10,4%
	Personnel issues: Hygiene/Clothing	11	5,7%		
	Personnel issues: Training	8	4,1%		
Equipment	Design and Maintenance of Equipment	6	3,1%	6	3,1%
Maintenance	Design and Maintenance of premises	31	16,1%	31	16,1%
Procedures	Batch release procedures	5	2,6%	43	22,3%
	Cleaning validation	1	0,5%		
	Documentation - quality system elements/procedures	16	8,3%		
	Handling and control of packaging components	3	1,6%		
	In-process controls - control and monitoring of production operations	3	1,6%		
	Investigation of anomalies	2	1,0%		
	Process validation	12	6,2%		
	Sampling - procedures and facilities	1	0,5%		
Quality Control	-	0	0%	0	0%
Records	Computerised systems - documentation and control	2	1,0%	15	7,8%
	Documentation - manufacturing	4	2,1%		
	Documentation - specification and testing	5	2,6%		
	Status labeling - work in progress, facilities and equipment	4	2,1%		
Specifications	Contamination, chemical/physical - potential for	17	8,8%	53	27,5%
	Contamination, microbiological - potential for	20	10,4%		
	Housekeeping - cleanliness, tidiness	12	6,2%		
	Line clearance, segregation and potential for mix-up	2	1,0%		

	Regulatory issues: Non-compliance with manufacturing authorisation	1	0,5%		
	Regulatory issues: Non-compliance with marketing authorisation	1	0,5%		
Testing	-	0	0%	0	0%

As stated before, it is expected that given these inspections classified as critical, the deficiencies found reveal great concern regarding potentially harmful consequences for human and animal health.[11] Consequently, categories of critical deficiencies will likely prove to be the ones with a higher percentage of incidence. This is evident in Figure 5.4, as the specifications category became the leading category in the inspections classified as critical findings. Specifications category represented 27,5% of the total deficiencies. This means that for every four deficiencies, one of them is related to deficiencies in specifications. 80% of all deficiencies are explained by the first four categories illustrated in the figure below.

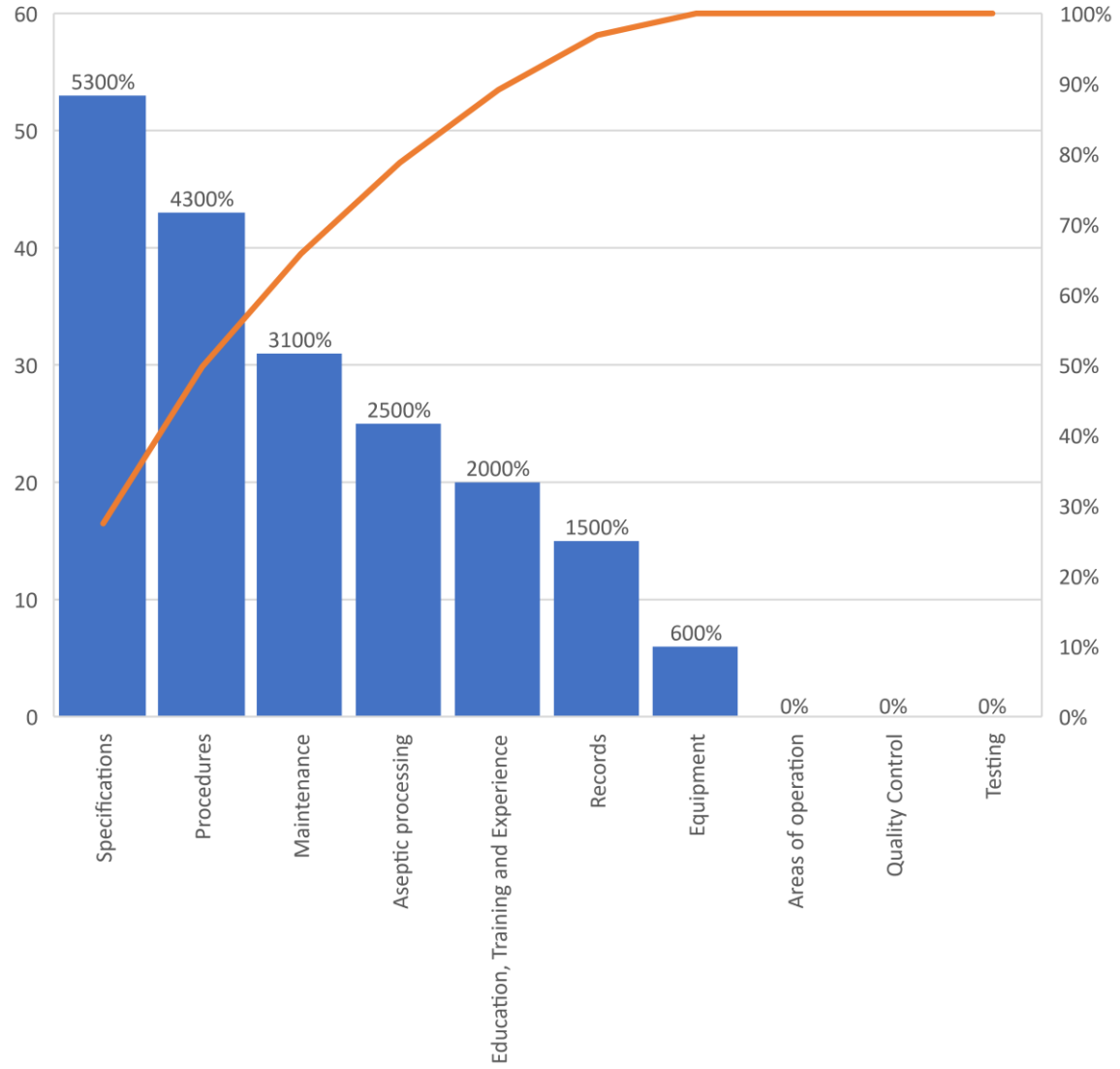

Figure 5.4- Frequency of Critical Findings per category

In 316 inspections of manufacturers of finished drug products in the EEA, 159 critical deficiencies were accounted for, representing 2,13% of the total deficiencies, as demonstrated in Table 5.3. The Active Ingredients manufacturers were inspected 119 times in the EEA; 34 accounted for critical deficiencies (1,65% of the total deficiencies found between 1995 and 2005).[11]

Table 5.11 puts forward the top 10 categories of critical GMP deficiencies found in the finished product and active ingredient manufacturers by ranking and incidence.

Just like in previous sections, EMA's GMP deficiency categories were sorted into broader categories. The category attributed to each GMP deficiency is shown in the second column.

Table 5.11- Comparison of the ranking of the top 10 critical GMP deficiencies between manufacturers of finished product vs. active ingredient

Category of GMP deficiency	Category	Finished product manufacturers		Active ingredient manufacturers	
		Ranking	Incidence (%)	Ranking	Incidence (%)
Design and Maintenance of premises	**Maintenance**	1	17,6	4	8,8
Contamination, chemical/physical - potential for	**Specifications**	2	10,1	8	2,9
Contamination, microbiological - potential for	**Specifications**	3	9,4	2	14,7
Documentation - quality system elements/procedures	**Procedures**	4	7,5	3	11,8
Housekeeping - cleanliness, tidiness	**Specifications**	5	6,9	12	2,9
Personnel issues: Hygiene/Clothing	**Education, Training, and Experience**	6	5,7	7	5,9
Environmental control	**Aseptic processing**	7	5,0	6	5,9
Personnel issues: Training	**Education, Training and Experience**	8	5,0	-	-
Sterility Assurance	**Aseptic processing**	9	4,4	17	2,9
Environmental monitoring	**Aseptic processing**	10	3,8	9	2,9
Process validation	**Procedures**	11	3,8	1	17,6
Design and Maintenance of equipment	**Equipment**	12	3,8	-	-

The total incidence for both finished drug products and active ingredient manufacturers of the newly established categories is displayed in Table 5.12.

Table 5.12- Finished Product and Active Ingredient incidence per category

Category	Total incidence Finished Product (%)	Total incidence Active Ingredient (%)
Areas of operation	0	0
Aseptic processing	13,2	11,7
Education, Training and Experience	10,7	5,9
Equipment	3,8	-
Maintenance	17,6	8,8
Procedures	11,3	29,4
Quality Control	0	0
Records	0	0
Specifications	26,4	20,5
Testing	0	0

Figure 5.5 presents the incidence of the categories between the finished product and active ingredient and the total percentage per category.

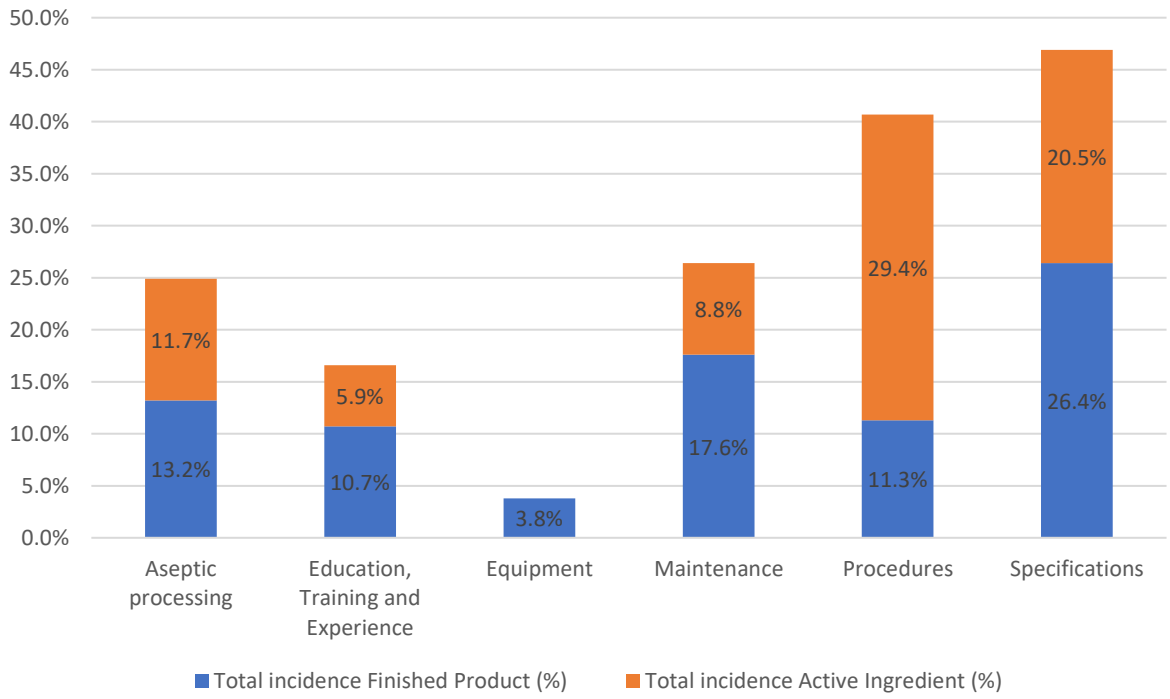

Figure 5.5- Incidence per category of Finished Product and Active Ingredient

5.2 Food and Drug Administration (FDA)

FDA's database presents data from inspections performed in various project areas. The first step in collecting relevant data was to apply a filter in the Project Area section. The Drug Assurance filter was applied. Since it is impossible to know which of the products were inspected and considering that this thesis focuses mainly on ophthalmologic products, data collected was relative to Alcon and Bausch & Lomb as they are companies that only produce products related to Ophthalmology. Besides, as previously said, the number of inspections disclosed in the database does not correspond to the actual number of inspections realized.

As the data collected from the database was not a significant sample, the FDA was contacted, and a FOIA form was submitted to obtain more relevant data.

The request was accepted, and the data was sent via E-mail on an Excel File. The file disclosed the inspection date, name of the company and country, whether a 483 Form was issued, and the inspection's classification. A separate tab referred to as "Citations" disclosed the CFR infringed and a short description. However, not all of the inspections listed in the two Excel tabs as some of the FDA Form FDA-483s are manually prepared and not entered into this database. Therefore, it was impossible to cross-reference between the Citations tab and Inspections tab. This made it difficult to identify the CFR infringed for each type of inspection classified as minor, major and critical, as was done in the EMA analysis.

The purpose of this was to facilitate data analysis as an inspection can have multiple CFR infringed associated with it.

The data disclosed in the public FDA Inspection Database from Alcon and Bausch & Lomb was not in the file sent by the FDA. This data was also included for this analysis as it was not previously included in the document provided and given that it was relevant to GMP deviations.

5.2.1 Inspections Classification tab

While analyzing the data on the second tab, *Citations,* it was noticed that there was data that was not relevant to what was requested. Through the CFR infringed column, it was possible to apply a filter to reduce the data only to the relevant data regarding GMP deviations, i.e., sections 211.

Through the FEI code, FDA Establishment Identifier, the data of the first tab was also reduced to correspond only to data related to GMP deviations. As this table does not identify the infringed CFRs and has more inspection dates not included in the other analysis, it was assumed that these inspections were related to GMP inspections regarding finished ophthalmic products.

Together they resulted in 73 registered inspections from 2008 to 2019. These were conducted in several countries, as shown in Figure 5.6. The United States had the highest inspection frequency, representing 86% of all inspections, 63 out of 73.

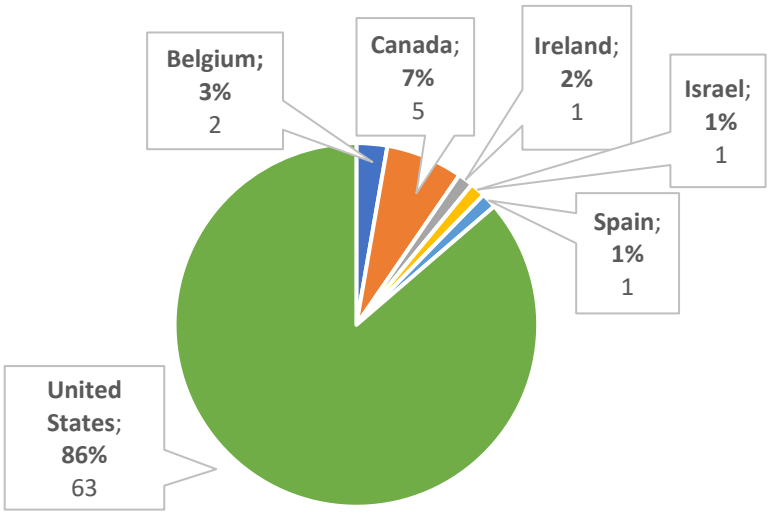

Figure 5.6- FDA's inspected facilities location

The companies that were inspected during this period were:

- Akorn, Inc.;
- Alcon Cusi, S.A.;
- Alcon Puerto Rico Inc.;
- Alcon Research LLC;
- Allergan Pharmaceuticals Ireland;
- Bausch & Lomb Incorporated;
- Bausch & Lomb Surgical, Inc.;
- Bausch Health Americas, Inc.;
- Bausch Health Companies Inc.;
- Biomedica Biological Testing Laboratories;
- Bio-TechnologYes General (Israel), Ltd.;
- Delasco Inc;
- KC Pharmaceuticals, Inc.;
- LA Labs;
- McNeil PPC Inc.;
- n.v. Alcon-Couvreur s.a.;
- Nomax Inc;
- Oasis Medical, Inc.;
- Oculus Surgical, Inc.

Bausch & Lomb Incorporated represented 34% of all inspections; it was the most inspected company of the data collected, 25 out of 73 inspections. Figure 5.7 displays the frequency of inspections per company and the cumulative percentage of the total number of occurrences. The first nine companies represent roughly 80% of all carried-out inspections.

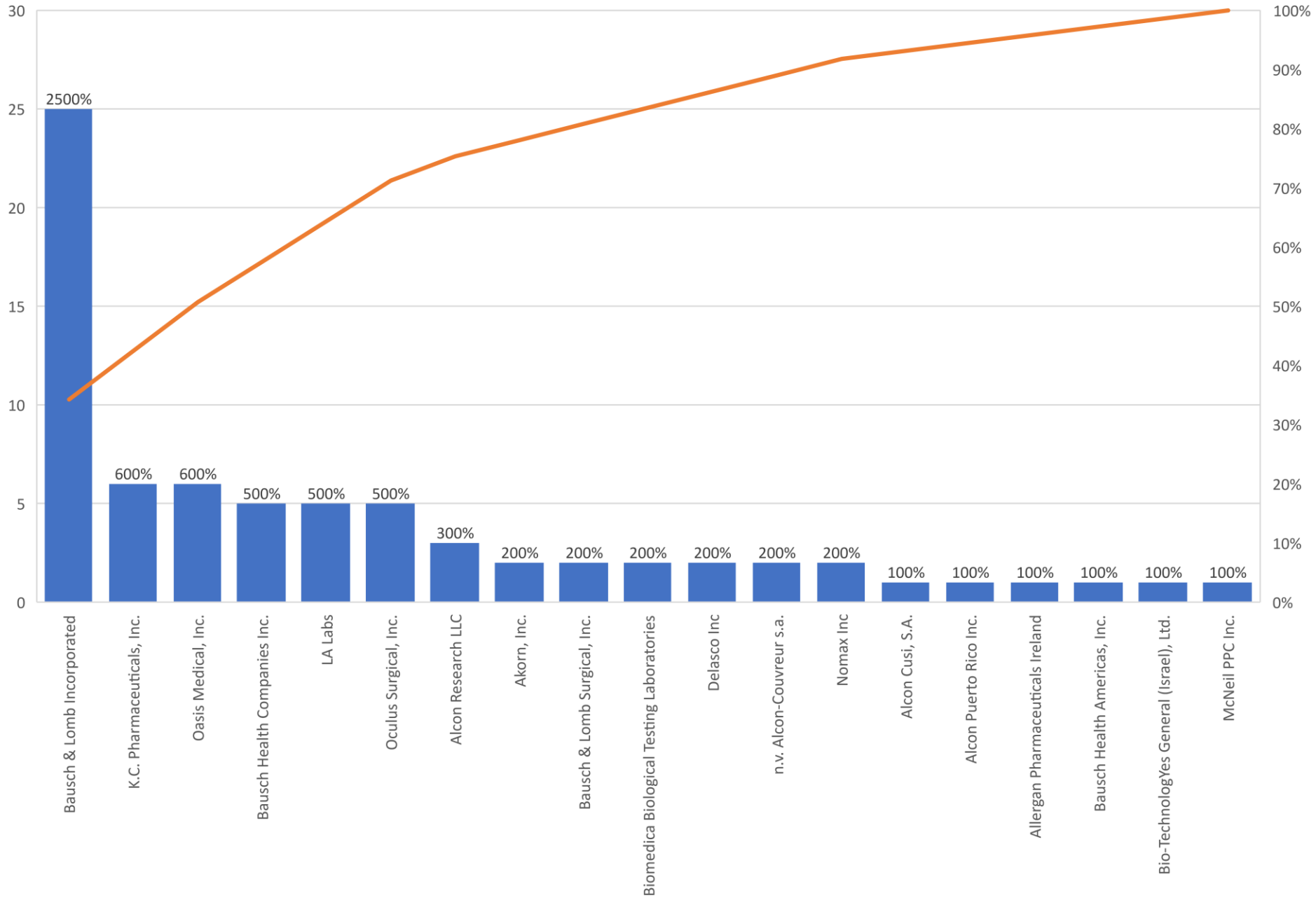

Figure 5.7- Inspection Frequency per company from 2008 to 2019

In the e-mail sent, FDA pointed out that not all of the inspections received a final classification and, hence, some of the entries were left blank. It also mentioned that not all of the inspections result in issuing an FDA- Form 483.

According to the data, the inspections were majorly classified as VAI, representing **77%** of all inspections, Figure 5.8 (56 out of 73). Annex F presents the inspection classification throughout the years, from 2008 to 2019.

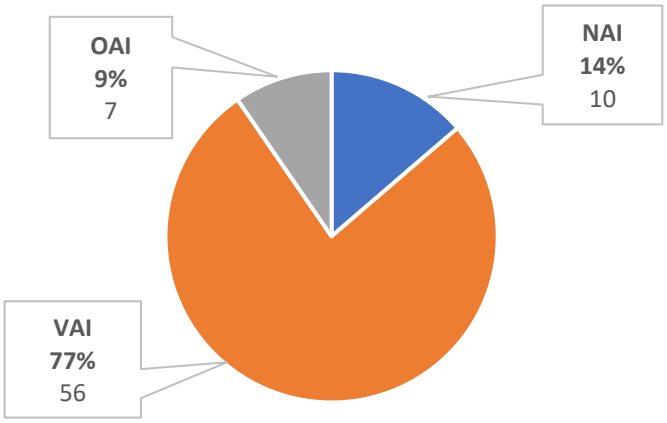

Figure 5.8- FDA's Inspection Classification from 2008-20

FDA- Form 483 entry was left blank and issued 40% of all inspections, respectively, Figure 5.9.

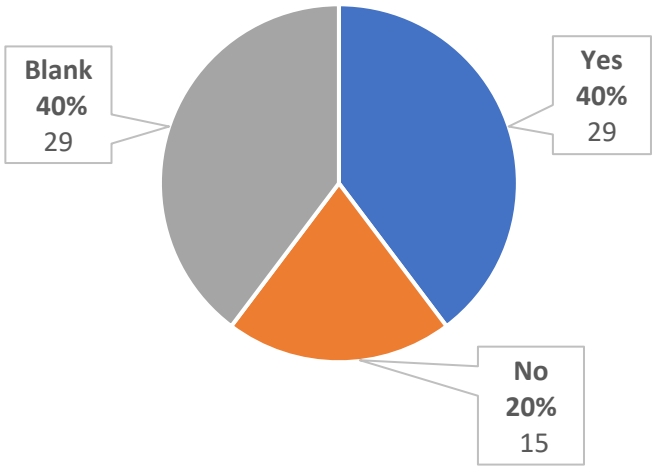

Figure 5.9- FDA 483 Form issued

Having this in mind, it is likely that a 483 Form is issued for most VAI inspections and not issued for most NAI inspections. Figure 5.10 and Figure 5.11 demonstrate this. In Figure 5.10, it is possible to observe that whenever a form is issued, 86% of them are issued for inspections classified as VAI. This

is expected as it is known a form is issued whenever inspections have an action indicated. On the other hand, Figure 5.11 shows that most inspections are classified as NAI when a form is not issued. As previously mentioned, inspections classified as NAI have, as the name indicates, no action indicated. This means that no observations were made and, as such, no form is issued.

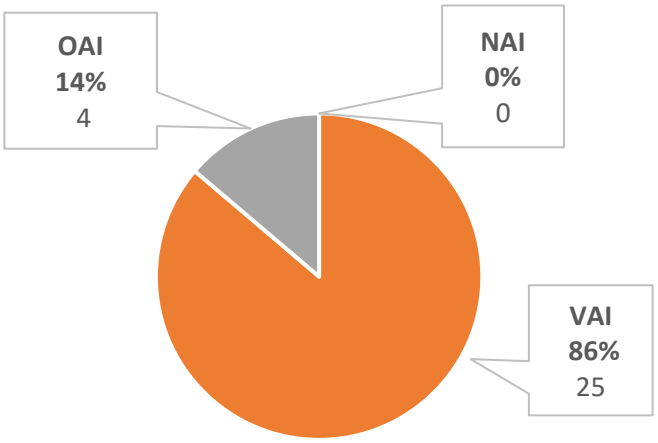

Figure 5.10- FDA Form 483 was issued

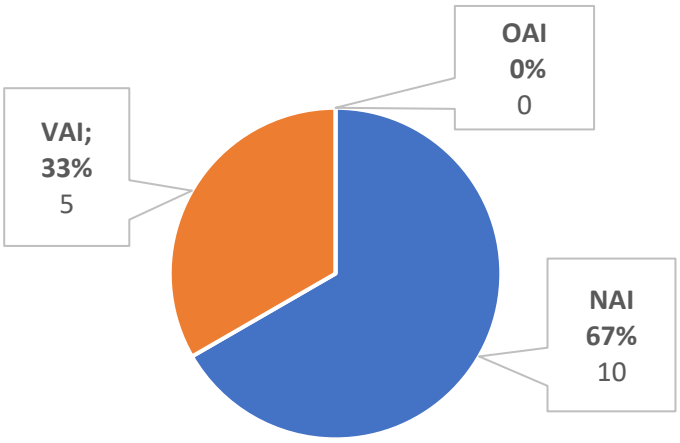

Figure 5.11- FDA Form 483 was NOT issued

Whenever the Form 483 entry was left blank, 67% of the inspections were classified as NAI, Figure 5.12. We can assume that a form was not issued for the entries left blank for NAI inspections and issued for VAI inspections. The database was left blank probably because they were manually entered.

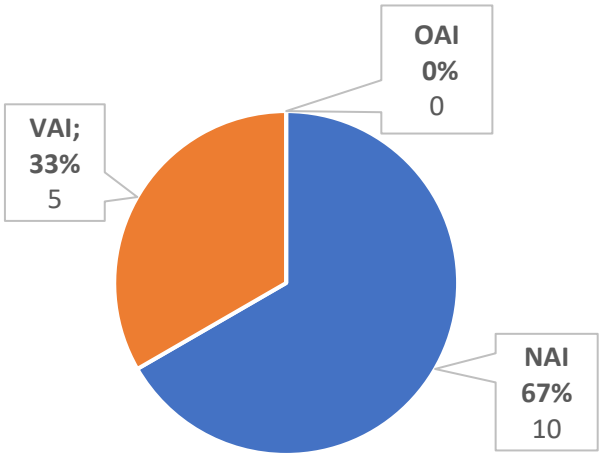

Figure 5.12- FDA 483 Form left blank

5.2.2 Citations tab

The second tab displays 145 entries that correspond to 35 inspections carried out between 2008 and 2019. These were conducted mainly in the United States, 84% of them, Figure 5.13.

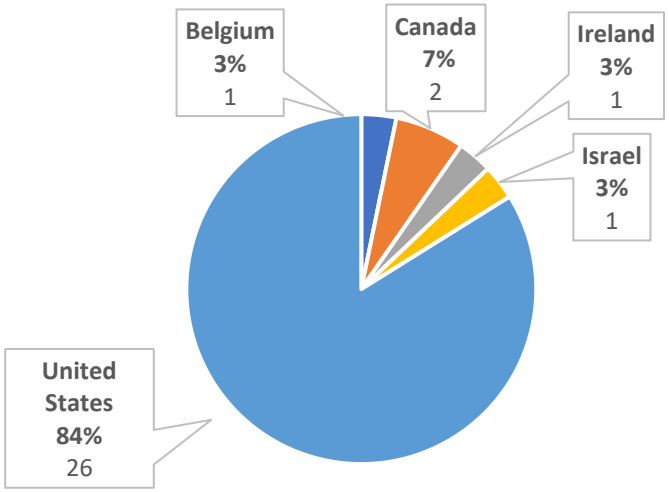

Figure 5.13- FDA inspected facilities location

Bausch & Lomb Incorporated and KC Pharmaceuticals, Inc. had the largest number of inspections, 7 out of 35 inspections each, Figure 5.14. Together they represent 40% of all companies inspected. The number of entries is higher than the number of inspections because inspections can have more than one CFR deviation. The graph represented in Figure 5.14 also presents the cumulative percentage

of all companies inspected from 2008 through 2019. 80% of all inspections are explained by approximately the first ten companies illustrated below.

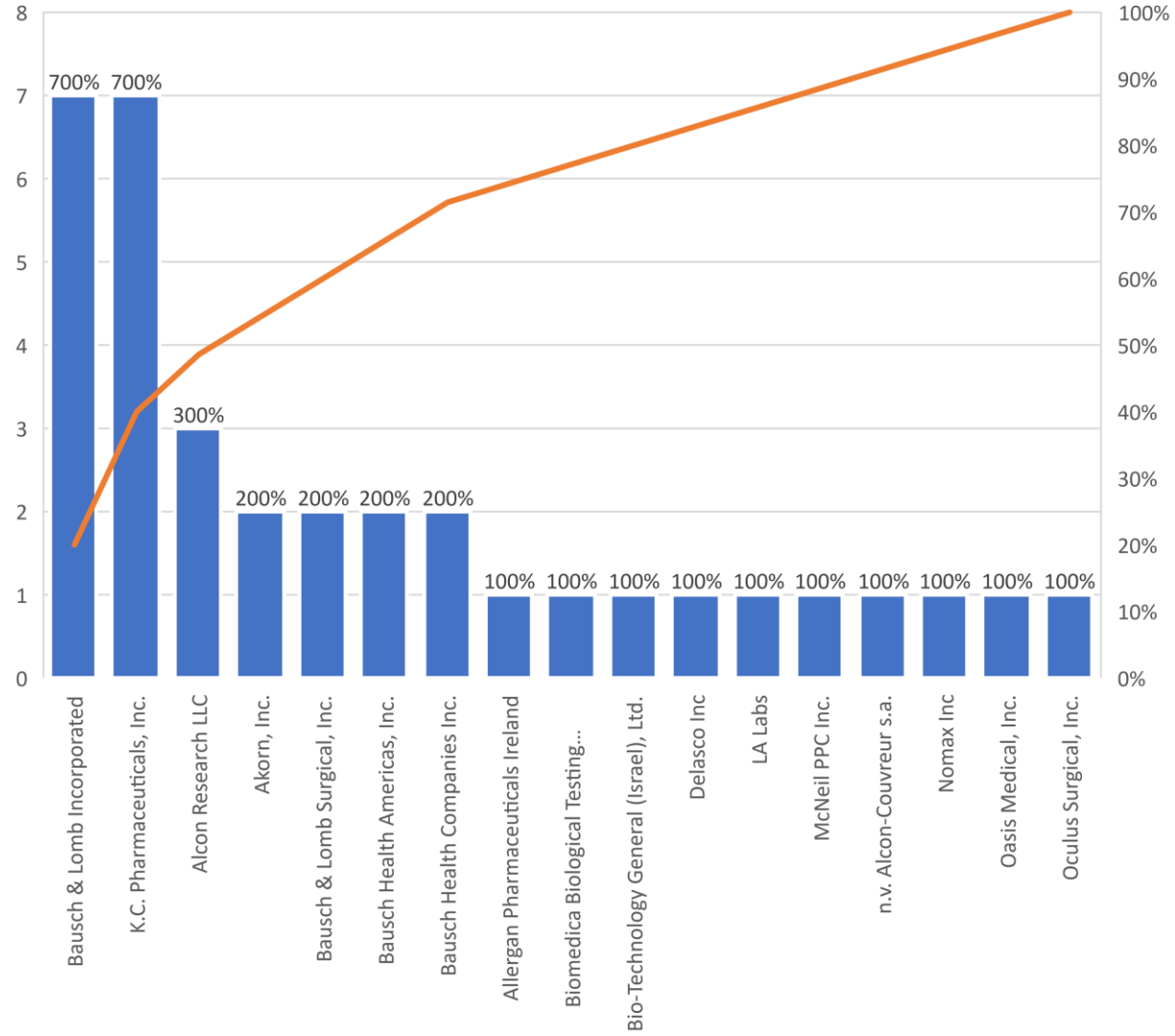

Figure 5.14- Number of inspections non-conformity carried out by FDA per company

In chapter 4, it is mentioned that the guidance only lists CFR relevant to the aseptic processing of sterile drug products. The other CFR, not mentioned in the guidance, are general aspects of cGMP of finished drug products. However, companies must be compliant with all CFR applicable to their product, in this case, all 21 CFR part 211- relevant to GMP for Finished Pharmaceuticals. For this thesis, the CFR mentioned in the guidance was labeled as Sterile Products CFR, while the other relevant GMP CFR was labeled as General Finished Drug Product CFR.

It was found that of all CFRs infringed, 76% of these were relative to CFR presented in the Guidance for Sterile Drug Products, Figure 5.15.

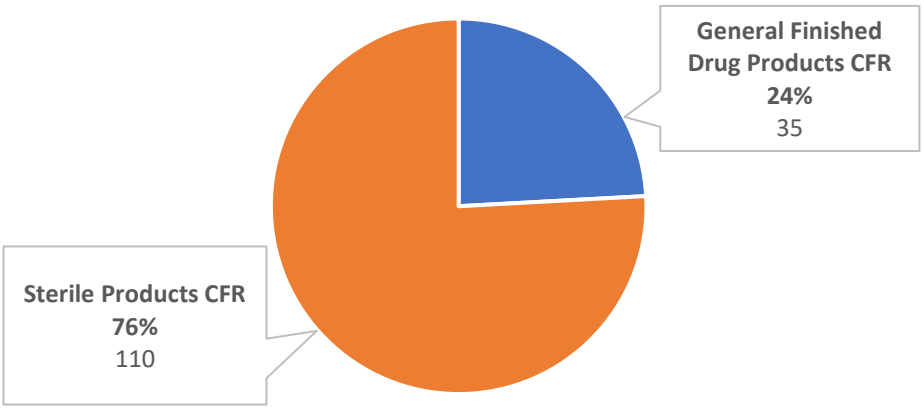

Figure 5.15- Deviations found by type of CFR infringed

In addition, Bausch & Lomb Incorporated was also the company that most infringed CFR and most CFR of sterile products, 41 of 145 and 30 of the 110 cases respectively, see Figures 5.16. Figures 5.16 show the number of deviations found and the cumulative percentage. You can notice that the first seven companies explain 80% of all deviations accounted for.

Figure 5.17 shows the type of CFR infringement per company.

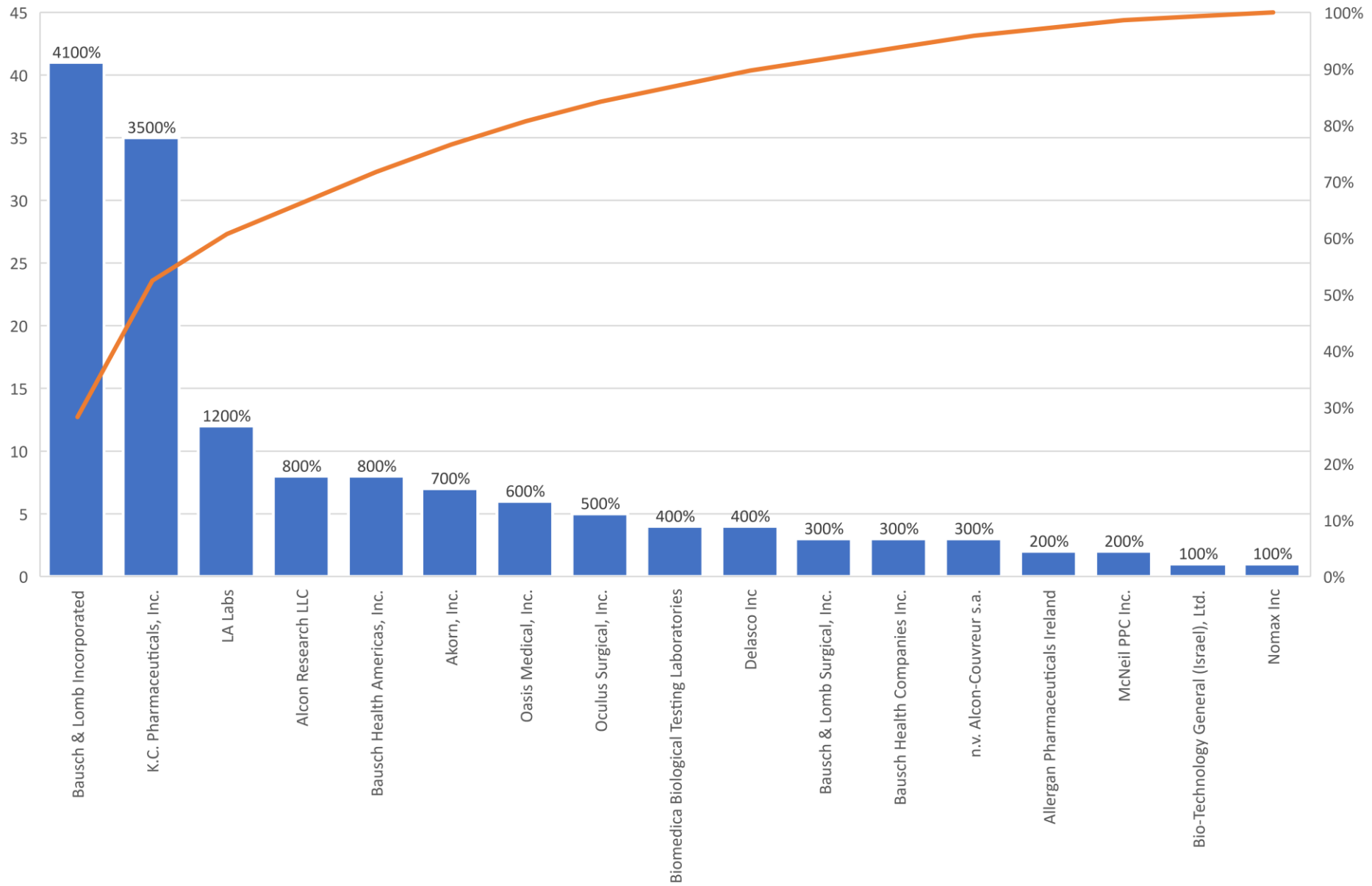

Figure 5.16- Number of deviations found per company

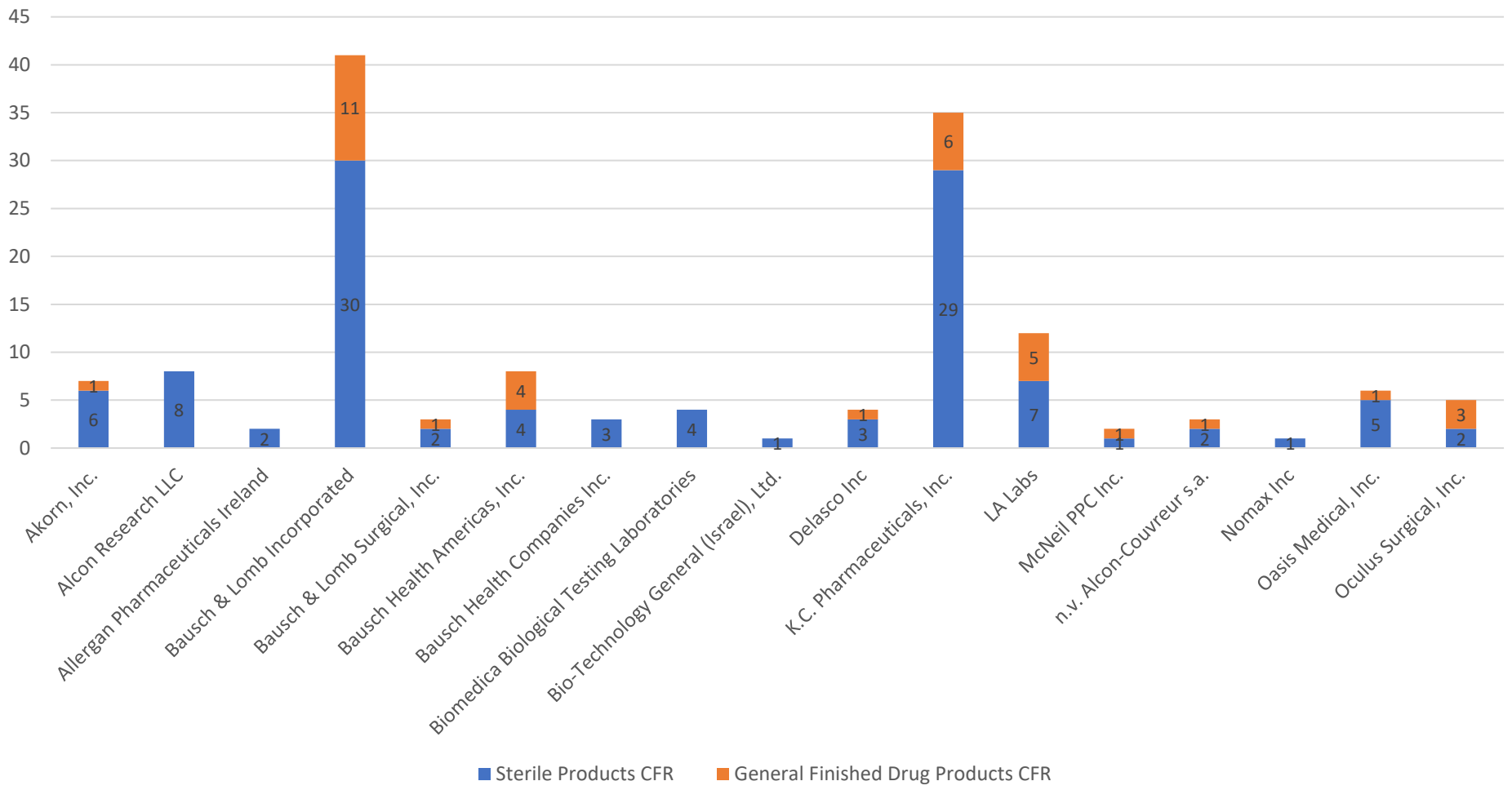

Figure 5.17- Type of CFR infringed by a company

Annex G presents the frequency and type of CFR deviations from 2008 to 2019.

The database provides us with CFRs that were not being met. As such, their frequency was analyzed. Figure 5.18 shows the various CFRs mentioned in the guidance by frequency of the CFR infringed and its cumulative percentage. The first eight CFR codes, represented below, account for 80% of all CFR infringed. Sections 192, 160, and 22, from 21 CFR 211, revealed the most frequently deviated sections. These correspond to 17, 16, and 13, respectively, of the 145 registered. The Title of these three, according to the FDA website, are Production Record Review, General Requirements (Laboratory Controls), and Responsibilities of Quality Control Unit, respectively.[30–32]

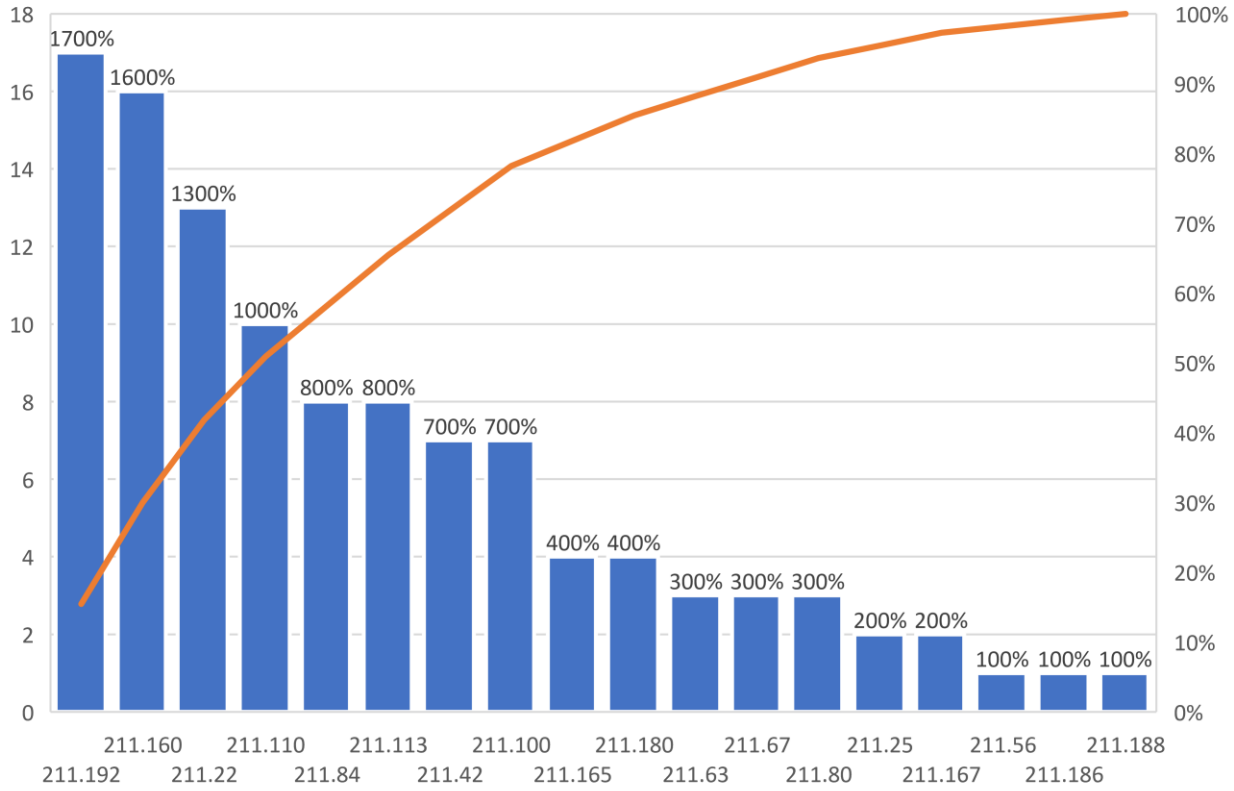

Figure 5.18- FDA Inspections Non-Conformity by Guidance for Sterile Drug Products' Codes

Because the CFR infringed and the short description provided, each 145 Excel entry was categorized into ten categories.

It was found that the two most prevalent categories are procedures and records, representing 61 and 43 out of 145 infringements, as can be seen from Figure 5.19. The cumulative percentage of all categories is presented in the following Figure.

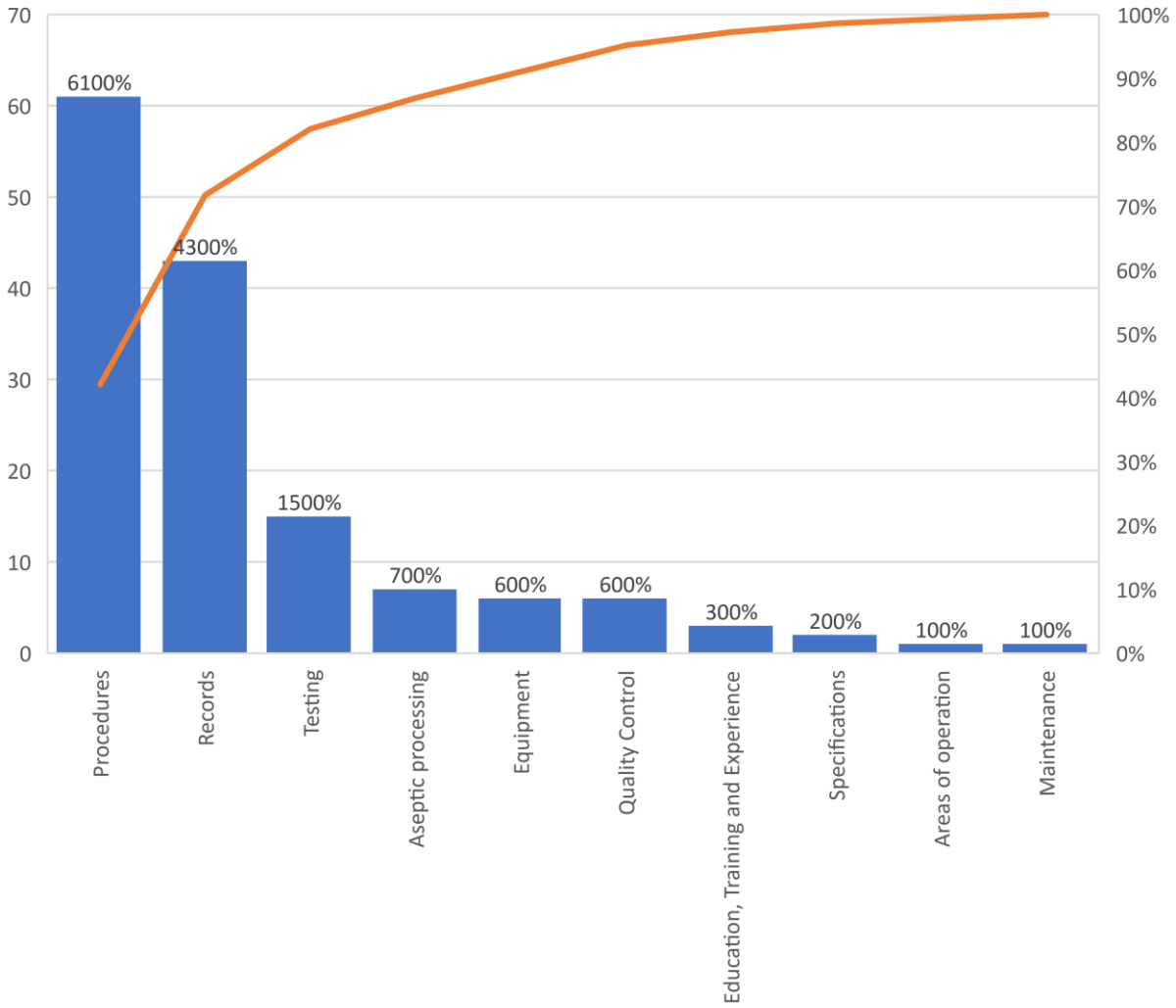

Figure 5.19- Number of deviations per category

The frequency of these categories throughout the years is presented in Annex H.

5.2.2.1 Procedures

The procedures category was sorted into more detailed groups to understand which types of procedures were most deviated. The reasoning behind the classifications of these groups was, according to the CFR infringed, the short and long descriptions available. These subcategories are:

- Calibration Procedures;
- Control Procedures;
- Laboratory Controls;
- Not followed;
- Not written;
- SOPs not followed / documented;
- Stability Procedure;
- Validation.

As previously shown, the Procedures category had 61 entries. The two most common subcategories are the **Not written** and **Not followed**, Figure 5.20. The first four categories are behind 80% of all Procedures deviations.

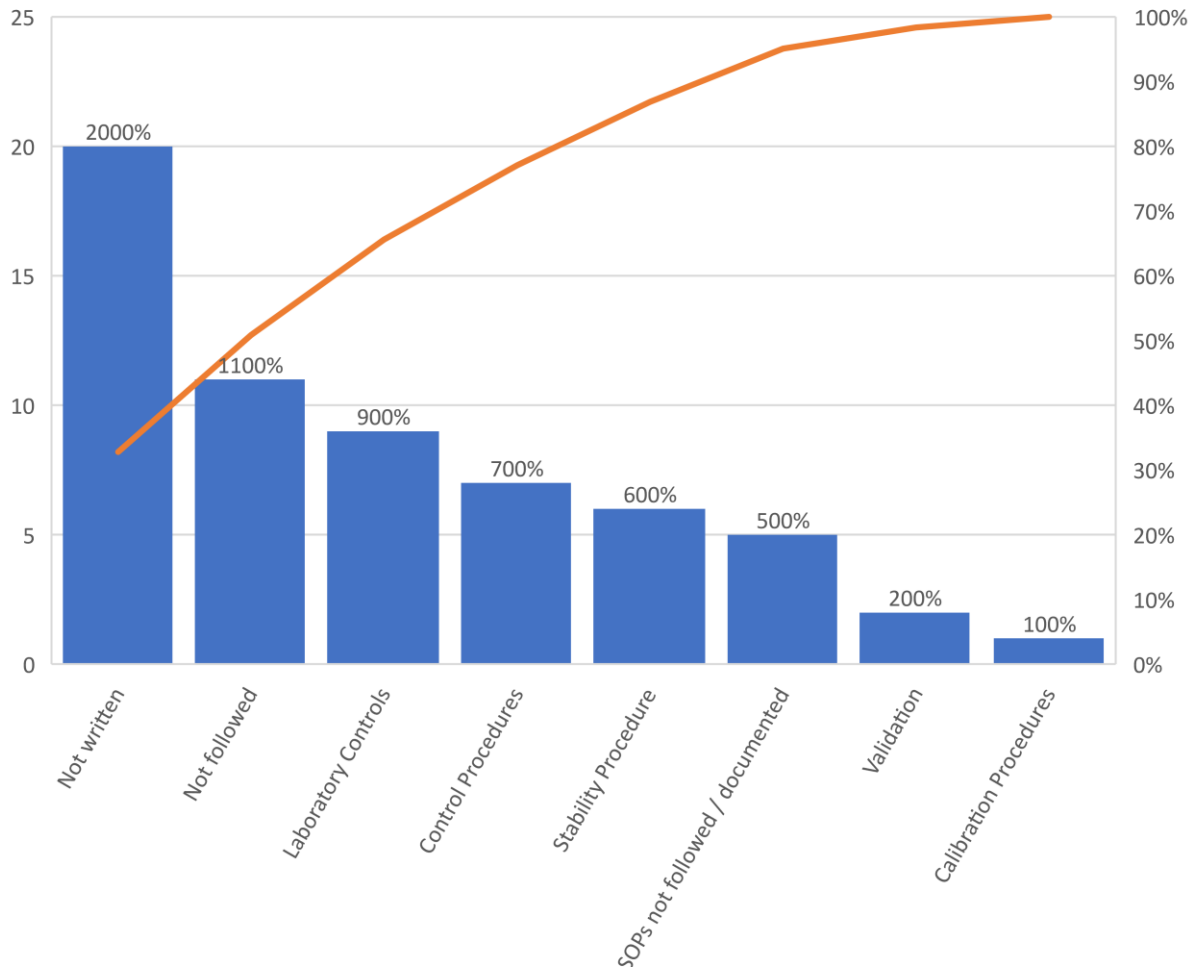

Figure 5.20- Number of deviations per Procedures subcategory

Being this is a major issue for the industry since it stuck to the heart the core objectives of the industry, the consistency of results, procedures, and processes over time.

This can have major implications for the company, leading to the loss of the license to operate as a pharmaceutical manufacturer for a specific product line or site.

5.2.2.2 Records

Like Procedures, the Records category was subcategorized into smaller and more detailed groups given the CFR infringed, short and long description. Table 5.13 displays the subcategories as well as what they involve.

Table 5.13- Name and a short description of Records subcategory

Subcategories	Description
Certificates	Any type of records regarding results of an analysis
Complaints	Records of complaints by the Quality Control Unit or Procedures
Investigation	Review of records Investigations of discrepancies, failures- not written or incomplete Deviations from laboratory controls

Figure 5.21 presents the distribution of the Records subcategory. Clearly, approximately 80% of all Records deviations are due to the fact that investigations are not followed through.

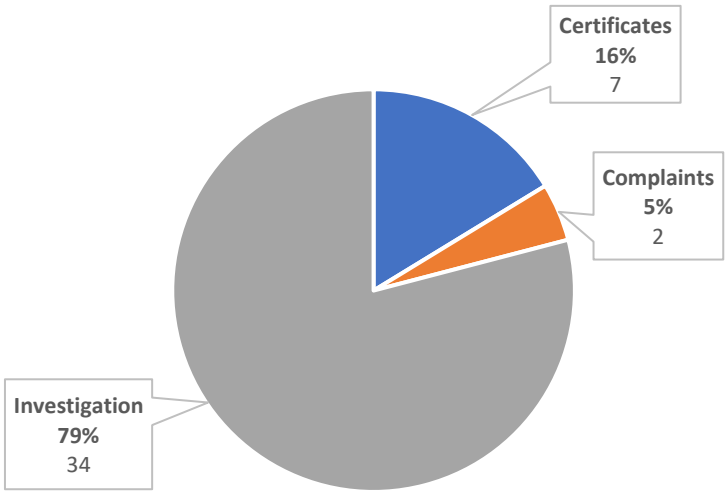

Figure 5.21- Number of deviations per Records subcategory

Records are at the core of GMP compliance since they act as evidence of previous batches and activities of the organizations that impact the final quality of the product. Missing available or tempered data are always a basis for actions by the health authorities.

5.3 Overview

The primary data is summed up in the following table, Table 5.14.

Table 5.14- Overview of the data collected between FDA and EMA

EMA		**FDA**	
Number of inspections	435	**Number of inspections**	73
Most common deficiency	**Procedures** (31,1%)	**Most common deficiencies**	**Procedures (42%)** - Not written (33%) - Not followed (18%) **Records (30%)** - Investigation (79%)
Minor infringements	8323 (87%) **Procedures-** 29,5% **Records-** 21,4%	**Sterile infringements**	110 of 145 (76%)
Major infringements	1003 (11%) **Procedures**- 19,8% **Specifications**- 32,2%	**NAI**	10 (14%)
Critical infringements	193 (2%) **Procedures**- 22,3% **Specifications**- 27,5%	**VAI**	56 (77%)
		OAI	7 (9%)

6. Conclusions

The *Good Manufacturing Practice: An analysis of regulatory inspection findings in the centralised procedure* reports a total of 435 inspections carried out by EMA from 1995 to 2005. After analyzing the data and systematizing them by categories, the most common deficiency found during that time period falls under the Procedures category, representing 31,1%. There were 9465 deficiencies found, of which 87% (8323) of them were minor. These were sorted into categories; the two most prevalent categories were Procedures (29,5%) and Records (21,4%). Major infringements account for 11% (1003) of the total deviations. 19,8% and 32,2% of these infringements correspond to the Procedures and Specifications categories, respectively. In the end, only 2% of the infringements (193) were classified as critical. Of those critical infringements, 27,5% were related to the Specifications category and 22,3% with the Procedures category. In the last two cases, the Specifications category is the top category. This is likely to happen as it is known that these deficiencies reveal to be of great concern regarding potentially harmful consequences for human and animal health, thus being classified as critical.

Given the available public database and the data provided, there were 73 accounted for in-depth analysis. Of those, 10 were classified as NAI (14%), 56 as VAI (77%), and 7 as OAI (9%). There was a total of 145 deviations, 110 of them linked to infringements of CFR Sterile Codes presented in the *Guidance for Industry*. Deviations were sorted into categories, being the most common deficiency in the Procedures category (42%). In a more in-depth analysis of the FDA's inspections data, this mostly happened because there were no written Procedures 33% of the time, and 18% of those written were not followed. The Records category, the second-highest, represented 30% of all deviations in the FDA's inspections, from which 79% are of investigations not followed through.

This thesis identifies the main challenges of the inspections, allowing manufacturers to prepare themselves before an inspection. At the same time, the fact that they are more prepared for it allows the inspection to run more smoothly. In the end, even if some deviations are found, like the ones identified above, there is already greater knowledge by the organization around the subject. Therefore, they are also more prepared to implement CAPA actions for post-inspection.

According to the data shown previously, the most frequent CFR infringed on FDA inspections on Ophthalmic manufacturers were the CFRs mentioned in *Guidance for Industry for Sterile Drug Products*. As such, it is recommended that manufacturers read, interpret and implement FDA's recommendations to prevent any deviations.

Manufacturers should generally have their entire documentation, meaning procedures and records, on track since these were the two categories most deviated in inspections carried out by both regulatory authorities. Manufacturers are advised to develop a comprehensive checklist based on guidances' like *ICH/GMP* and *FDA's Guidance for Industry for Sterile Drug Products* as a way to ensure that requirements are met.[13]

Mock inspections are a way of preparing staff in the event of an unannounced inspection. They allow staff to practice interviews by answering and discussing who will be responsible for information regarding each area of operation. Staff should be advised to:[13]

- “Be concise and answer only the questions that are asked.
- Do not volunteer information outside of what is asked.
- Do not guess or speculate.
- Do not refuse information requests or argue with inspectors.”

In conclusion, the rule for complaint operations and sucessful GMP inspections, must always be that of the 5 P’s rule: **P**rior **P**reparation **P**revents **P**oor **P**erformance.

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Annexes

Annex A - FOIA submission Acknowledgement Letter

U.S. FOOD & DRUG ADMINISTRATION

May 25, 2021

In Reply refer to
FOIA Control #:
2021-3420

Requester reference:

INSTITUTO SUPERIOR TÉCNICO
SARA COUTINHO
Rua Virgílio Correia nº9, 1ºDTO
Lisboa PT

Dear Requester:

The Food and Drug Administration (FDA) has received your Freedom of Information Act (FOIA) request for records regarding:

I would like to ask for the data of inspections carried out on ophthalmologic products, that is, company name, classification with brief observations, CFR code, Date and Country.

We will respond as soon as possible and may charge you a fee for processing your request. If your informational needs change, and you no longer need the requested records, please contact us to cancel your request, as charges may be incurred once processing of your request has begun. For more information on processing fees, please see http://www.fda.gov/RegulatoryInformation/FOI/FOIAFees/default.htm.

Due to an increase in the number of incoming requests, we may be unable to comply with the twenty-working-day time limit in this case, as well as the ten additional days provided by the FOIA. The actual processing time will depend on the complexity of your request and whether sensitive records, voluminous records, extensive search, and/or consultation with other HHS components or other executive branch agencies are involved. Please note that requests for medical device approval records (e.g. 510K, PMA, DEN) may take up to 18 to 24 months to process.

If you have any questions about your request, please call Rochelle A. Coleman, Information Technician, at (301) 796-8982 or write to us at:
Food and Drug Administration
Division of Freedom of Information
5630 Fishers Lane, Room 1035
Rockville, MD 20857

If you call or write, use the FOIA control number provided above which will help us to answer your questions more quickly.

You also have the right to seek dispute resolution services from:

Office of Government Information Services
National Archives and Administration
8601 Adelphi Road – OGIS
College Park, MD 20740-6001
Telephone:202-741-5770
Toll-Free: 1-877-684-6448
Email:ogis@nara.gov
Fax: 202-741-5769

and/or

FDA FOIA Public Liaison
Office of the Executive Secretariat
US Food Administration
5630 Fishers Lane, Room 1050
Email: FDAFOIA@fda.hhs.gov

Sincerely,

SARAH KOTLER
Director

Annex B - FDA E-mail Response

Gmail **Sara Coutinho <sara.mcoutinho@gmail.com>**

Fwd: FDA FOI Response - 2021-3420

1 message

Sara Maria Mateus Coutinho <sara.coutinho@tecnico.ulisboa.pt> Sat, Jul 17, 2021 at 6:03 PM
To: sara.mcoutinho@gmail.com

-------- Original Message --------
Subject: FDA FOI Response - 2021-3420
Date: 2021-06-04 19:27
From: "Kelsey, Leigh" <Leigh.Kelsey@fda.hhs.gov>
To: "sara.coutinho@tecnico.ulisboa.pt" <sara.coutinho@tecnico.ulisboa.pt>

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Rockville, MD 20857

Instituto Superior Técnico

Rua Virgílio Correia nº9, 1

DTO, Lisboa, , PT

Attn: Sara Coutinho

+351917673044

sara.coutinho@tecnico.ulisboa.pt

Dear Requestor:

This is in response to your requests dated 5/25/2021 for records from the Food and Drug Administration pursuant to the Freedom of Information Act regarding:

Date Range: 01/10/2008 - 05/24/2021; I am currently finishing my Master's Thesis in Pharmaceutical Engineering at Instituto Superior Técnico in Lisbon, Portugal. My thesis focuses on Ophthalmic Drug Products and Regulatory Agencies, primarily FDA and EMA. I would like to ask for the data of inspections carried out on ophthalmologic products, that is, company name, classification with brief observations, CFR code, Date and Country.

_ _

Please note the following information about the attached response:

* _Not every inspection has a received a final classification, therefore in those cases there is no information present in the field "CLASSIFICATION" on the "INSPNS" tab._
* _Not every inspection results in the issuance of an FDA-Form 483, the "FDA483?" column on the "INSPNS" indicates whether one was issued ("Y") or was not ("N")._
* _The data are presented on two separate tabs in order to assist with presenting the information in a manageable manner since one Inspection can have multiple Citations associated to it. The "INSPNS" tabs provides the majority of the information requested with the exception of the Citation Data which are present on the "CITATIONS" tab. You can use

Annex C - List of other major Regulatory Authorities Worldwide[12]

* adapted from Geetanjali Sengar

Country	Name of Regulatory Authority
USA	Food and Drug Administration (FDA)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
India	Central Drug Standard Control Organization (CDSCO)
Canada	Health Canada
Europe	European Medicines Agency (EMEA)
Denmark	Danish Medicines Agency
Costa Rica	Ministry of Health
New Zealand	Medsafe - Medicines and Medical Devices Safety Authority
Sweden	Medical Products Agency (MPA)
Netherlands	Medicines Evaluation Board
Ireland	Irish Medicines Board
Italy	Italian Pharmaceutical Agency
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
Ukraine	Ministry of Health
Singapore	Centre for Pharmaceutical Administration Health Sciences Authority
Hong Kong	Department of Health: Pharmaceutical Services
Paraguay	Ministry of Health
Sweden	Medical Products Agency (MPA)
Thailand	Ministry of Public Health
China	State Food and Drug Administration

Germany	Federal Institute for Drugs and Medical Devices
Malaysia	National Pharmaceutical Control Bureau, Ministry of Health
Pakistan	Drugs Control Organization, Ministry of Health
South Africa	Medicines Control Council
Sri Lanka	SPC, Ministry of Health
Switzerland	Swissmedic, Swiss Agency for Therapeutic Products
Uganda	Uganda National Council for Science and Technology (UNCST)
Brazil	Agencia Nacional de Vigiloncia Sanitaria (ANVISA)
Japan	Ministry of Health, Labour & Welfare (MHLW)
INTERNATIONAL ORGANIZATIONS	
World Health Organization (WHO)	
Pan American Health Organization (PAHO)	
World Trade Organization (WTO)	
Pharmaceutical Inspection Co-operation Scheme (PIC/S) *	
International Conference on Harmonization (ICH)	
World Intellectual Property Organization (WIPO)	

* added to the list, list by Geetanjali Sengar

Annex D - An Example of Notice of Inspection FDA Form 482

NOTICE OF INSPECTION

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO. New England District Office One Montvale Avenue, 4th Floor Stoneham, MA 02180-3500 781-587-7500

TO	2. NAME AND TITLE OF INDIVIDUAL	3. DATE
	Francis Farmer - Farm Manager	XX/XX/20XX
	4. FIRM NAME Growing Things, LLC	5. HOUR: 8:30 a.m. / p.m.
	6. NUMBER AND STREET XX Farmer Hill Lane	
	7. CITY AND STATE & ZIP CODE Townville, ME 04XXX	8. PHONE NO. & AREA CODE 207-XXX-XXXX

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*
Ingrid Igorssun	Ingrid Igorssun, Produce Inspector II

[1] Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

Act), and research data (other than data relating to new drugs, antibiotic drugs, devices, and tobacco products and subject to reporting and inspection under regulations lawfully issued pursuant to section 505 (i) or (k), section 519, section 520(g), or chapter IX and data relating to other drugs, devices, or tobacco products, which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j)). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail; (B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice; (C) persons who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in research, teaching, or chemical analysis and not for sale; (D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704(b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, tobacco product, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[2] Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F – Licensing – Biological Products and Clinical Laboratories and* * * * *

Sec. 351(c) "Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation

(Continued on Page 3)

of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F – * * * * * *Control of Radiation.

Sec. 360 A (a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

* * * * * *

(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information Any regulation establishing a requirement pursuant to clause (1) of the preceding sentence shall (A) authorize such dealers and distributors to elect, in lieu of immediately furnishing such information to the manufacturer to hold and preserve such information until advised by the manufacturer or Secretary that such information is needed by the manufacturer for purposes of section 359, and (B) provide that the dealer or distributor shall, upon making such election, give prompt notice of such election (together with information identifying the notifier and the product) to the manufacturer and shall, when advised by the manufacturer or Secretary, of the need therefore for the purposes of Section 359, immediately furnish the manufacturer with the required information. If a dealer or distributor discontinues the dealing in or distribution of electronic products, he shall turn the information over to the manufacturer. Any manufacturer receiving information pursuant to this subsection concerning first purchasers of products for purposes other than resale shall treat it as confidential and may use it only if necessary for the purpose of notifying persons pursuant to section 359(a)."

* * * * * *

Sec. 360 B.(a) It shall be unlawful–

(1) * * *

(2) * * *

(3) "for any person to fail or to refuse to establish or maintain records required by this subpart or to permit access by the Secretary or any of his duly authorized representatives to, or the copying of, such records, or to permit entry or inspection, as required or pursuant to section 360A."

* * * * * *

Part G - Quarantine and Inspection

Sec. 361(a) "The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

Annex E - An Example of FDA 483 Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10 Waterview Blvd., 3rd Floor Parsippany, NJ 07054 (973)331-4900 Fax:(973)331-4969	7/23/2018-8/30/2018* FEI NUMBER 2246848

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Michael P Stehn, Vice President and General Manager

FIRM NAME	STREET ADDRESS
Akorn Inc.	72 Veronica Ave
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Somerset, NJ 08873-3426	Sterile Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

QUALITY SYSTEM

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A) Azelastine Hydrochloride Ophthalmic Solution, 0.05% (Sterile) batches 6K89A, 6K90A, 6K92A failed CRT stability testing for multiple time points (6M, 9M, 12M, 18M); these batches remained in the market until they were recalled during the current inspection. Investigation PR# 58999 into the failure of batch 6K89A was initiated on 05/23/2017 after the 6M stability time point failed for the impurity (b) (4) with a result of 0.6% (Specification Limit: (b) (4)). The stability data for these time points was not readily available for review during the beginning of the inspection. We observed that the employees started filling the notebook pages and certificate of analysis during our inspection. The QC Manager stated that the delay was due to the observance of failing stability results and the need to complete investigations and perform recalculations.

For example, original stability results obtained for Azelastine Hydrochloride Ophthalmic Solution, 0.05% (Sterile) batch 6K89A, (b) (4) Impurity were modified or recalculated later and new entries were made into laboratory notebooks during the current inspection as shown in the table below:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Tamil Arasu, Investigator Guerlain Ulysse, Investigator Ko U Min, Chemist/Biologist Atul Agrawal, Non Reporting User X Tamil Arasu Investigator Signed By: 2001563486 Date Signed: 08-30-2018 15:59:26	8/30/2018

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE **INSPECTIONAL OBSERVATIONS** PAGE 1 of 22 PAGES

Available at: https://www.fda.gov/media/120699/download

Annex F - An Example of FDA Warning Letter

WARNING LETTER

Akorn Inc.

MARCS-CMS 568173 — JUNE 13, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Douglas S. Boothe
Chief Executive Officer
Akorn Inc.
1925 West Field Court Suite 300
Lake Forest, IL 60045
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I
10 Waterview Blvd, 3rd Floor
Parsippany, NJ 07054
United States

WARNING LETTER
CMS # 568173

June 13, 2019

VIA UPS Next Day Air

Mr. Douglas S. Boothe
Chief Executive Officer
Akorn, Inc.
1925 West Field Court
Suite 300
Lake Forest, IL 60045

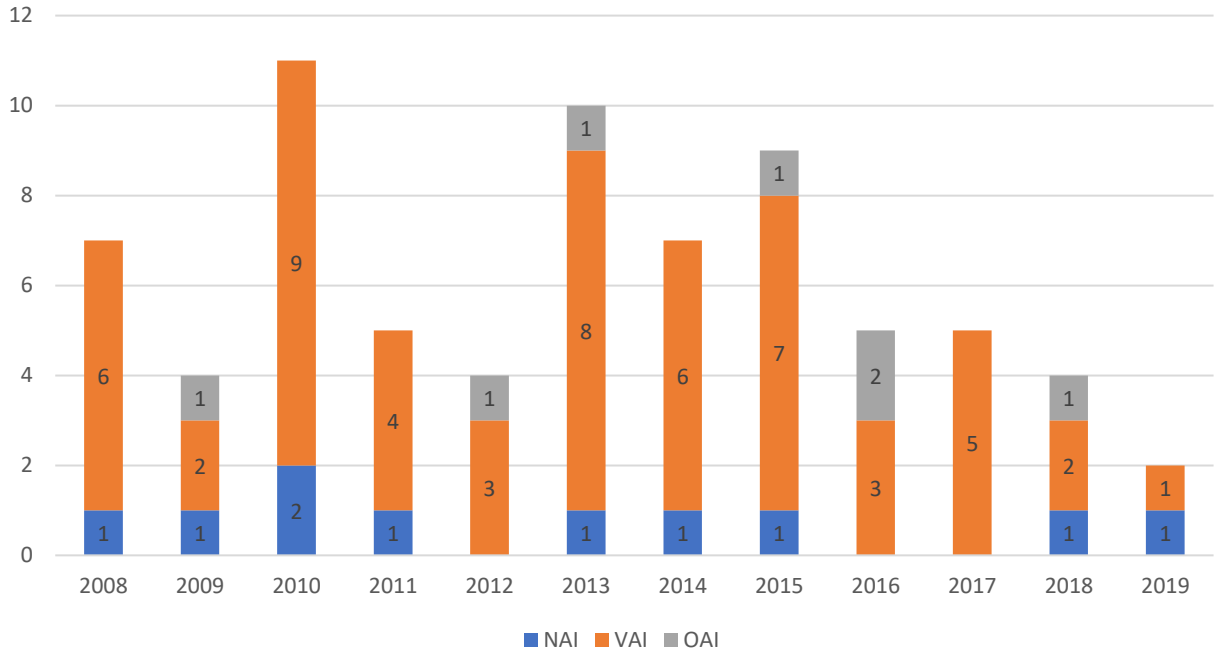
Dear Mr. Boothe:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Akorn Inc. at 72 Veronica Avenue, Somerset, New Jersey, from July 23 to August 30, 2018.

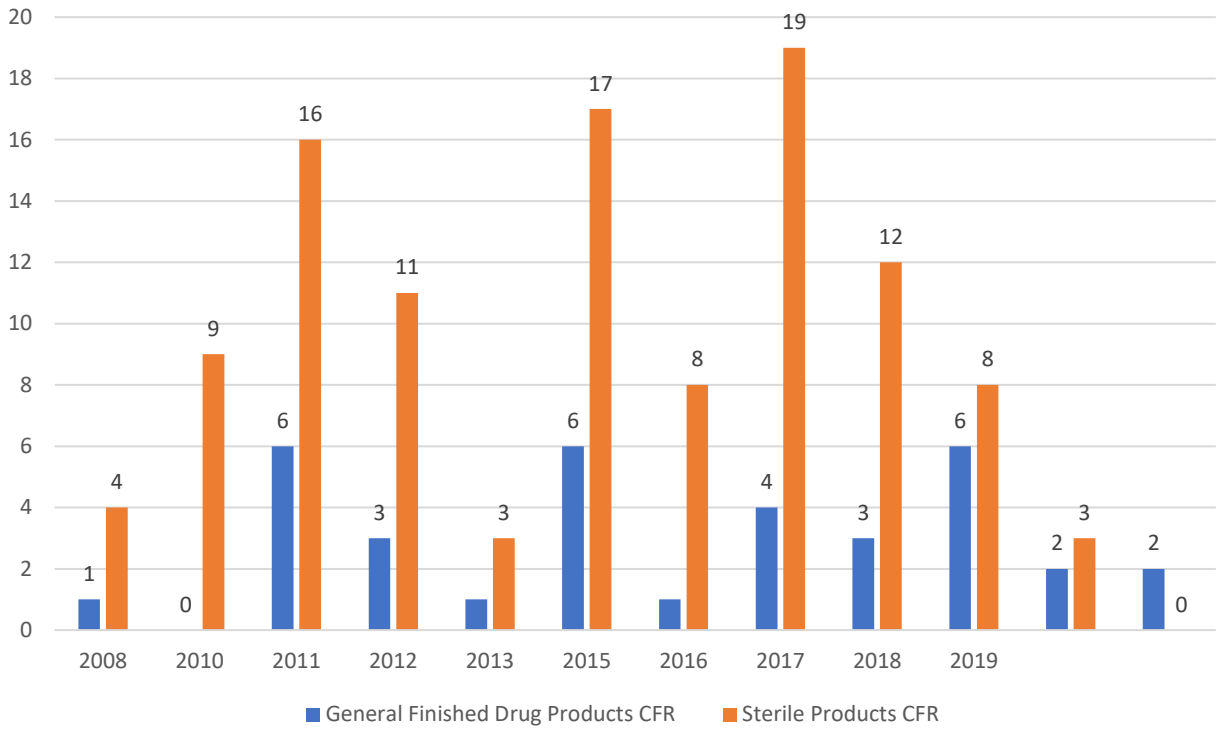
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/akorn-inc-568173-06132019

Annex G - FDA Inspection Classification from 2008 to 2019



Annex H -FDA Non-conformities per type of CFR and year



Annex I - Frequency of FDA deviations per category and year