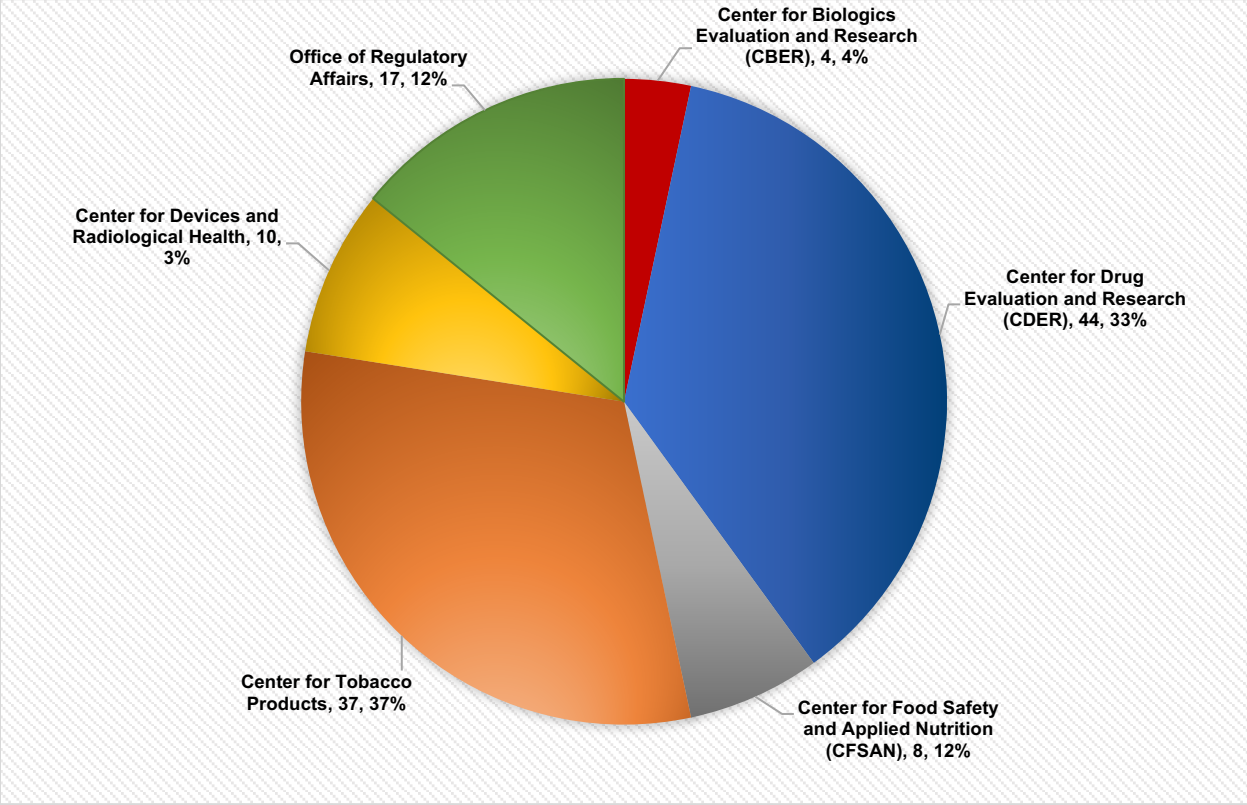
TCG Newsletter

April 2024

FDA Enforcement Trends: Q1 2024

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 of Warning Letters by Issuing Centers is provided below in Figure 1.

FIGURE 1: 120 WARNING LETTERS ISSUED BY CENTERS[1]



The FDA issued 120 Warning Letters during the first quarter of 2024. The global distribution of Warning Letters is presented below in Table 2, with the United States having the majority of Warning Letters (97 out of 120) issued followed by China, Thailand, and others.

TABLE 1: Q1 WARNING LETTERS BY COUNTRY

Country	Total Number of WL	Percentage
USA	97	81%
China	7	6%
Thailand	3	3%
UK	2	2%
Germany	2	2%
Czechia	1	1%
Canada	1	1%
India	1	1%
Japan	1	1%
Jordan	1	1%
Mexico	1	1%
Puerto Rico	1	1%
South Korea	1	1%
Vietnam	1	1%

FIGURE 2: WARNING LETTERS ISSUED BY QUARTER

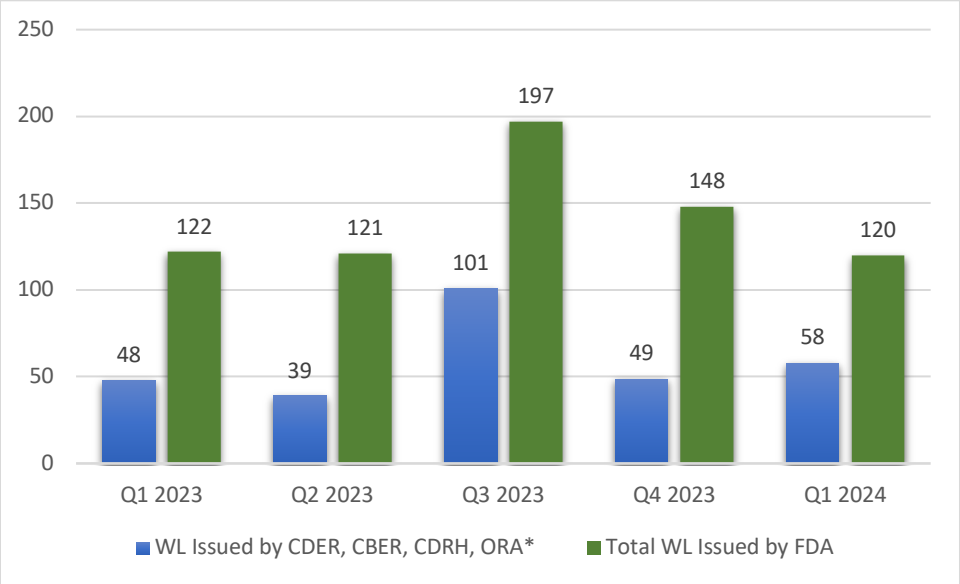


Figure 2 looks at Warning Letters issued on a Quarterly basis, we see Q1 2024, comparable to Q1 2023 in terms of Warning Letters issued with a higher proportion of Warning Letters being issued for GMP violations via CBER, CDER, CDRH and ORA in Q1 2024 (58 vs 48). The FDA issued more Warning Letters in the 2nd half of the year peaking with the Q3, this was due to a larger increase in Warning Lettes issued by the Center for Tobacco Products (72) and CDER (65).

TCG focuses on FDA enforcement activity for Pharmaceutical, Biologics and Medical Devices for human use, therefore we filtered out Warning Letters issued by CFSAN, Center for Tobacco Products, and ORA (based on finding type) to focus on those issued by CDER, CBER, CDRH which resulted in a total of 58 Warning Letters.

SUMMARY OF KEY INSPECTION POINTS FOR GMP WARNING LETTERS

- Of the 58 Warning Letters issued, 21 were for foreign inspections, and 9 (43%) of these inspections resulted in the FDA placing the inspected company on Import Alert 66-40 or 55-03.
- 13 out of 58 (22%) 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 5% of the assessed Warning Letters.
- 6.3 months was the average lag time between when a site is inspected and when a Warning Letter is issued.

TCG then did a deep dive into 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 25 Warning Letters. Out of the 25 Warning Letters the top six reoccurring CFR citations are provided in Table 3 below.

TABLE 2: TOP WARNING LETTER CITATIONS

Top CFR Citations	Description	Number of Citations	Percentage
21 CFR 211.84	Testing and approval or rejection of components, drug product containers, and closures	11	52%
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	48%
21 CFR 211.100	Written procedures and deviations	9	36%
21 CFR 820.30	Design controls	9	36%
21 CFR 820.198	Complaint files	4	20%
21 CFR 211.165	Testing and release for distribution	4	16%

Citations related to 21 CFR 211.84 continue to be the top item, consistent with TCG's previous newsletters for 2023. During 2023, 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. The other major topic in this category includes not testing Isopropyl Alcohol for the presence of methanol. Over half of the findings for these issues are for foreign firms, which may be indicative of the awareness of these newer guidance's still not being fully disseminated outside of the US.

FDA issued several guidances[2,3] in 2023 to help companies with meeting FDA expectations with regards to both of these issues.

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. It appears that the FDA has recently been using this CFR reference more broadly to include items typically cited under other regulations. For example, Failure to conduct adequate investigations into nonconformances (211.192) or complaints (211.198(a)) are grouped under the broader 211.22.

We also try to keep a keen eye on the more interesting citations and have included one of the more memorable ones for this quarter. The example below reminds me of the kind of response a young student may provide to a teacher when asked about missing homework.

FDA cited QC personnel for admitting to not having written down the test results but rather relying on their memory indicating "I haven't written it yet" and "its in my head."

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.

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]Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol Guidance for Industry, October 2023 https://www.fda.gov/media/173005/download