Human and Veterinary Drug; cGMP Violations and Trends

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On June 12th, 1992, the United States filed action against Barr Laboratories, alleging they violated sections 331(a) and 351(a) (2) (B) of the Food and Drug Cosmetic Act (FDCA). Specifically, the Code of Federal Regulations in violation were cGMP regulations, 21 CFR Part 210, Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs; General and 21 CFR Part 211, Current Good Manufacturing Practice For Finished Pharmaceuticals. Barr Laboratories failed to validate equipment-cleaning processes, failed to conduct failure investigations, and released their batches using selective data. In the present and more than fifteen years later, the exact cGMP violations to section 351(a) (2) (B) of the Food and Drug Cosmetic Act (FDCA) are still prevalent in the drug industry. In fact, the drug industry has been plagued with several cGMP violations in the form of FDA 483s and Warning Letters.

FDA 483s document violations to the FDA's Code of Federal Regulations whereas Warning Letters reiterate those violations, but also serve as a legal threat to an organization. At this point, I would like to provide you with an overview of some cGMP violation trends I have seen in the industry.

Standard operating procedures (SOPs) and forms continue to be a problem for drug companies, as they often lack procedures and associating forms for their own processes. The FDA requires companies to have documented procedures for their processes in hopes companies will exercise control over their respective business processes. Unfortunately, I have recently seen a lack of SOPs as well as a failure to carry out SOP instructions from one employee to another.

A failure to follow your own SOPs leads to inconsistency. Many times, employees interpret instructions in the SOP differently; therefore, business processes are often inconsistent across the boards. I repeatedly see this problem in the industry. Another common violation is the lack of personnel qualifications.

I have seen software developers commonly author the software validation deliverables of a drug related software application. It is acceptable to have their input and perhaps have them author some technical documents such as design documents or code review, but not the general umbrella documents such as a Validation Master Plan and Test Plan. The end result of such actions has led to the failure to ensure a software application has been tested per its intended use. The FDA requires a system to be tested against predetermined specifications and if the wrong unqualified personnel are authoring umbrella type validation documents, the specifications are unlikely to be correct. Another trend of cGMP violations is the lack of external training employees' gain.

I often see employees only attending company derived training classes as opposed to external training conferences. Although internal training is essential, external training conferences provide an industry perspective on select topics and can be used to further document an employee's qualifications.

Now that we have looked at cGMP violations and trends[1], let's take a look at the specific cGMP violations documented from 2006 to present. Please see below for highlights of violations as well as the "Gregor Index" for a summary.[2]

21 CFR Part 211.100(b) written procedures; deviations

Failure of drug firms to: document deviations, implement a standard operating procedure (SOP) governing deviations, document within a deviation SOP the criteria needed to be met for a deviation, and obtain Quality Assurance approval. These cGMP violations are typical in the industry, as projects move faster than

[1] Cgmp Trends 2006-2007
[2] The Gregor Index is the first of its kind and was developed solely by Mr. Michael J. Gregor, CEO of Compliance Gurus Inc. The Gregor Index is an index that tracks the compliance level of the FDA regulated industry, as it pertains to GxP.

Figure 1

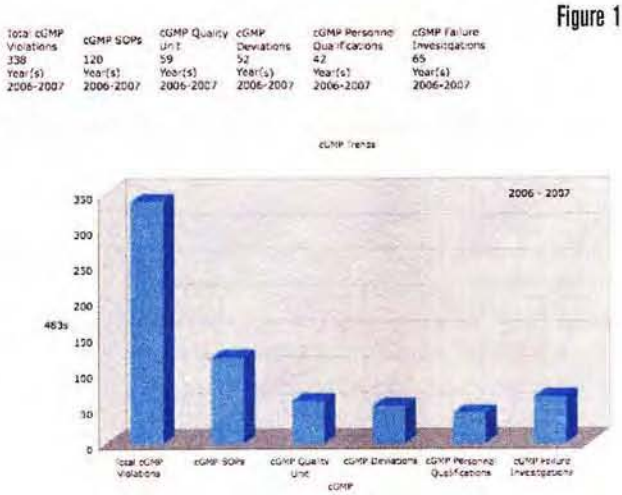
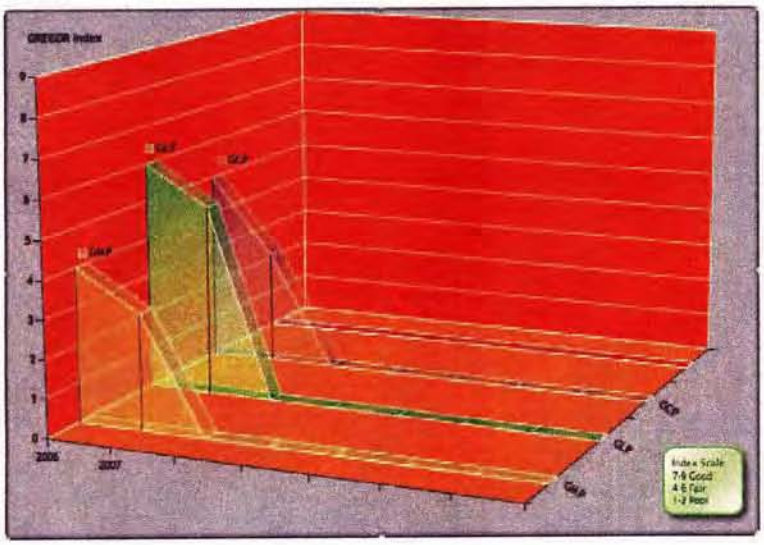


Figure 2



compliance in many cases. Often times, management will endorse "planned deviations" for the sake of a project timeline. Although it is important for a business to run smoothly and efficiently, it is equally important not to abuse the concept of a deviation. Planned deviations take away from the quality of the project and can lead to adulterated product if a firm is not careful how they use planned deviations. Unplanned deviations pose a risk to a project and/or product and must be carefully documented, reviewed, and approved by all relevant parties including an independent quality assurance unit.

Sec. 211.25(a) Personnel qualifications

Failure of drug firms to: document training of it personnel and consultants, train its personnel and consultants on current standard operating procedures before they are required to perform tasks governed by the standard operating procedures, and train their employees in cGMPs. Conducting and documenting training is essential for a drug firm. Most firms fail to effectively document their training appropriately. Although training is often conducted, the integrity of the training records is poor. It is important for drug firms to identify the training needed per an employee's job function, document the required training, conduct the training, and document the training itself. Many companies are using an electronic means to deliver the training and store the training records. Therefore, it is important for drug firms to remember to validate the application used to conduct the training and store the training records. Furthermore, the application must be validated against its intended use. Integrity of the training records are reliant on this validation, as it ensures the intended functionality and security are in place. Lastly, remember to validate against the applicable part of 21 CFR Part 11 if you are using the application to conduct the training or store its output.

Sec. 211.192 Production record review

A drug firm was cited for: "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 [21 CFR 211.192]. The investigation of a complaint submitted by a customer on 8/11/06 regarding a possible reaction of two dogs to Pyrantel Pamoate Suspension Canine-2X (4.54 mg / mL), Lot [redacted], was not thoroughly and/or completely documented. The assay of the product returned by the customer found 142.7% label claim. The specifications for this product are [redacted] % of label claim. The letter to the customer says the higher assay value indicates that the bottle was not shaken well. However, there is no documentation of the receipt and examination of the returned sample. In addition, the report of the investigation of the complaint does not indicate that the batch record, process validation data or stability information was reviewed as part of the investigation."

Drug firms continue to struggle with assessing unexplained discrepancies or failures of a batch or its components. As stated in the above-referenced observation, the drug firm did not produce any documentation of the receipt and examination of the returned sample nor did the firm document the review of the batch record, process validation data or stability information. Documentation is key for any drug firm, therefore, it is imperative for any firm to not only document the standard operating procedure that governs

investigation reviews, but to also document the investigations per established procedures. This observation is further evidence the drug industry is struggling to comply with cGMP regulations such has failure investigations, as Barr Laboratories was cited for the same failure over fifteen years ago.

Sec. 211.22 Responsibilities of quality control unit

A drug firm failed to "establish and follow written responsibilities and procedures applicable to the quality control unit [21 CFR 211.22(d)]." Drug companies ability to follow their own procedures whether it be apply to the quality control unit related procedures or any other company standard operating procedures continues to haunt the industry. In many cases, when drug firms fail to follow their own established standard operating procedures, they also fail to document the fact they neglected to follow their own procedures. Unfortunately, this spells disaster, as it paints a picture to an outside party such as a FDA investigator a company does not have control over their own processes and procedures. Failure to have control leads to adulterated product many times. It is always a good idea to perform an annual review of your standard operating procedures to ensure you are following your respective procedures and to ensure you have documented procedures for each process. I suggest companies prioritize their procedures and perform a review of the high-risk procedures first, then subsequently work their way down the list to less critical procedures. This cGMP violation is by far the most common violation in the last two years. Many companies continue to battle the everlasting requirement of documenting and following their own procedures. As a result, more and more 483s are issued with this type of cGMP violation. A dangerous path the industry is walking, as failure to establish procedures compounded with a failure to follow current procedures can very easily lead to adulterated product going out the door and into the hands of physicians and consumers.

Conclusion

Although the above-referenced cGMP violations are not an all inclusive list of 483s, they are the most common violations recorded in the last two years. It is important to remember there can be an indirect impact on patient safety if standard operating procedures are not followed or created accordingly. After all, isn't patient safety what we are in the business of ensuring?