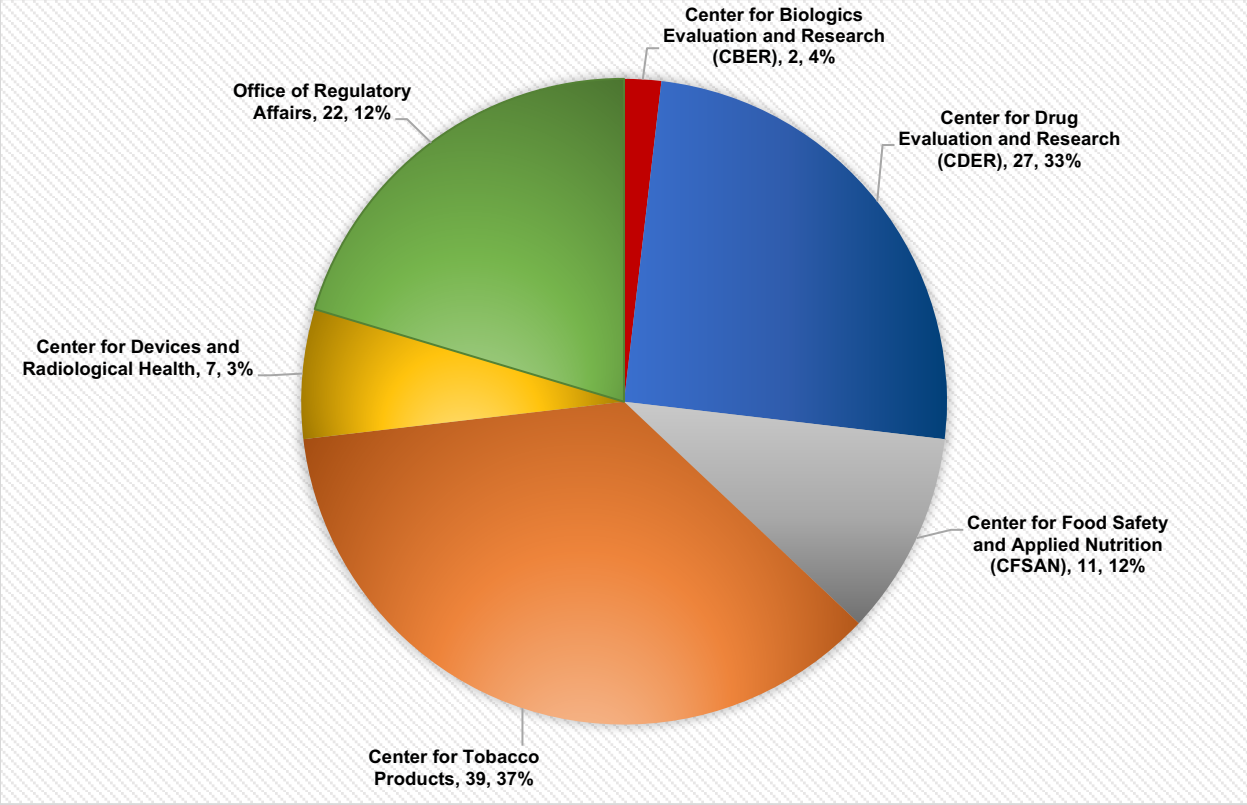
TCG Newsletter

July 2024

FDA Enforcement Trends: Q2 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: 1108 WARNING LETTERS ISSUED BY CENTERS[1]

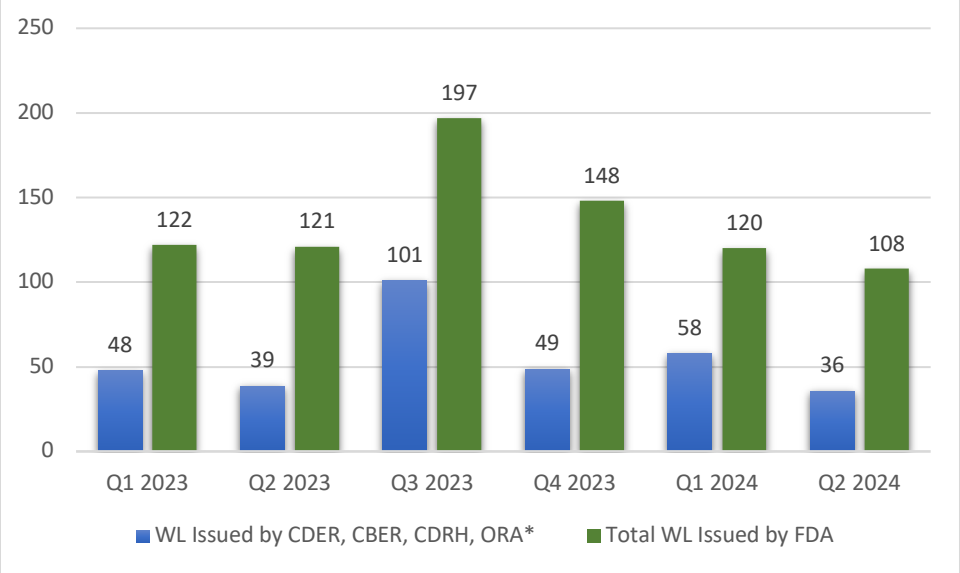


The FDA issued 108 Warning Letters during the second quarter of 2024. The global distribution of Warning Letters is presented below in Table 2, with the United States having the majority of Warning Letters (85 out of 108) issued followed by China, South Korea, and others.

TABLE 1: 2024 Q2 WARNING LETTERS BY COUNTRY

Country	Total Number of WL	Percentage
US	85	79%
China	6	6%
S Korea	4	4%
Canada	2	2%
India	2	2%
Czechia	2	2%
Grenada	1	1%
Malaysia	1	1%
Mexico	1	1%
Portugal	1	1%
Thailand	1	1%
Aruba	1	1%
Uruguay	1	1%

FIGURE 2: WARNING LETTERS ISSUED BY QUARTER



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 36 Warning Letters.

SUMMARY OF KEY INSPECTION POINTS FOR GMP WARNING LETTERS

- Of the 36 Warning Letters issued, 18 (50%) were for foreign inspections, and 13 of these inspections resulted in the FDA placing the inspected company on Import Alert 66-40 or 55-05.
- 16 out of 36 (44%) 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 6% of the assessed Warning Letters.
- 7.9 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). The top 5 reoccurring CFR citations are provided in Table 2 below.

TABLE 2: TOP WARNING LETTER CITATIONS

Top CFR Citations	Description	Number of Citations	Percentage
21 CFR 211.100	Written procedures and deviations	13	36%
21 CFR 211.84	Testing and approval or rejection of components, drug product containers, and closures	12	33%
21 CFR 211.165	Testing and release for distribution	10	28%
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	9	25%
21 CFR 211.160	General requirements	5	14%

Citations related to 21 CFR 211.100 were the top item this quarter. The next category (211.84) continues the theme of FDA citing companies for not testing each lot of incoming components that are at high risk for diethylene glycol (DEG) or ethylene glycol (EG) contamination.

As more companies move to fully virtual or semi fully virtual operations the reliance on CMOs, CDMOs, CROs, CTOs has increased dramatically over the past 10 years. Although more activities are being delegated to CxOs, the responsibility of the Sponsor cannot be delegated. To that end we highlight several citations related to oversight of outsourced activities below:

One Warning Letter illustrates this issue with Sponsors not complying with their responsibilities as required per 21 CFR 312.

"…you stated that based on communications with the Contract Research Organization (CRO), you were under the impression that **the CRO** *was handling the emergency IND and any communications with FDA. You stated …you were under the impression that the protocol amendment was approved. You further stated that* **the CRO** *did not instruct you to submit the amended protocol to FDA or to the IRB, but rather to* **the CRO** *itself. You also stated that if you had known that the FDA was not aware of the amended protocol allowing for additional drug dosing, you would not have continued the additional dosing."*

The FDA stated, “We emphasize that as a sponsor-investigator, it was your responsibility to ensure that this study was conducted in accordance with the investigational plan and in compliance with FDA regulations, to protect the rights, safety, and welfare of study subjects.”

While the WL above is pertaining to a Clinical study, similar examples are found for commercial production of drugs and biologics when using CMOs.

Along a similar theme related to oversight another Warning Letter highlights the need for oversight of suppliers for a medical device firm.

Failure to adequately establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50.

“Specifically, our inspection found that your… Procedure to outline product requirements, confirm purchased products have met these requirements, and conduct supplier qualification activities, has not been adequately established. Your firm’s procedure does not require that data to demonstrate product requirements are met is reviewed and evaluated during supplier qualification activities…Furthermore, no data was received from the supplier and/or evaluated at the time of supplier qualification to ensure that other product requirements included in the PRD document were met.”

These two examples illustrate the need to maintain adequate oversight of both suppliers of materials as well as service providers. As more companies move to virtual supply chains, they need to ensure robust controls are in place for service provider/supplier oversight. While sponsors can delegate activities to suppliers, they cannot abdicate their responsibility for compliance with the regulations to a supplier or service provider.

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.

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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).