TCG Newsletter

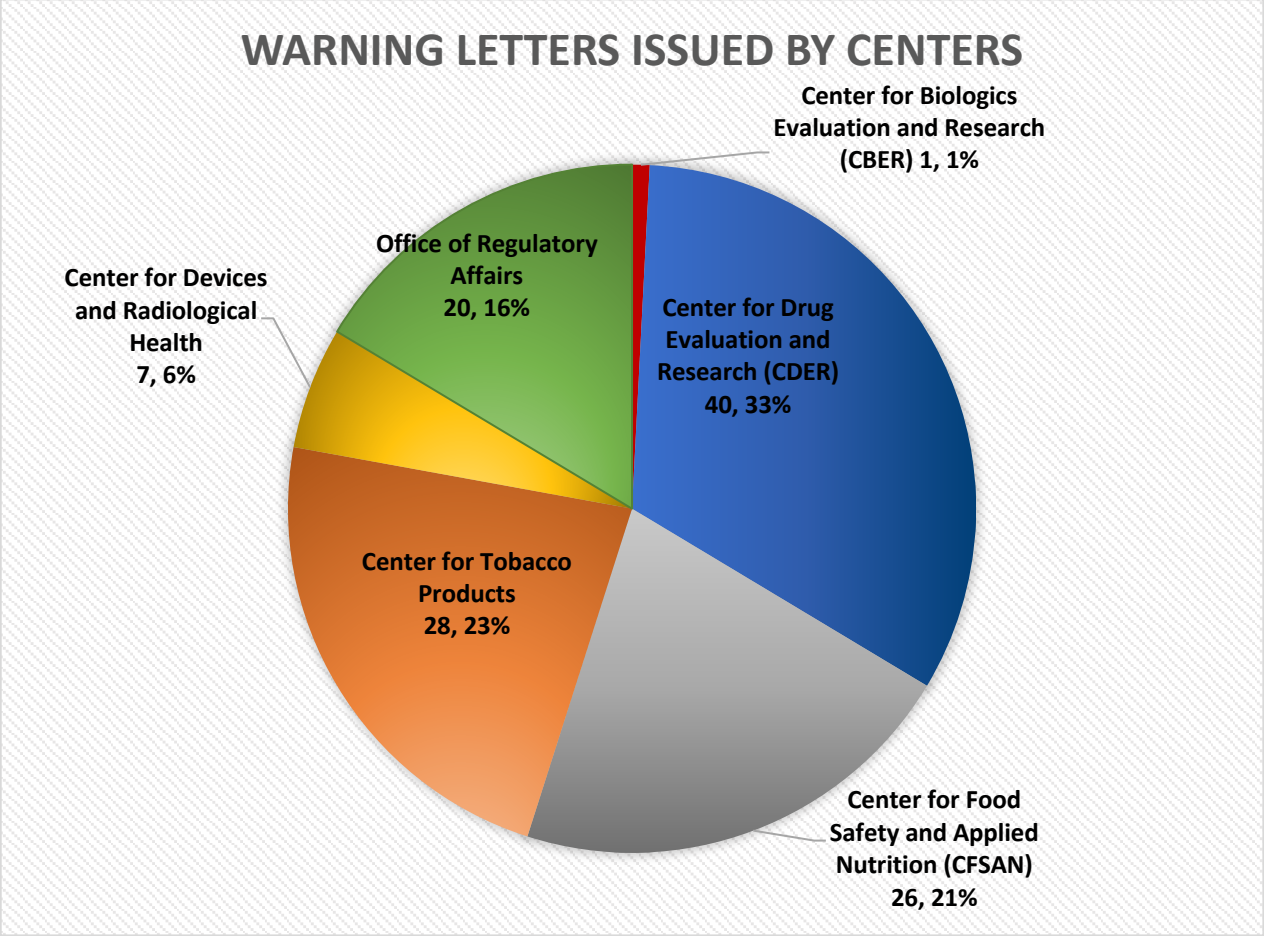
April 2023

FDA Enforcement Trends: Q1 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: 122 WARNING LETTERS ISSUED BY CENTERS[1]



After assessing the full list of 122 Warning Letters issued this quarter, TCG removed Warning Letters issued by CFSAN, ORA, and Center for Tobacco Products to focus on those primarily issued by CDER, CBER, or CDRH which resulted in a total of 48 Warning Letters. ORA was removed from the assessment as the subject matter this last quarter was primarily focused on the Division of Human and Animal Food

Operations, and this newsletter focuses on Pharmaceutical, Biologics and Medical Devices for human use. The United States led in the number of Warning Letters (35 out of 48) issued followed by Japan, Puerto Rico, Canada, Netherlands, Costa Rica, India, Germany, and Turkey. (Table 2). This is not surprising as the US received the most inspections during this period.

TABLE 2: Q1 GMP WARNING LETTERS BY COUNTRY

Country	Total Number of GMP WL	Percentage
US	35	73%
Japan	3	6%
PR	3	6%
Canada	2	4%
Costa Rica	1	2%
Germany	1	2%
India	1	2%
Turkey	1	2%
Netherlands	1	2%

SUMMARY OF KEY INSPECTION POINTS

- Of the 48 Warning Letters issued, 13 were for foreign inspections, and only 3 out of 13 (23%) of these inspections resulted in the FDA putting the inspected company on Import Alert.
- 14 out of 48 (29%) 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 saw a small percentage of Data Integrity focused citations in that start of 2023 coming in at only 2% of the assessed Warning Letters.
- Approximately 5 months was the approximate 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 30 Warning Letters. Out of the 30 Warning Letters the top five reoccurring CFR citations are provided in Table 3 below.

TABLE 3: TOP CFR 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.	13	43%
21 CFR 211.100	Written Procedures; Deviations	13	43%
21 CFR 211.22	Responsibilities of Quality Control Unit	11	37%
21 CFR 211.165	Testing and release for distribution	7	23%
21 CFR 820.30	Design Controls	5	17%

Inadequate investigations related to deviations and laboratory failures, and lack of adequate Quality oversight continue to be "hot topic" issues across all product types. Seven of the 13 findings for 211.84 are related to relatively new manufacturers of hand sanitizer that are lacking in fundamental systems for testing of incoming API, excipients and critical components. A few other findings were related to companies that did not test glycerin for the limit of Diethylene Glycol (DEG) and Ethylene glycol (EG) prior to their use in manufacturing. The use of glycerin contaminated with diethylene glycol (DEG) has resulted in various lethal poisoning incidents in humans worldwide. To this end the FDA has created a specific guidance for Industry; Testing of Glycerin for Diethylene Glycol, May 2007.

The pandemic years appear to have resulted in new entrants to the market with little GMP experience and other companies becoming lax in the compliance arena. As a result, FDA is trying hard to catch-up on performance of on-site inspections, and we are seeing an increase in these inspections, compared to remote inspections, which appear to have been less efficient in identification of deficiencies. We will likely see a lot of Warning Letters this year as the reins are tightened across the different product types in our industry.

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

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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).