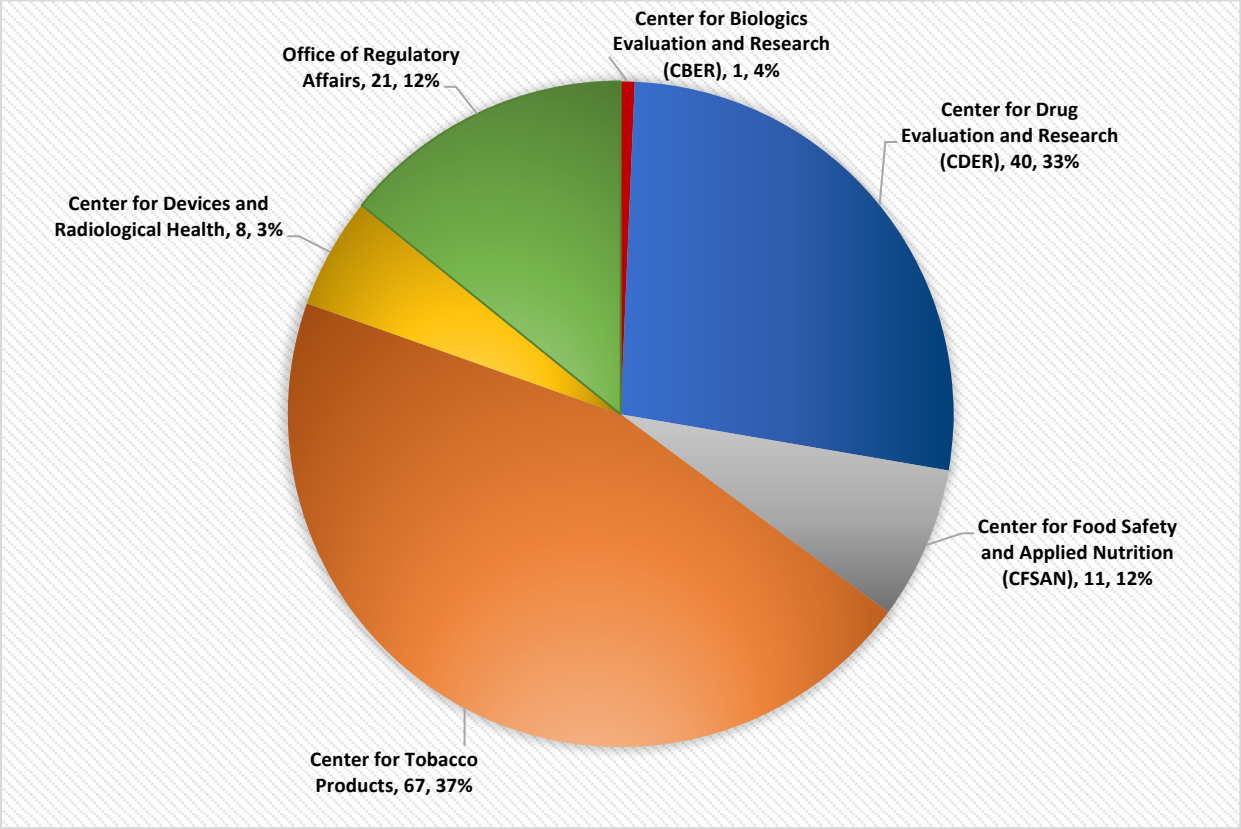
TCG Newsletter

February 2024

FDA Enforcement Trends: Q4 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 provide insight into FDA's active enforcement areas. The distribution by Issuing Centers is provided below in Figure 1.

FIGURE 1: 148 WARNING LETTERS ISSUED BY CENTERS[1]



The FDA conducted a total of 3,983 inspections in the subject areas of Drugs, Medical Devices and Biologics during 2023. Of these inspections 2,927 (73%) were domestic inspections and 1,056 (27%) were foreign inspections. The FDA issued 148 Warning Letters during the fourth quarter of 2023. The global distribution of Warning Letters is presented below in Table 2, with the United States having the majority of Warning Letters (128 out of 148) issued followed by China, India, and others.

TABLE 2: Q4 WARNING LETTERS BY COUNTRY

Country	Total Number of WL	Percentage
US	128	86%
China	5	3%
India	5	3%
Turkey	3	2%
S. Korea	2	1%
Singapore	1	1%
Sweden	1	1%
Malaysia	1	1%
Germany	1	1%
Argentina	1	1%

TCG removed Warning Letters issued by CFSAN, Center for Tobacco Products, and ORA (due to applicable findings) to focus on those issued by CDER, CBER, CDRH which resulted in a total of 49 Warning Letters. This newsletter focuses on Pharmaceutical, Biologics and Medical Devices for human use.

SUMMARY OF KEY INSPECTION POINTS

- Of the 49 Warning Letters issued, 17 were for foreign inspections, and 12 (71%) of these inspections resulted in the FDA placing the inspected company on Import Alert 66-40 or 66-79.
- 16 out of 49 (33%) 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 4% of the assessed Warning Letters.
- 7.3 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	11	39%
21 CFR 211.84	Testing and approval or rejection of components, drug product containers, and closures	11	39%
21 CFR 211.166	Stability testing	8	29%
21 CFR 820.30	Design controls	6	21%
21 CFR 820.100	Corrective and preventative action	5	18%
21 CFR 211.165	Testing and release for distribution	5	18%
21 CFR 211.100	Written procedures; deviations	5	18%

Citations related to 21 CFR 211.84 continue to be the top item, consistent with TCG's previous newsletters for 2023. During Q4, the FDA continued 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.

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.

Of note were 2 Warning Letters issued to Amazon, a company not traditionally associated with cGMP violations. The Warning Letters had to do with the distribution of unapproved and misbranded drug products which were labeled as dietary supplements.

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,

George Toscano, TCG, President
E: gtoscano@thetcg.org
P: (786) 201-3663

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