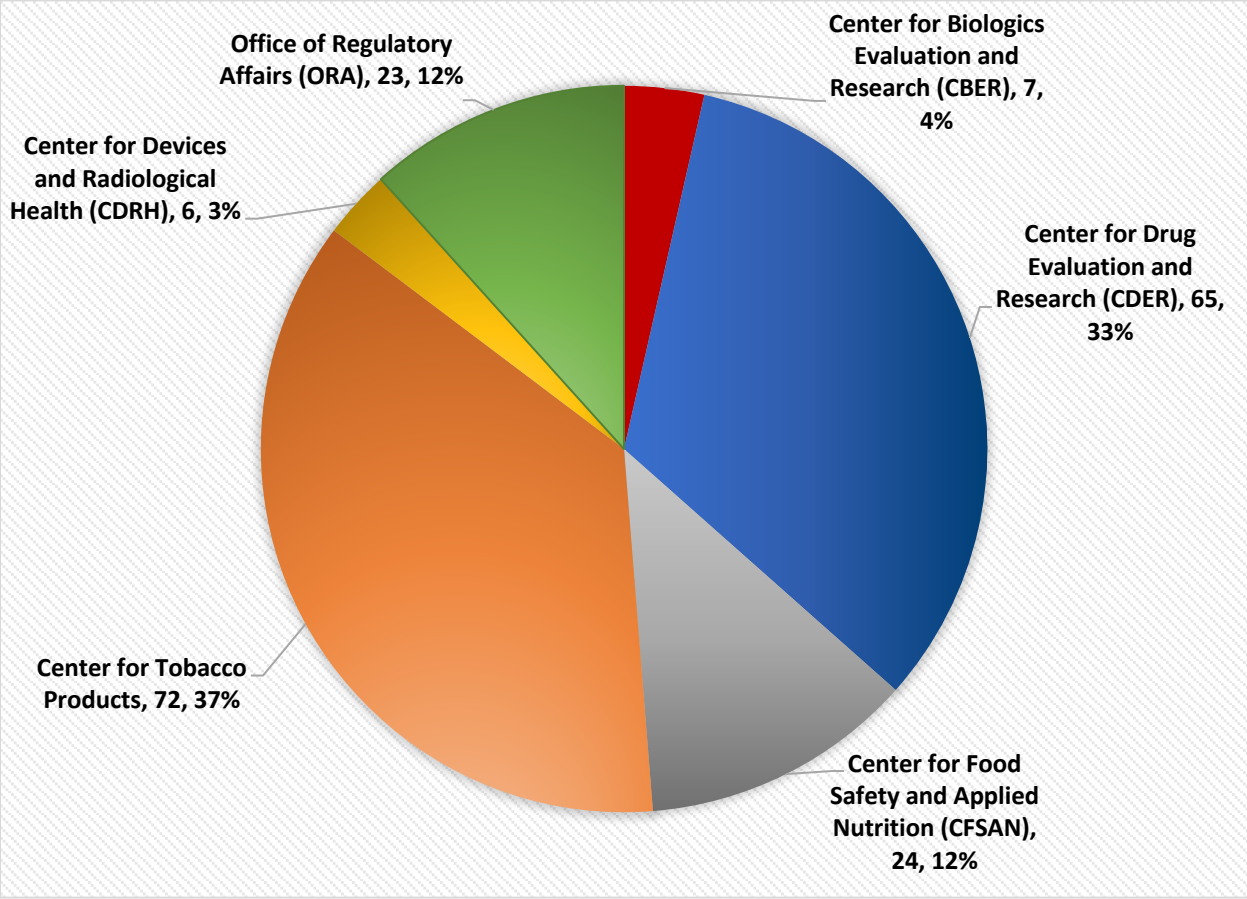
TCG Newsletter

October 2023

FDA Enforcement Trends: Q3 2023

Toscano Consulting Group, Inc. (TCG) provides Quality and Regulatory consulting services to companies within the Pharmaceutical, Biologics, and Medical Device sectors. TCG continuously monitors FDA's Regulatory Enforcement activities to keep abreast of current regulatory enforcement trends. This newsletter provides a summary of Warning Letters issued from the various centers to deliver insight into FDA's active enforcement areas. The distribution by Issuing Centers is provided below in Figure 1.

FIGURE 1: 197 WARNING LETTERS ISSUED BY CENTERS[1]



The FDA conducted a total of 2,508 inspections in the subject areas of Drugs, Medical Devices and Biologics during the first 3 quarters of 2023. Of these inspections 1,892 (75%) were domestic inspections and 616 (25%) were foreign inspections. The FDA issued 197 Warning Letters this quarter; TCG removed Warning Letters issued by CFSAN and Center for Tobacco Products to focus on those issued by CDER, CBER, CDRH, and ORA which resulted in a total of 101 Warning Letters. This newsletter focuses on Pharmaceutical, Biologics and Medical Devices for human use. The global distribution of Warning Letters is presented below in Table 2, with the United States having the majority of Warning Letters (76 out of 101) issued followed by India, South Korea, and others.

TABLE 2: Q3 GMP WARNING LETTERS BY COUNTRY

Country	Total Number of GMP WL	Percentage
US	76	75%
India	9	9%
South Korea	6	6%
Switzerland	1	1%
Thailand	1	1%
Turkey	1	1%
Mexico	1	1%
Portugal	1	1%
Canada	1	1%
China	1	1%
Germany	1	1%

SUMMARY OF KEY INSPECTION POINTS

- Of the 101 Warning Letters issued, 23 were for foreign inspections, and 17 of these inspections resulted in the FDA placing the inspected company on Import Alert 66-40, 66-79 or 66-78.
- 25 out of 101 (25%) Warning Letters had recommendations for the company to obtain a 3rd party consulting firm qualified as set for in 21 CFR 211.34 to assist with addressing the citations.
- We continued to see a small percentage of Data Integrity focused citations accounting for 2% of the assessed Warning Letters.
- 3.7 months was the average lag time between when a site is inspected and when a Warning Letter is issued.

TCG further analyzed the Warning Letters with cGMP violations specifically for 21 CFR 210/211 (Pharmaceuticals), 21 CFR 820/803 (Devices), 21 CFR 312 (INDs) and 21 CFR 56 (Clinical Investigations) resulting in 22 Warning Letters. Out of the 22 Warning Letters the top six reoccurring CFR citations are provided in Table 3 below.

TABLE 3: TOP WARNING LETTER CITATIONS

Top CFR Citations	Description	Number of Citations	Percentage
21 CFR 211.22	The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another ...	24	65%
21 CFR 211.84	Testing and approval or rejection of components, drug product containers, and closures.	19	51%
21 CFR 211.100	Written procedures; deviations.	13	35%

Top CFR Citations	Description	Number of Citations	Percentage
21 CFR 211.160	The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified.	10	27%
21 CFR 211.113	Control of microbiological contamination.	10	27%

Citations related to 21 CFR 211.84 continue to be the top item, consistent with TCG's previous newsletters for the last two quarters. During Q3, the FDA cited companies for not testing each lot of incoming components that are at high risk for diethylene glycol (DEG) or ethylene glycol (EG) contamination. Many of these citations are for foreign inspections; however, there are several US firms that are also cited for the same issue. FDA issued a guidance[2] in May of this year, which outlines their expectations on this topic.

Not surprising FDA's citation for 21 CFR 211.22 indicate a firm failing to establish a quality unit with the responsibility and authority to approve or reject components, drug products labeling among others is often cited as a pair with 21 CFR 211.84. This may explain in part why these companies were not testing the high-risk components for DEG and EG.

Lastly, we saw the FDA focusing on ophthalmic products primarily from OTC drug manufacturers. The FDA is citing companies for marketing unapproved new drugs due to claims indicating their products are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or intended to affect the structure or any function of the body. These Warning Letters are often coupled with significant GMP violations. Ophthalmic drug products pose a greater risk of harm to users because the route of administration for these products bypasses some of the body's natural defenses. Given these facts along with recent headlines into Ophthalmic drug product contamination[3] it is not surprising that the FDA is focusing on these products.

Please do not hesitate to contact us here at TCG with any questions you may have. We are always here to provide help and clarity.

Sincerely,

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References:

[1] Note Warning Letters issued by certain offices such as the Office of Pharmaceutical Quality were grouped by the respective center (CDER).

[2]Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol Guidance for Industry, May 2023 https://www.fda.gov/media/167974/download

[3]https://www.webmd.com/eye-health/news/20230222/fda-warns-of-contanimated-eye-products