FDA Inspection Trends for the Biopharmaceutical Industry

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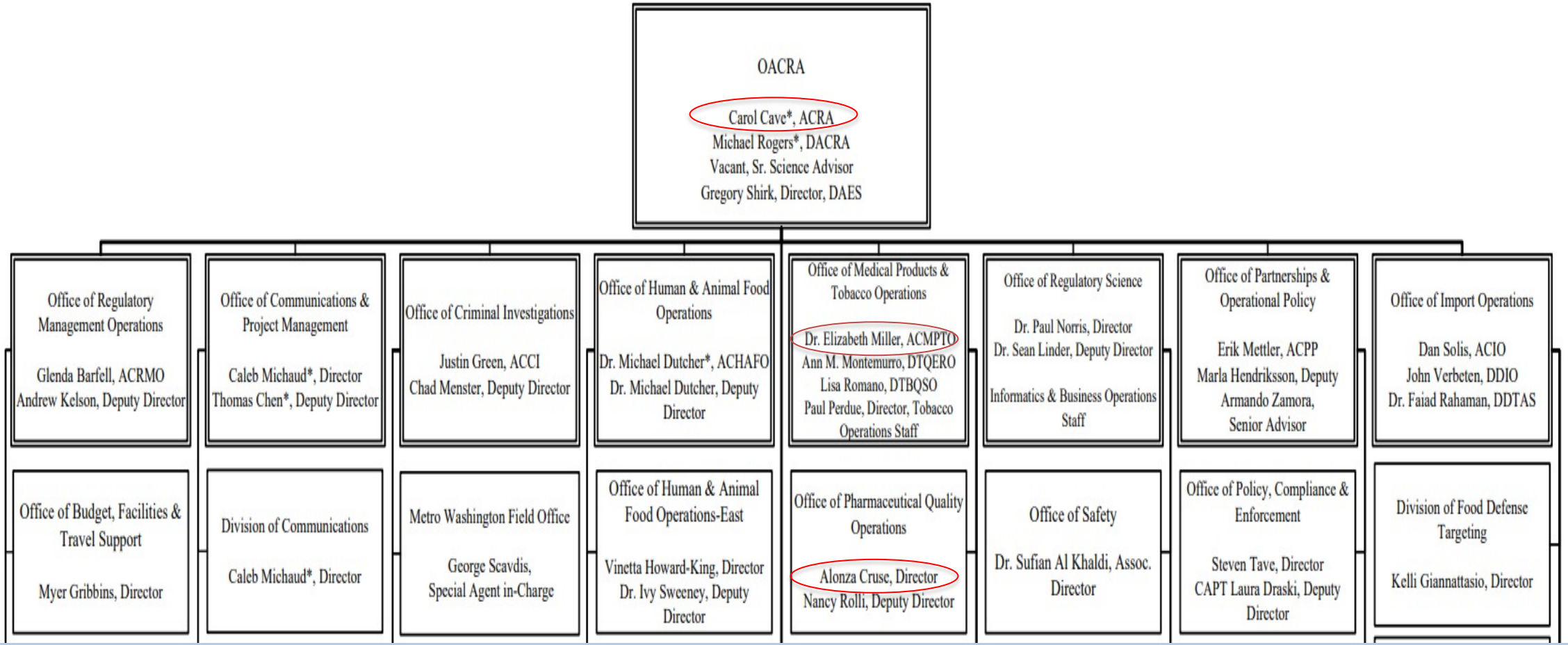
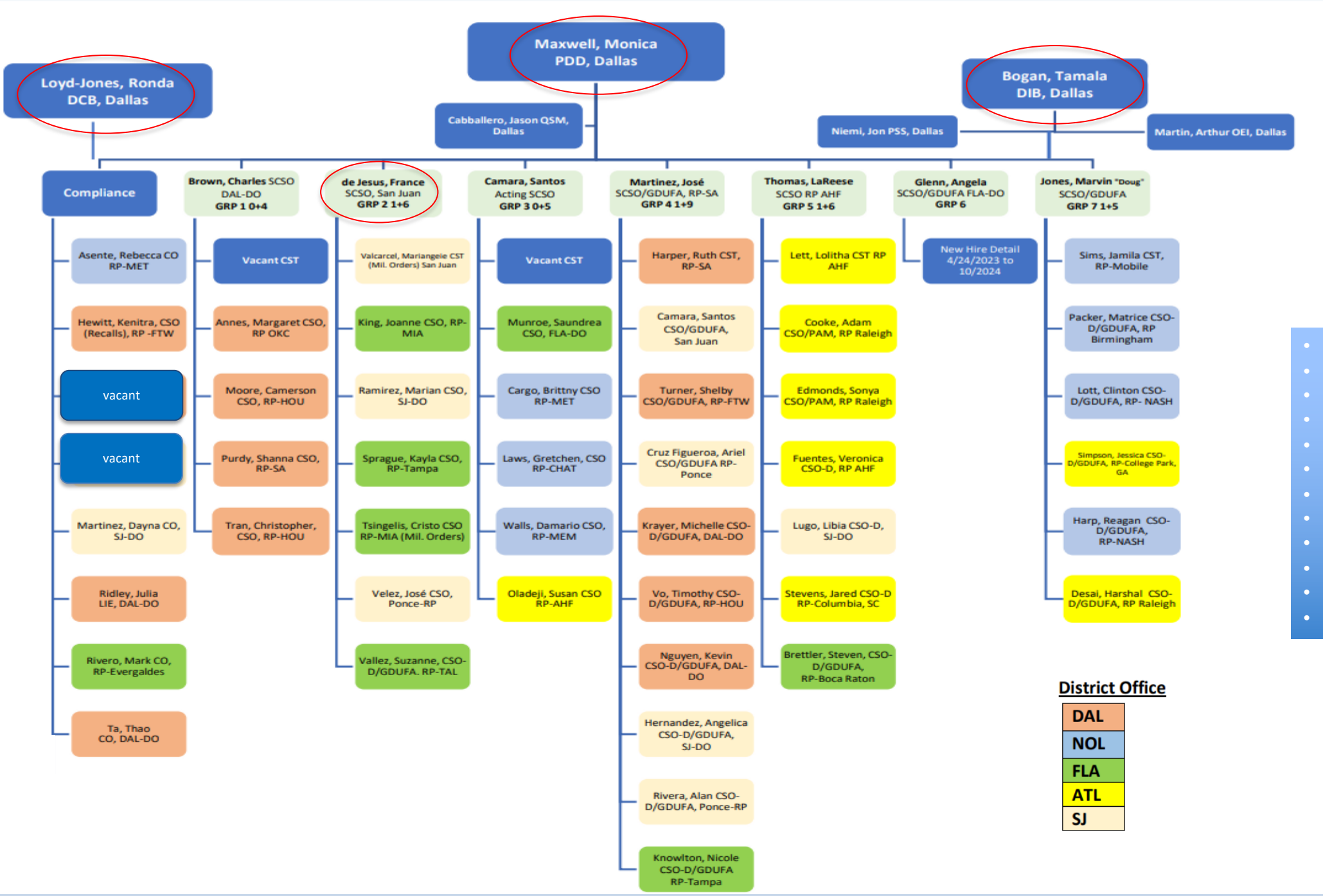
Outline

- Who we are and what we do…
  - ORA OPQO Div. 2 Organization Overview
  - Drug Establishment Inventory Overview
  - Number of drug Inspections conducted
- Compliance Program Updates
- Inspection Classification trends and enforcement action metrics

Office of Regulatory Affairs



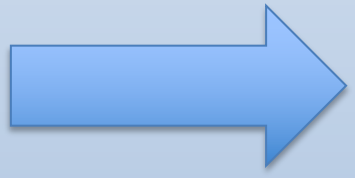


- Texas
- Oklahoma
- Arkansas
- Louisiana
- Mississippi
- Tennessee
- Alabama
- Georgia
- South Carolina
- North Carolina
- Florida
- Puerto Rico

FDA Drug Firm Inventory and number of drug inspections conducted

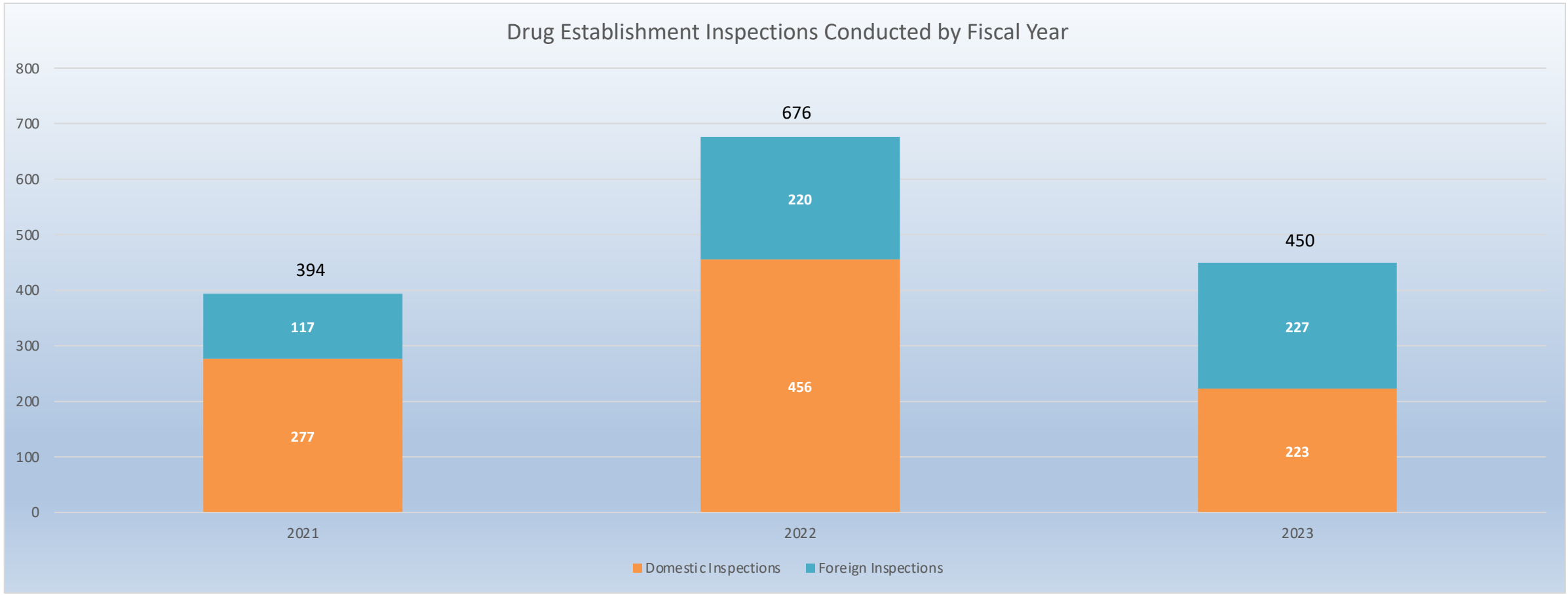
Drug Establishments in FY22 CDER Catalog

Country	Sites in FY2022 Catalog
United States	2,019
India	603
China	430
Germany	187
Canada	158
Italy	149
France	141
Japan	134
United Kingdom	105
South Korea	100
Spain	88
Switzerland	82
Mexico	64
Ireland	59
All Others	495
Total	**4,814**

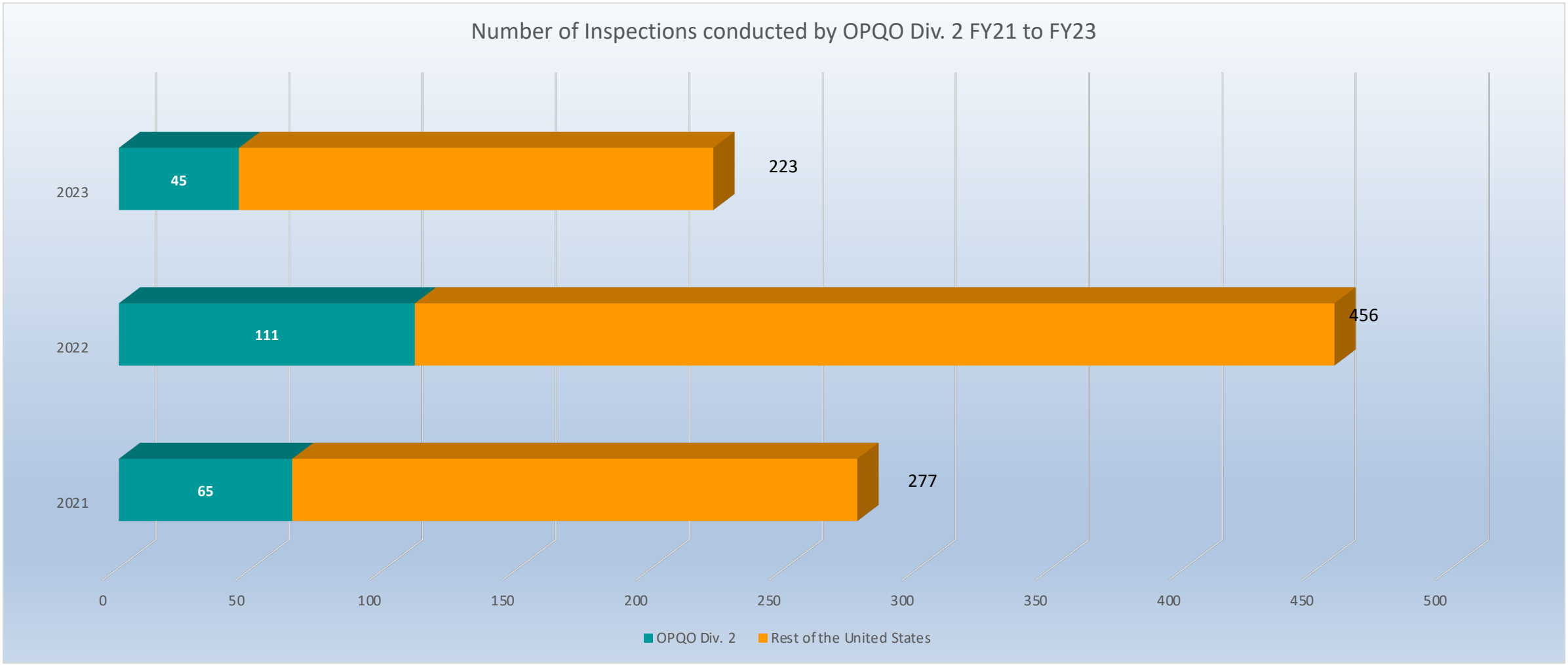


- 60% of sites manufacture at least one application product, including: BLAs, NDAs and ANDAs.
- The remining 40% of the drug establishments are in the “No Application Sector” (includes OTC monograph products), Unapproved prescription drug products and homeopathic products.

FY21-FY23 Domestic and Foreign Drug Establishment Inspection numbers



FY21- FY23 OPQO Division 2 Inspection numbers



Inspections conducted by OPQO Div. 2 account for approx. 20% of FDA drug establishment inspection workplan.

Overview
Compliance Programs Revisions

- Compliance Programs provide guidance to FDA staff conducting activities to evaluate industry compliance with the FD&C Act.
- Two key drug Compliance Program revisions became effective on October 17, 2022:
  - ➢7346.832 - Pre-Approval Inspections
  - ➢7356.002 - Drug Manufacturing Inspections

Summary of Revisions CP7346.832- Pre -Approval Inspections and CP7356.002 -Drug Manufacturing Inspections

- Revised to reflect modern pharmaceutical principles and support their implementation. Incorporates inspectional coverage of:
  - Key elements of knowledge management and the pharmaceutical quality system (FDA guidance on ICH Q10).
  - Indicators of an advance pharmaceutical quality system. (e.g. Quality Management Maturity)
  - Key principles of quality risk management (ICH Q9)
  - Key elements related to ICH Q12 implementation (Change Management & Reporting)

Summary of Revisions CP7346.832- Pre -Approval Inspections and CP7356.002 -Drug Manufacturing Inspections

- Include the use of Remote Regulatory Assessments (RRAs*) to support oversight of FDA-regulated establishments.
  - Establishes that RRAs may be used to determine whether an establishment meets CGMP requirements.
  - Highlight how RRAs may be an alternate tool to inspections that assist FDA in determining CGMP compliance.

*RRAs include records or other information requested directly from facilities and other inspected entities under 704 (a)(4) of FD &C Act and Remote Interactive Evaluations (RIEs)

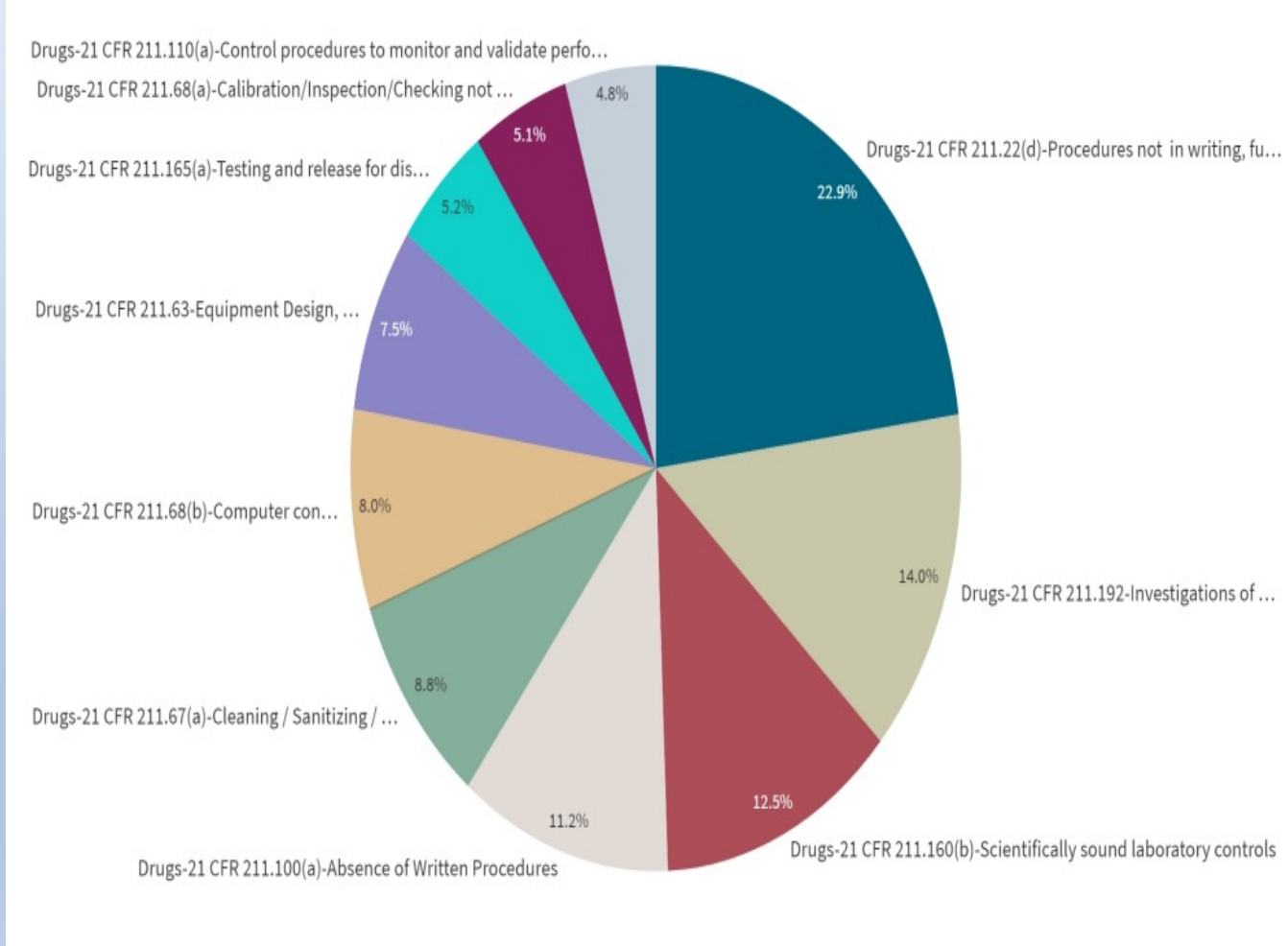
Summary of Revisions CP7346.832- Pre -Approval Inspections and CP7356.002 -Drug Manufacturing Inspections

- Provide inspectional guidance related to the control of nitrosamine impurities.
  - Establishes that a quality risk management program should ensure that:
    - hazardous impurity risk is assessed
    - control strategies are implemented to mitigate their risk (e.g., actions to address sources of variability, release testing, reduction or elimination of impurities, cleaning validation)
    - control strategies are reviewed following changes and throughout a product's lifecycle.

*see guidance for industry Control of Nitrosamine Impurities in Human Drugs.

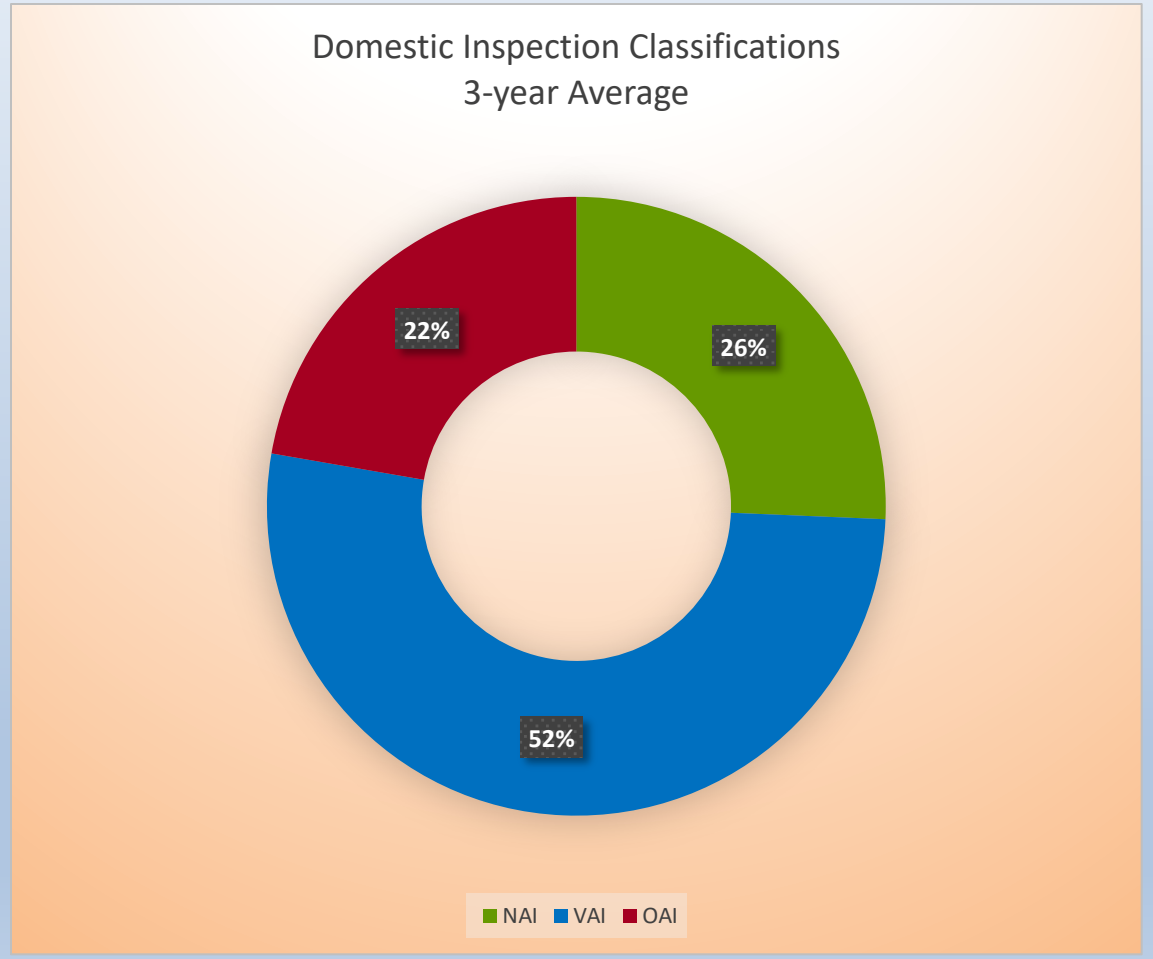
Inspection classification trends and enforcement action metrics

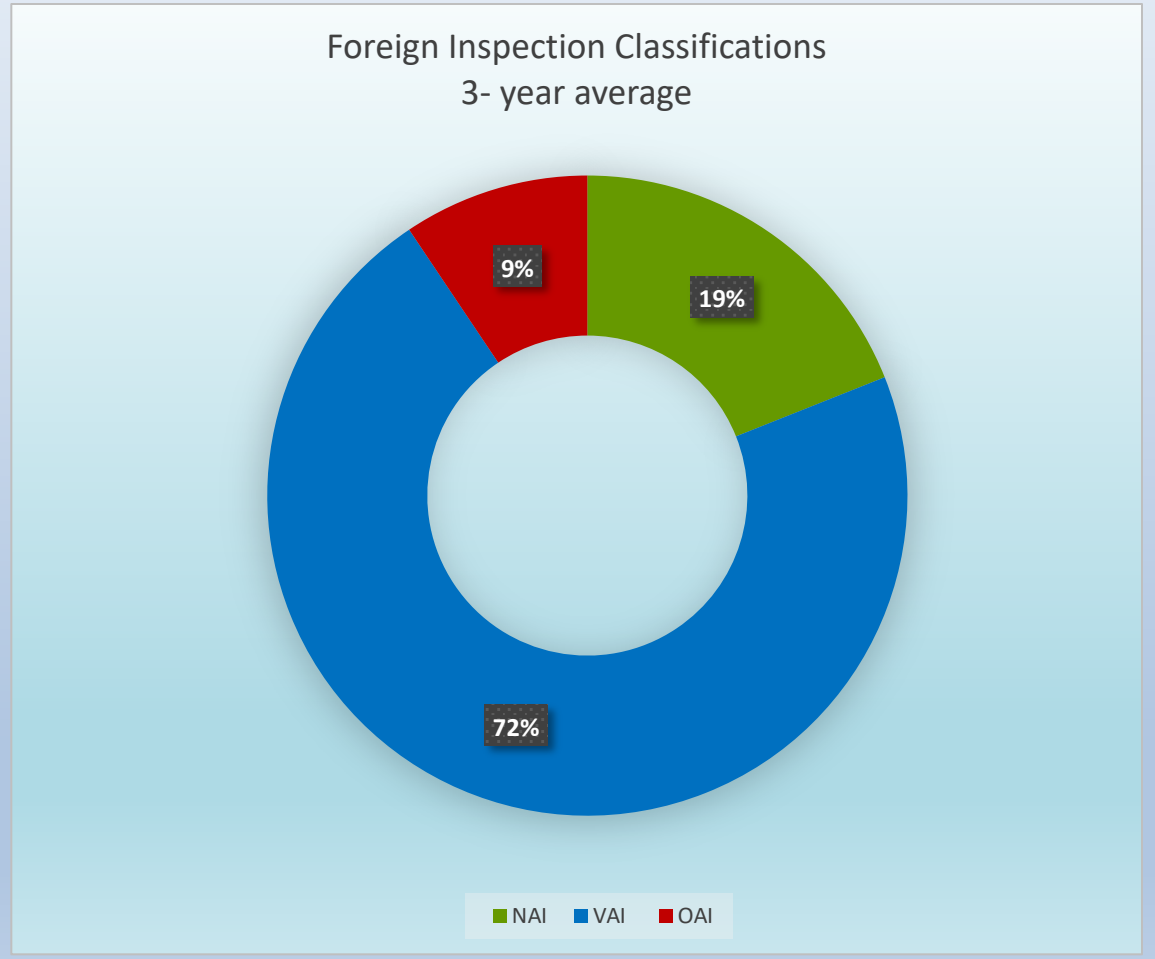
Top FDA-483 Citations FY21-FY23
*Foreign and Domestic



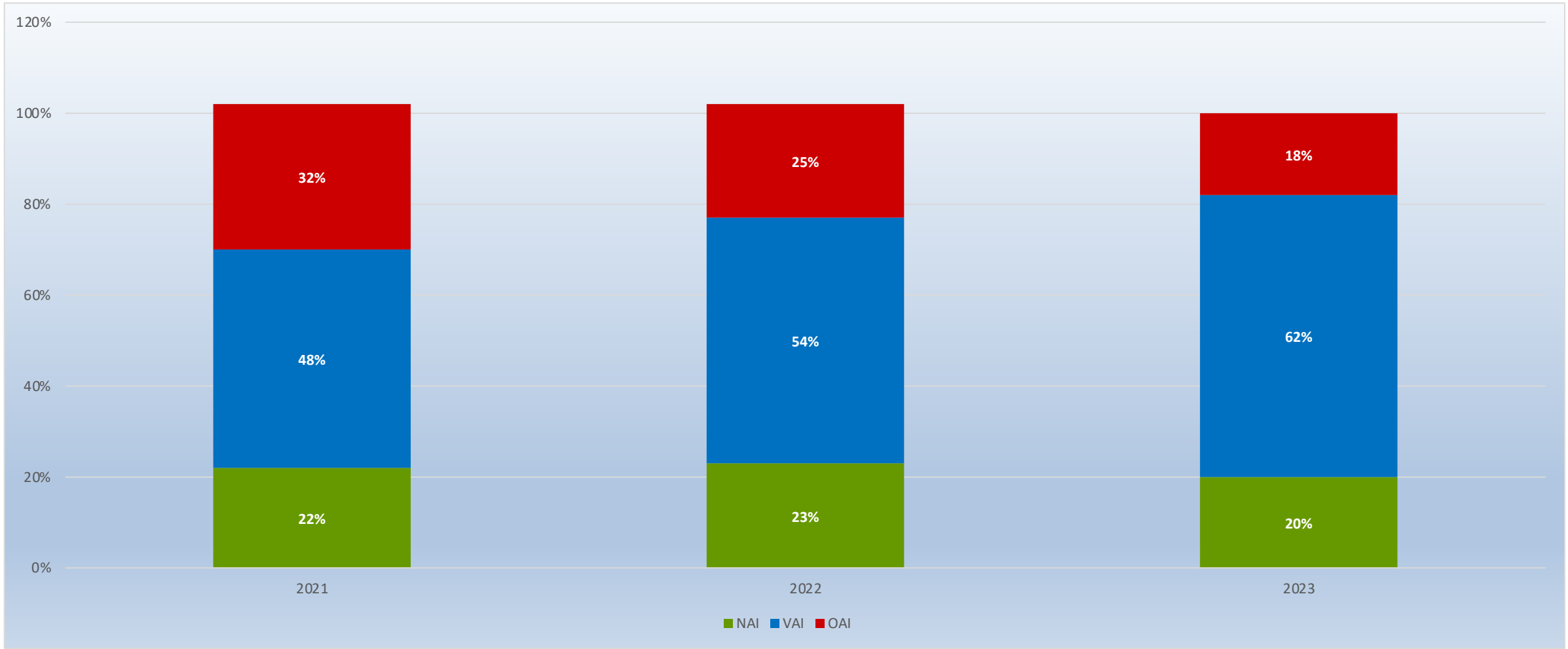
- 21CFR 211.22 (d)- Procedures not in writing, fully followed
- 21CFR 211.192 Investigations of discrepancies, failures
- 21CFR 211.160(b)- Scientifically Sound laboratory controls
- 21CFR 211.100(a)- Absence of written Procedures
- 21 CFR 211.67(a)- Cleaning/Sanitizing/Maintenance

Domestic and Foreign Drug Establishment Inspection Classification Averages





FY21- FY23 OPQO Div. 2 Classification data

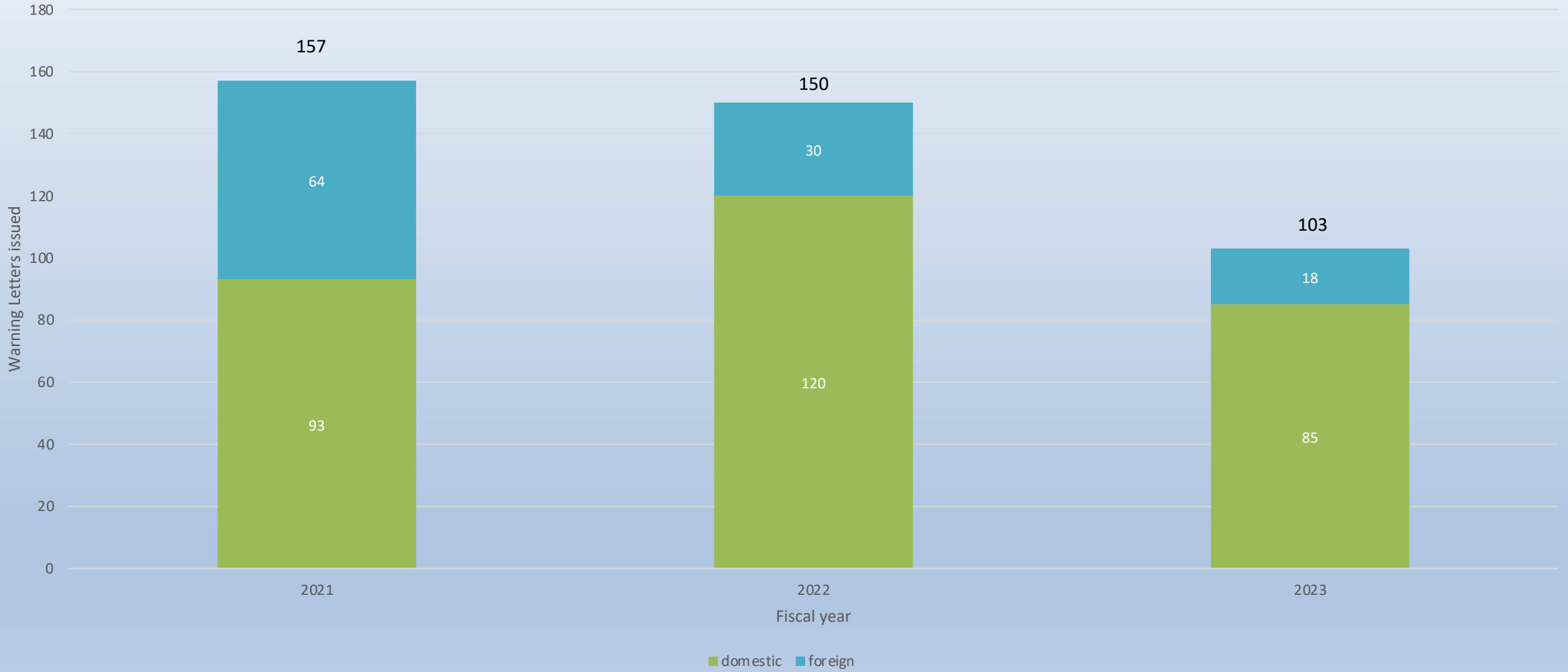


Inspections classified OAI in PR

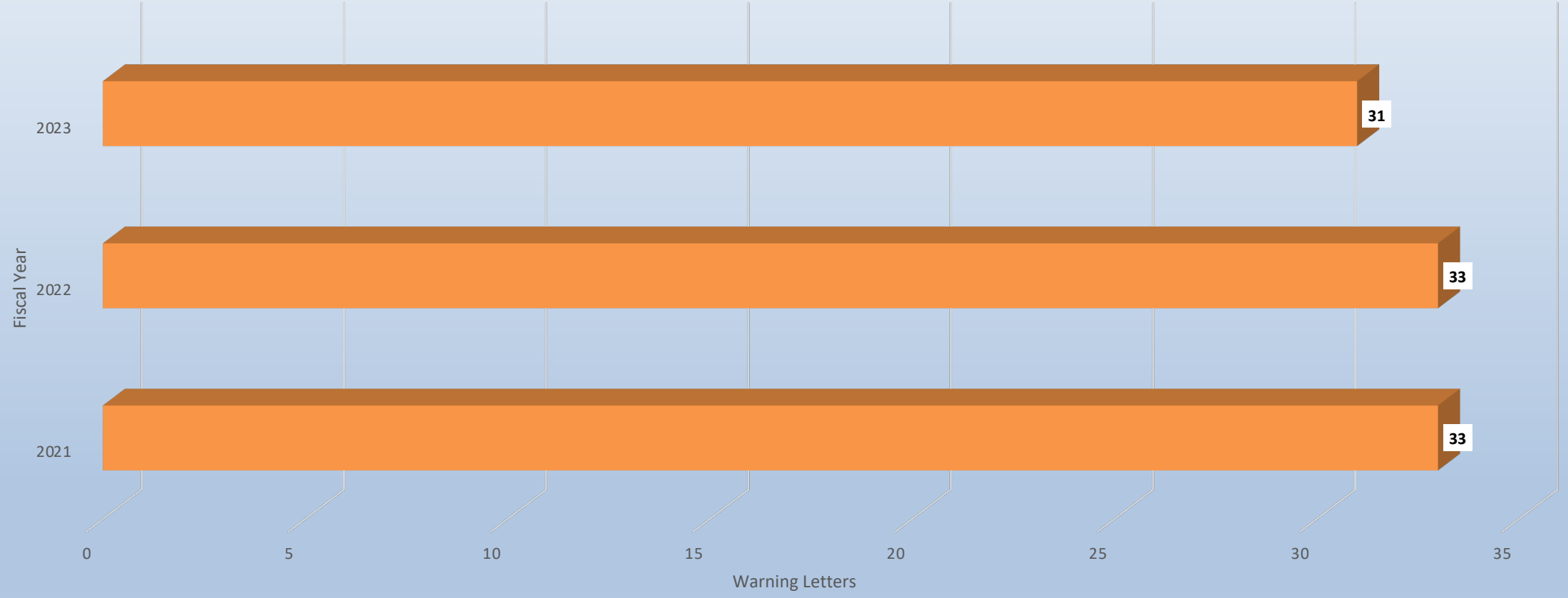
- ✓ **FY22- 4**
- ✓ **FY23- 1**

Warning Letters by Fiscal Year FY21-FY23

(domestic and foreign drug establishments)

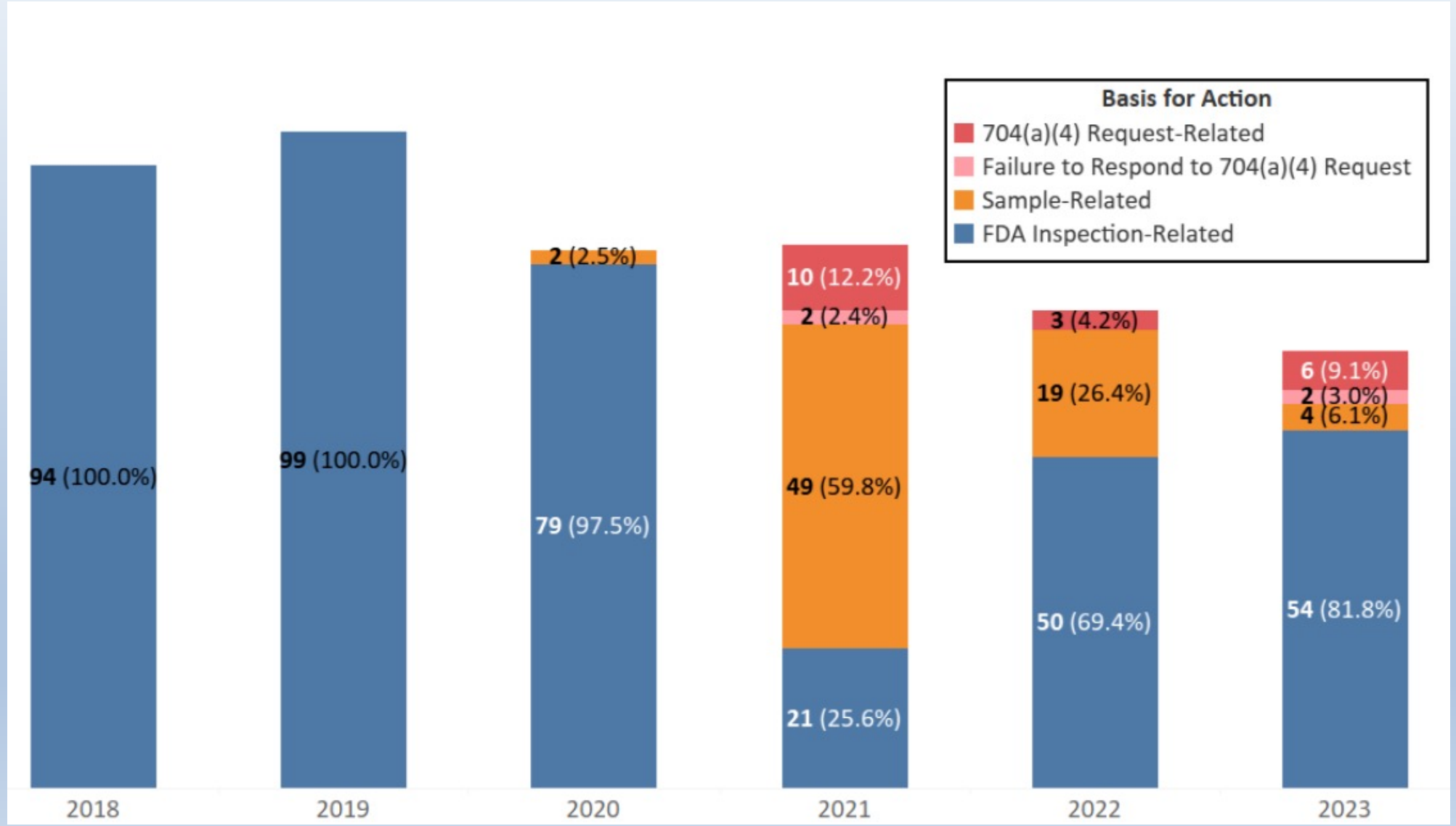


OPQO Division 2 Warning Letters by Fiscal Year FY21-FY23

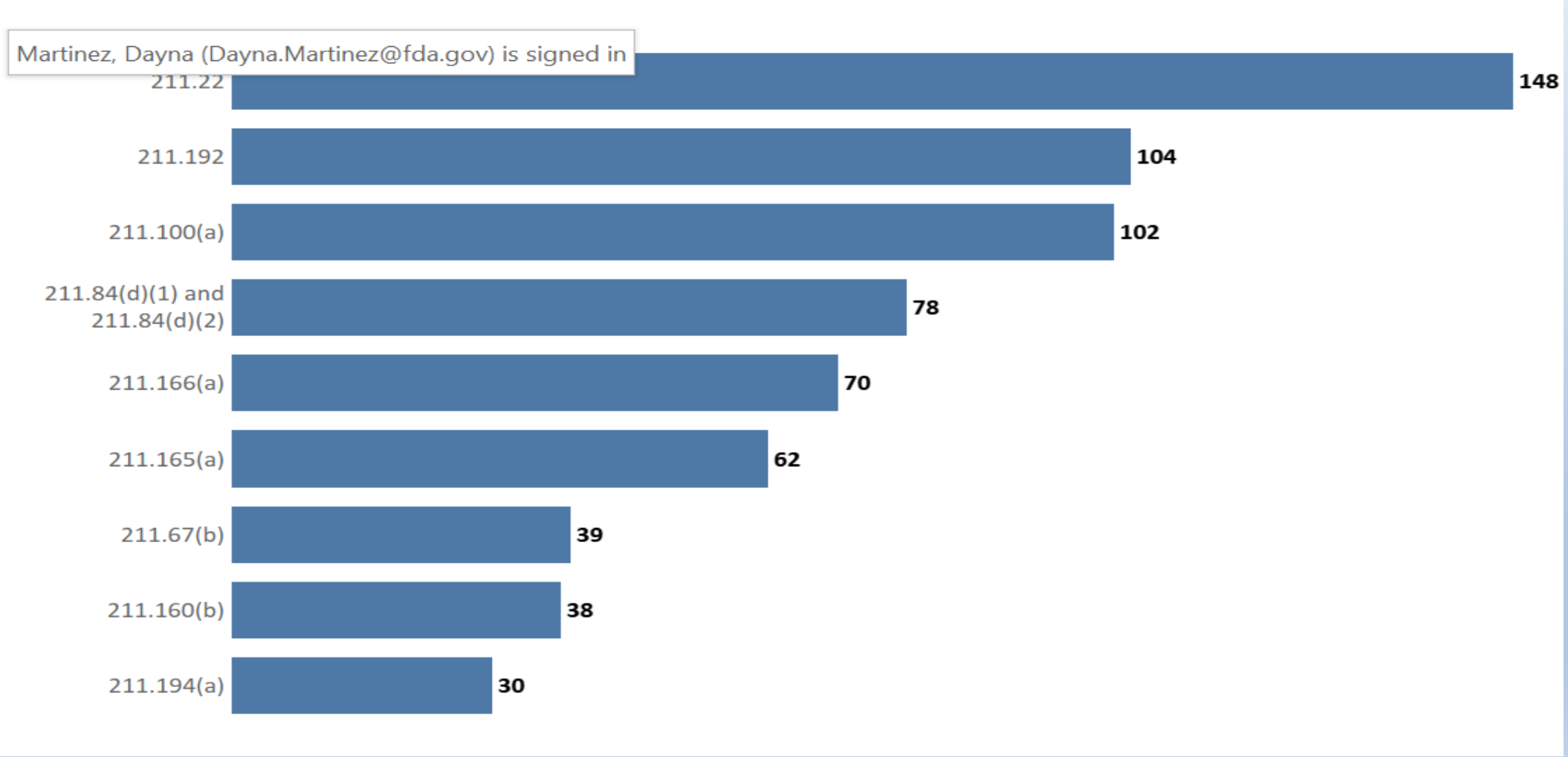


WLs issued in PR
FY22- 1 and FY23- 4

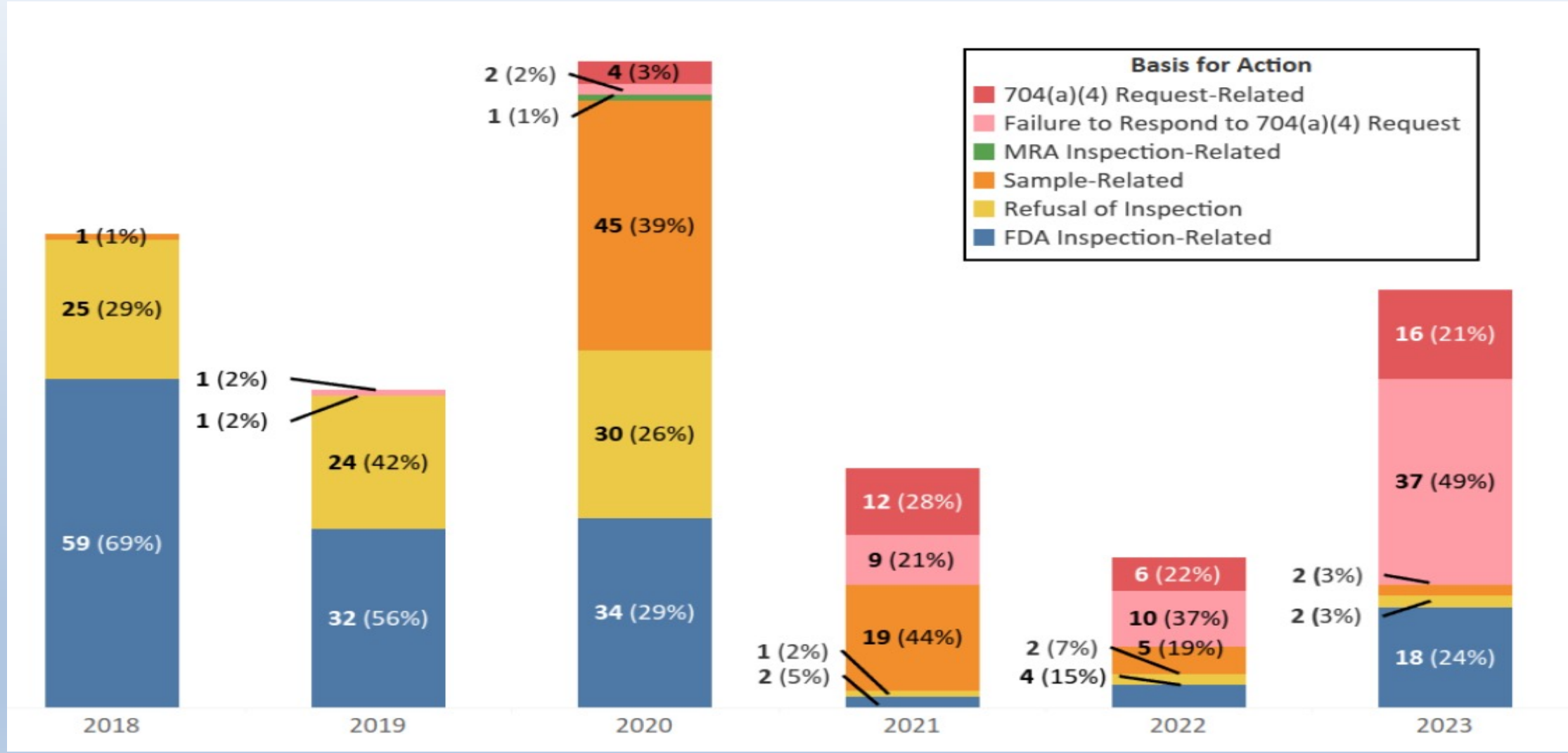
Shift in source of Warning Letters
(domestic and foreign)



Top Citations in Warning Letters issued to FDF Manufacturers FY18- FY22



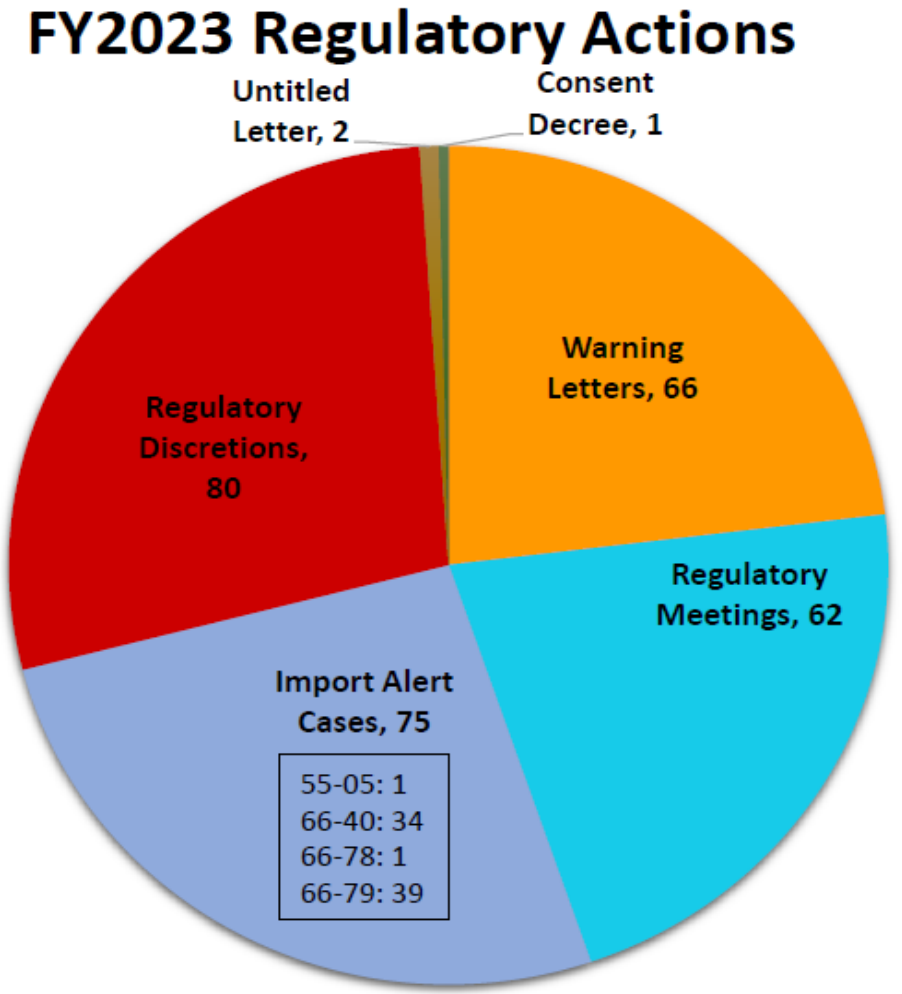
Import Alert Cases



Note: 89% of the firm's placed on import alert in 2022 produced non-application, non- sterile products (mostly sites producing hand sanitizer).

FY23 Summary- Enforcement and Advisory Actions

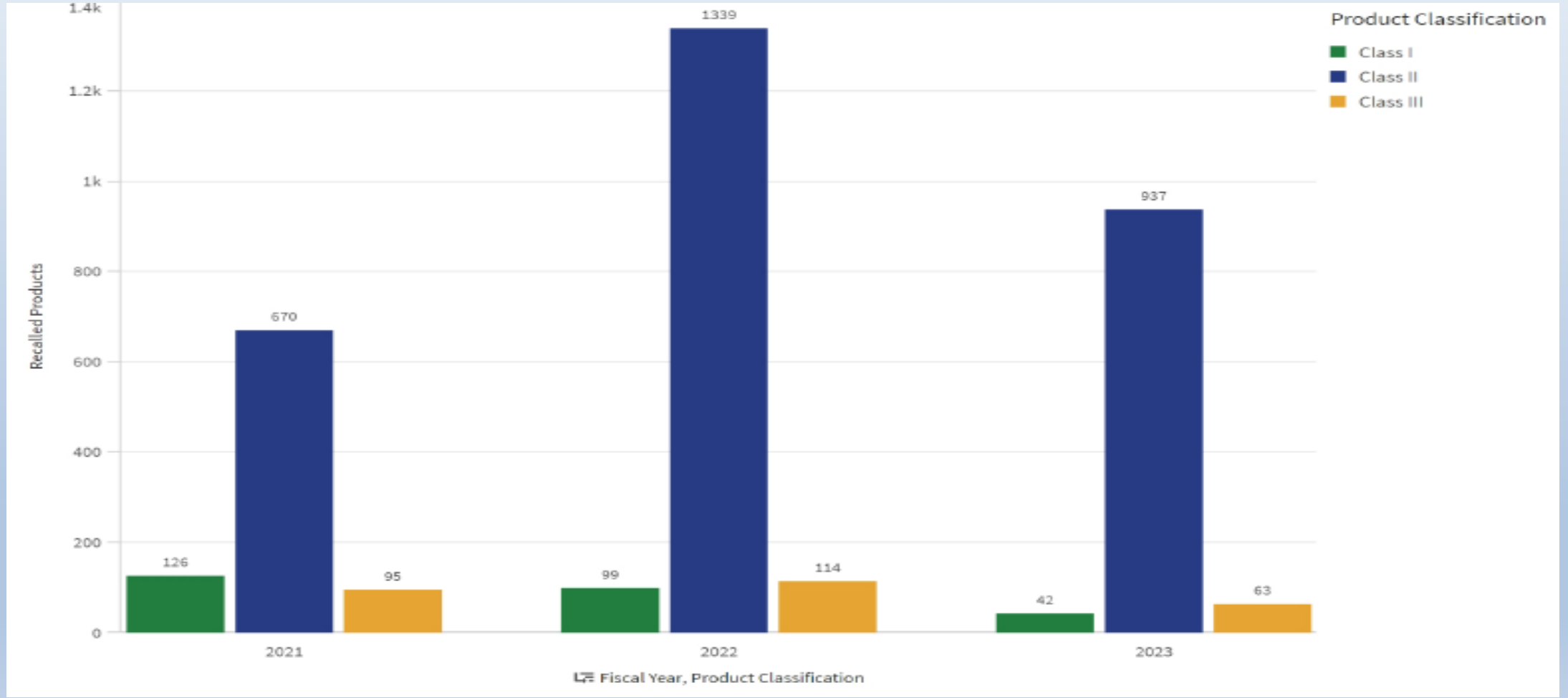
- Regulatory Meetings
- Injunctions
- Consent Decrees
- Import Alerts
- Seizures
- Warning Letters
- Untitled Letters
- Administrative Detention



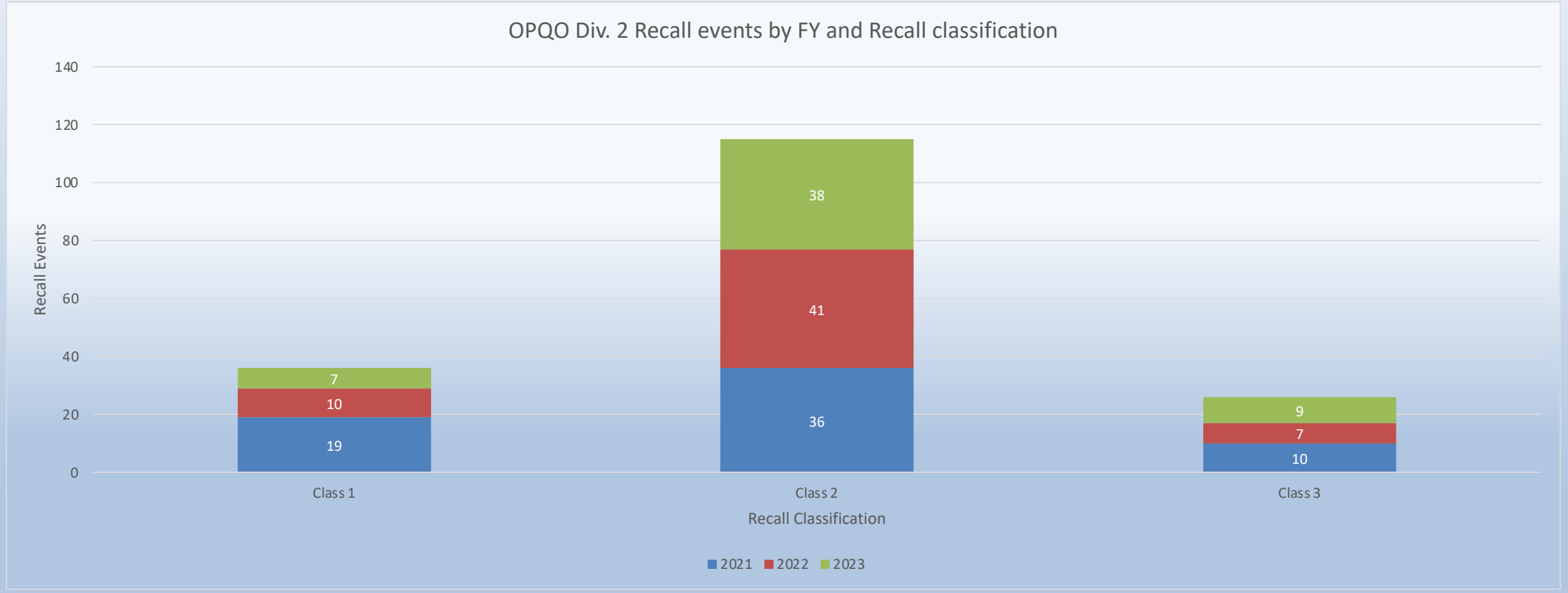
Excludes compounding-related actions

*Actions Taken October 1, 2022 to July 31, 2023

Drug Recalls by Fiscal Year (FY21-FY23) (foreign and domestic)

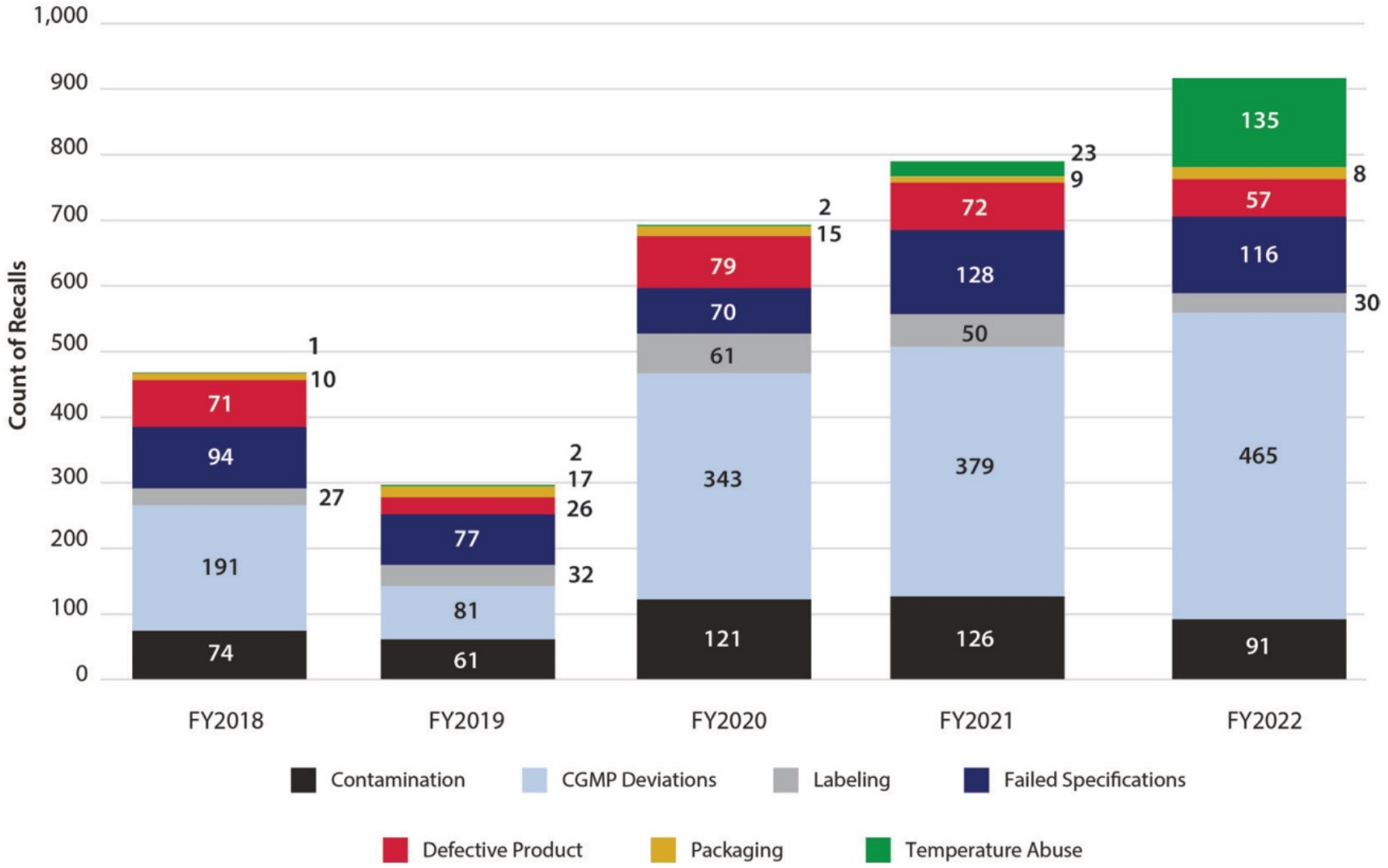


OPQO Division 2 Recalls Data



Recalls initiated by firms located in OPQO Div2 represent approximately 6% of the total recalls

Recalls by Defect Group FY18-FY22



Summary

- FDA implemented the use of alternate evidence sources to assess firm compliance during the pandemic.
- As we go back to normal and travel restrictions were lifted , inspection-based actions are also increasing. However, regulatory actions based on alternate evidence sources remain present. (Sampling and 704 (a)(4) Records requests.

References

- CP7346.832- Pre -Approval Inspections and CP7356.002 -Drug Manufacturing Inspections
- CDER Fiscal Year 2022 Report on the state of Pharmaceutical Quality- June 2023
- FDA Dashboards-FDA Dashboards – Home
- F. Godwin/CDER GMP Update (08/15/2023)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