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Short Communication

Inspections – Key Role in Quality of Medicines

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ABSTRACT

Global patients depend on medicinal product for their specific purposes. These drugs are manufactured both domestically and internationally. Regardless of where they are manufactured, the Food and Drug Administration (FDA) plays a pivotal role in the United States, regulating drugs, biologics, and devices by not only scrutinizing each marketing holder's application but also guaranteeing that the product's manufacturer complies with current good manufacturing practices (cGMP). This ensures that the product's quality is consistent and is manufactured securely for its intended use.

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INTRODUCTION

Billions of patients worldwide rely on medicinal products to improve their quality of life. For the purpose of this article, medicinal products include both drugs and biologics. Based on data compiled as part of the National Ambulatory Medical Care survey, over 1.0 billion drugs were provided or prescribed to patients in the US alone. ⁽¹⁾

These medications reach the market after undergoing a 5-step drug development process that comprises FDA review and post-market safety monitoring steps. While clinical trials provide information on a drug's safety and efficacy, the true picture of a drug's safety evolves over time. Manufacturer inspections are an important facet of the FDA post-market drug safety monitoring step. ⁽²⁾

In an era where manufacturing takes place both locally and internationally, maintaining public health through continuous oversight is crucial. The FDA ensures this by utilizing various strategies and tools. Manufacturers must adhere to relevant GMP regulations to uphold product quality. The FDA, through its inspections, verifies that manufacturing facilities are compliant per the applicable regulations and that the personnel manufacturing these medications are appropriately qualified. Depending on the inspection results, the FDA can use different methods to

provide feedback to manufacturers and classify the inspections according to the severity of the findings. If findings are not resolved, the FDA may enforce certain actions, thereby safeguarding public health.

This short article highlights a high-level understanding of the FDA inspections and tools at its disposal for ensuring quality compliance of the product.

cGMP

The FDA oversees medicinal products in the United States. Application holders must comply with applicable regulations to ensure that distributed products are safe and effective for their approved use. Manufacturers need to guarantee the consistency of the identity, strength, quality, and purity of drug products, which can be achieved by adhering to the FDA's cGMP regulations. The "c" in cGMP stands for current. The regulations can be very vague and can be interpreted in a variety of ways. That interpretation can change over time; hence, current means current interpretation. The goal of cGMP is to ensure consistent product quality that is safe and effective for its intended use. ⁽³⁾ All processes/manufacturing steps should follow cGMP and approved quality information as registered in module 3 of the registered dossier. The FDA assesses manufacturing facilities through inspection of various criteria, including but

not limited to facilities, equipment, systems, documentation, and personnel qualifications.

INSPECTIONS

The FDA's Office of Regulatory Affairs (ORA) leads inspections and enforcement. ⁽⁴⁾ The FDA ensures that regulated medicinal products meet strict quality, safety, and effectiveness standards, employing risk-based approaches to identify manufacturing facilities for inspections, both domestically and internationally.

The following provides a summary of the different kinds of inspections ⁽⁵⁾:

Surveillance Inspections – These are comprehensive assessments that scrutinize the manufacturing process to ensure it aligns with cGMP regulations and that the product's quality remains consistent.

For-cause Inspections – These are carried out when the FDA has grounds for concern based on previous findings or violations. They aim to verify that manufacturers have implemented the necessary corrective actions in response to past inspections. Like surveillance inspections, these also focus on product quality.

Other types of inspections may be conducted during the initial product application process. In such cases, the FDA inspects the facilities listed in the new product application. Furthermore, another type of inspection may concentrate on nonclinical and clinical data supporting applications under review.

Remote regulatory assessments

Typically, the FDA will be involved in physically inspecting manufacturing facilities; however, COVID-19 imposed restrictions on these activities. In response, the FDA leveraged the remote regulatory assessment tool to perform these inspections virtually to carry out its regulatory oversight. Although this tool was initially employed as a tool in response to the pandemic, the FDA recognizes the value of remote assessments and plans to continue utilizing the tool to ensure public health alongside traditional physical inspections. ⁽⁶⁾

Process of FDA Inspections

FDA inspections are typically unannounced, with a few exceptions. ⁽⁷⁾ For manufacturing facilities located outside of

the US, a formal notification is typically sent prior to an FDA inspection. In most instances, multiple inspectors conduct the inspection and focus on different areas to assess adherence to cGMP regulations.

After a brief overview of the inspection process and review of the site's organizational charts, FDA inspectors will begin the inspection with facility tours. During the tour, they may ask several questions, interview personnel working in the respective areas and request to see specific documentation after the tour. Most inspectors will also request to review a list of open and closed deviations and investigations. Inspections last several days and could consist of several tours of different areas such as manufacturing, QC labs, warehouses, clean utilities, etc. Over the course of the inspection, the inspectors will request to interview specific subject matter experts (SMEs) on various topics, including the quality management system (QMS). It is important to note that quality cannot be tested in a product. It can only be built in by following GMP at all times - at design, construction of facilities, manufacturing, testing, and storing.

Moreover, once the inspection is completed, FDA inspectors will issue an FDA form 483 based on the observations that may violate the FD&C Act and/or related acts. ⁽⁸⁾⁽⁹⁾

Inspection Classification and cGMP violations

The FDA classifies inspections based on their findings. These classifications ⁽¹⁰⁾ include the following:

- No action indicated (NAI), where no objectionable conditions or practices are identified.
- Voluntary action indicated (VAI), where objectionable conditions or practices are found but the FDA does not intend to act.
- Official action indicated (OAI), where the FDA recommends regulatory or administrative actions.
- The below figure shows the inspection classification by product type per the data available until July 2023 – biologics, devices, and drugs for the years 2013 – 2023. ⁽¹¹⁾

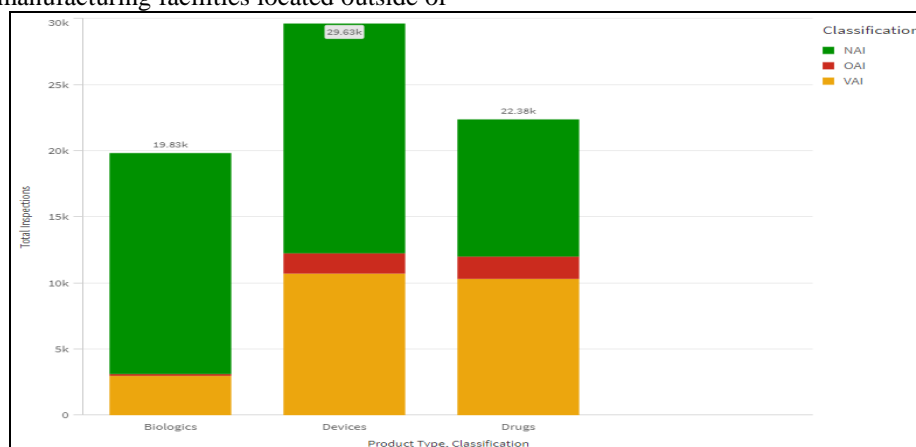


Figure 1: Inspection classification type based on product type

Depending on the results of an inspection and the severity of any violations found and potential impact on the quality of the product, the FDA may exercise its enforcement or request a company to recall drugs or even seize them. Through legal proceedings, the FDA can initiate a seizure or injunction where it seeks the confiscation of tainted drugs already on the market. The agency may also petition the courts to ensure that any cGMP violations are rectified.

In some instances, the FDA might even initiate criminal proceedings, seeking penalties or imprisonment based on the seriousness of the cGMP violations. For products manufactured by international manufacturers, they could be placed under import alerts, leading to detention or potential rejection if imported into the United States.⁽³⁾

The FDA enforces various methods to ensure that violations are corrected, which is largely based on the severity of violations and potential impact on the end users.

CONCLUSION

Quality is an important attribute in the highly regulated field of biopharmaceuticals and medicine. Consistent quality ensures that medicines are safe and effective for their intended use. The FDA plays a crucial role in this process, ensuring that industries adhere to good manufacturing practices and produce goods as approved. If there are violations in manufacturing, the FDA can employ its enforcement options according to the severity of the violation, taking necessary steps to ensure industry compliance.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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