cGMP Inspectional Deficiencies for Sterile Drug Products

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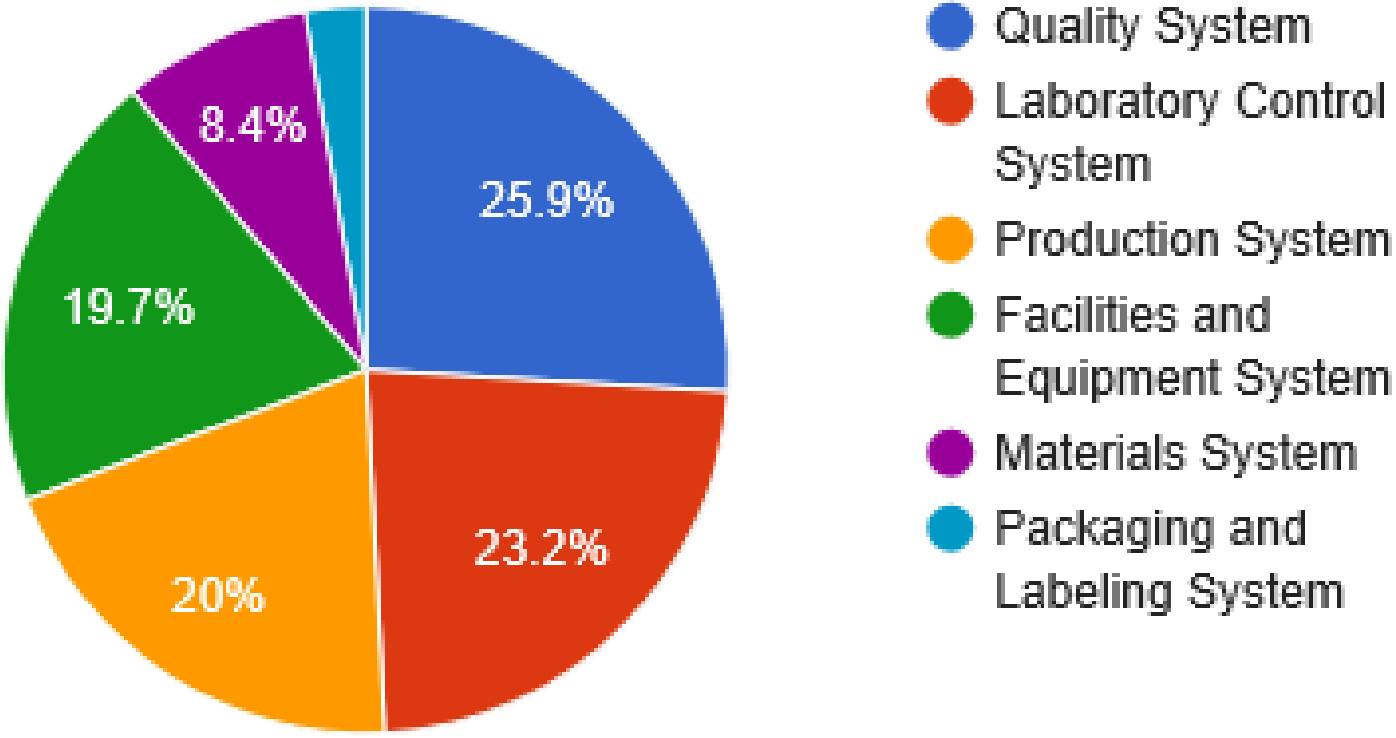
Outline

- 2019 cGMP Regulatory Actions by U.S. FDA
- Notable Trends and Examples of Deficiencies found during inspections of drug manufacturers

Distribution of Systems Cited



Top Ten FDA-483 Citations

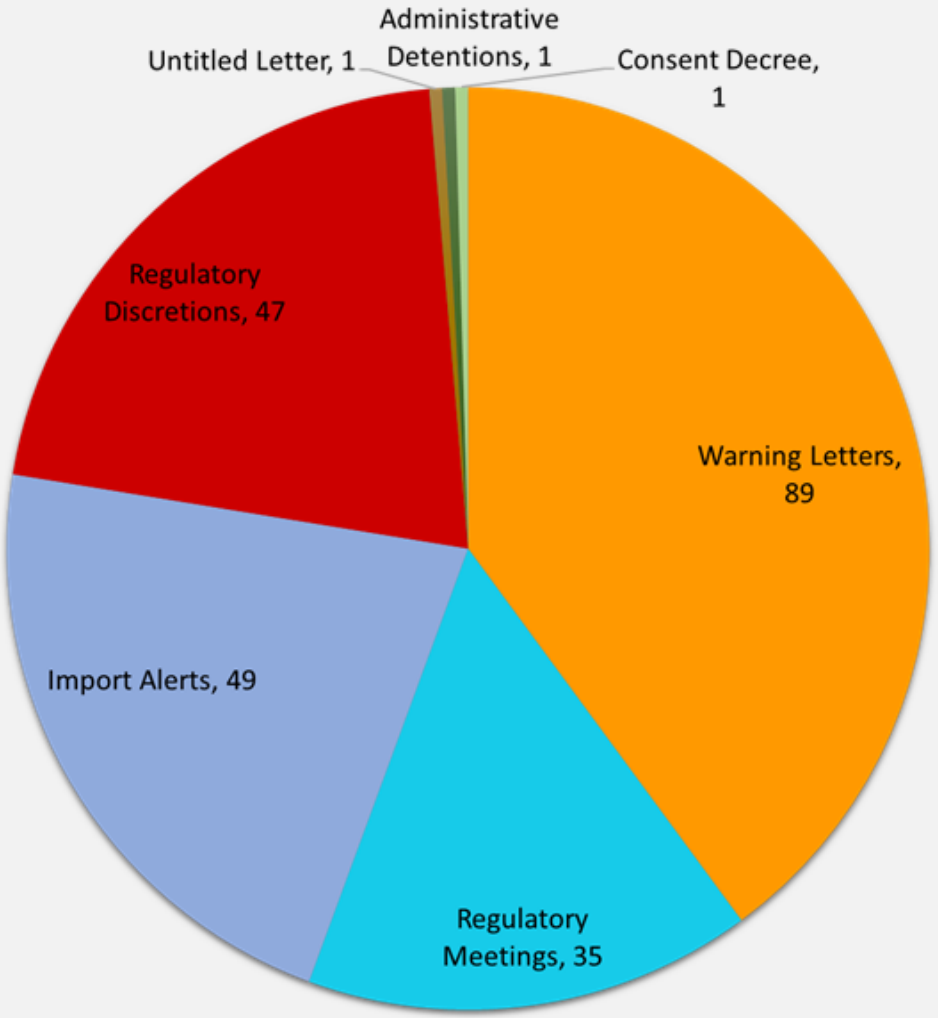
Total Citations with direct reference to 21 CFR Part 211 Section(s) = 15731

#	CFR Section	Subpart	Section Heading	Times Cited	Percentage
1	21 CFR 211.192	Records and Reports	Production record review.	1088	6.9%
2	21 CFR 211.22(d)	Organization and Personnel	Responsibilities of quality control unit.	863	5.5%
3	21 CFR 211.160 (b)	Laboratory Controls	General requirements.	624	4%
4	21 CFR 211.100 (a)	Production and Process Controls	Written procedures; deviations.	560	3.6%
5	21 CFR 211.25(a)	Organization and Personnel	Personnel qualifications.	531	3.4%
6	21 CFR 211.113 (b)	Production and Process Controls	Control of microbiological contamination.	530	3.4%
7	21 CFR 211.67(b)	Equipment	Equipment cleaning and maintenance.	442	2.8%
8	21 CFR 211.166 (a)	Laboratory Controls	Stability testing.	432	2.7%
9	21 CFR 211.110 (a)	Production and Process Controls	Sampling and testing of in-process materials and drug products.	380	2.4%
10	21 CFR 211.160 (a)	Laboratory Controls	General requirements.	365	2.3%

Enforcement and Advisory Actions

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

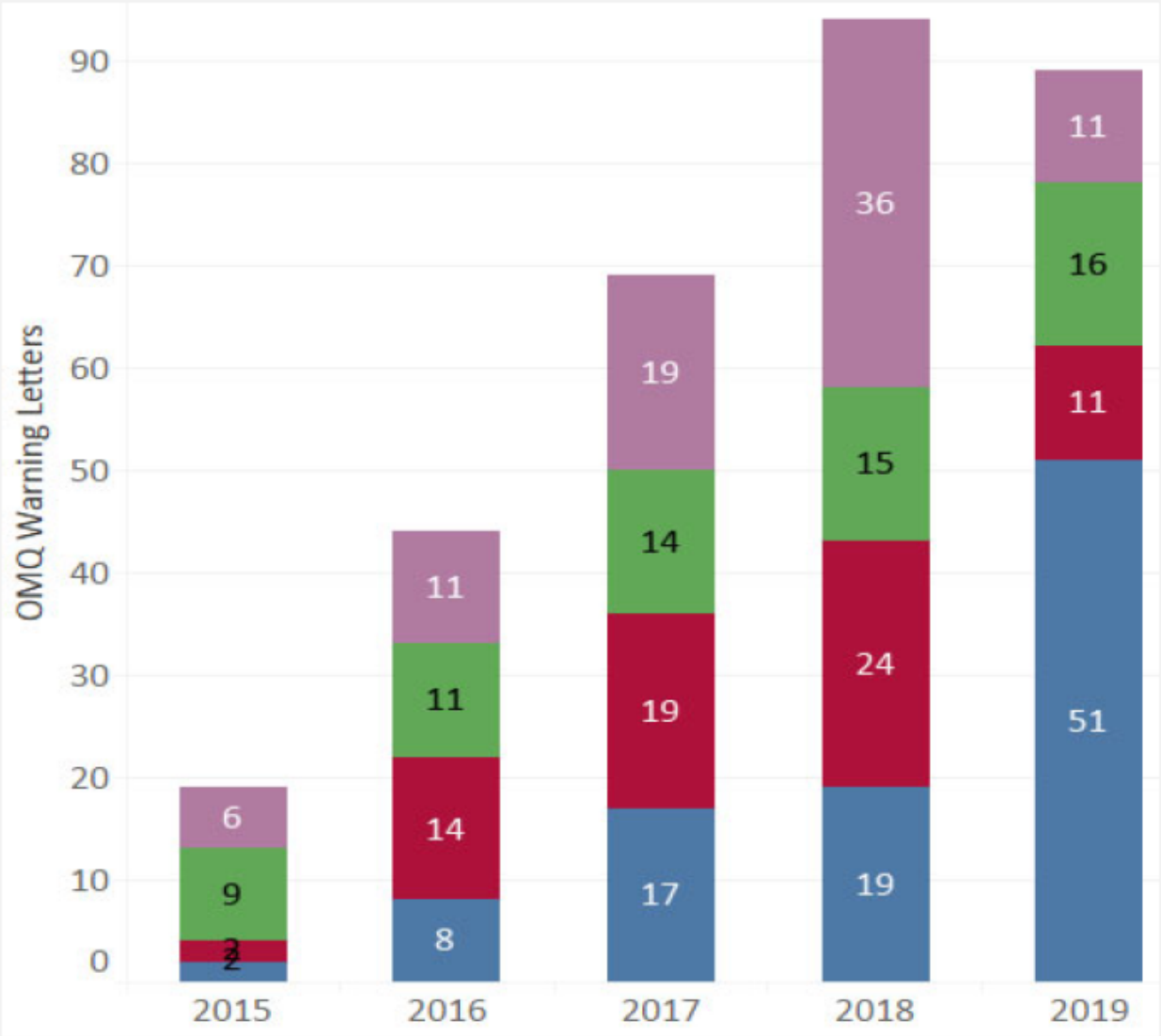
FY2019 Regulatory Actions



Actions during period of October 1, 2018 to August 16, 2019

Excludes compounding-related actions

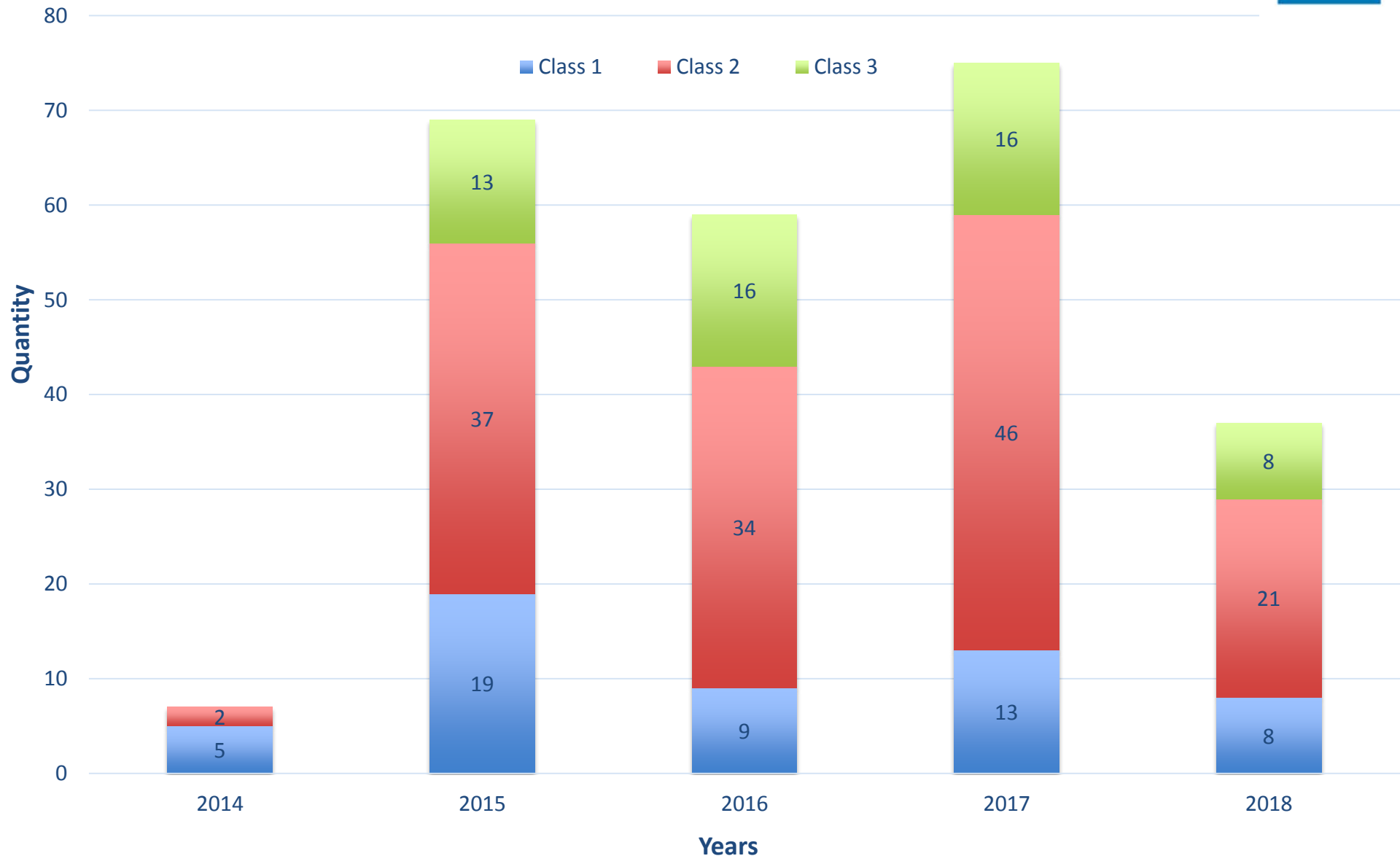
Office of Manufacturing Quality
FY15-19 Warning Letters*



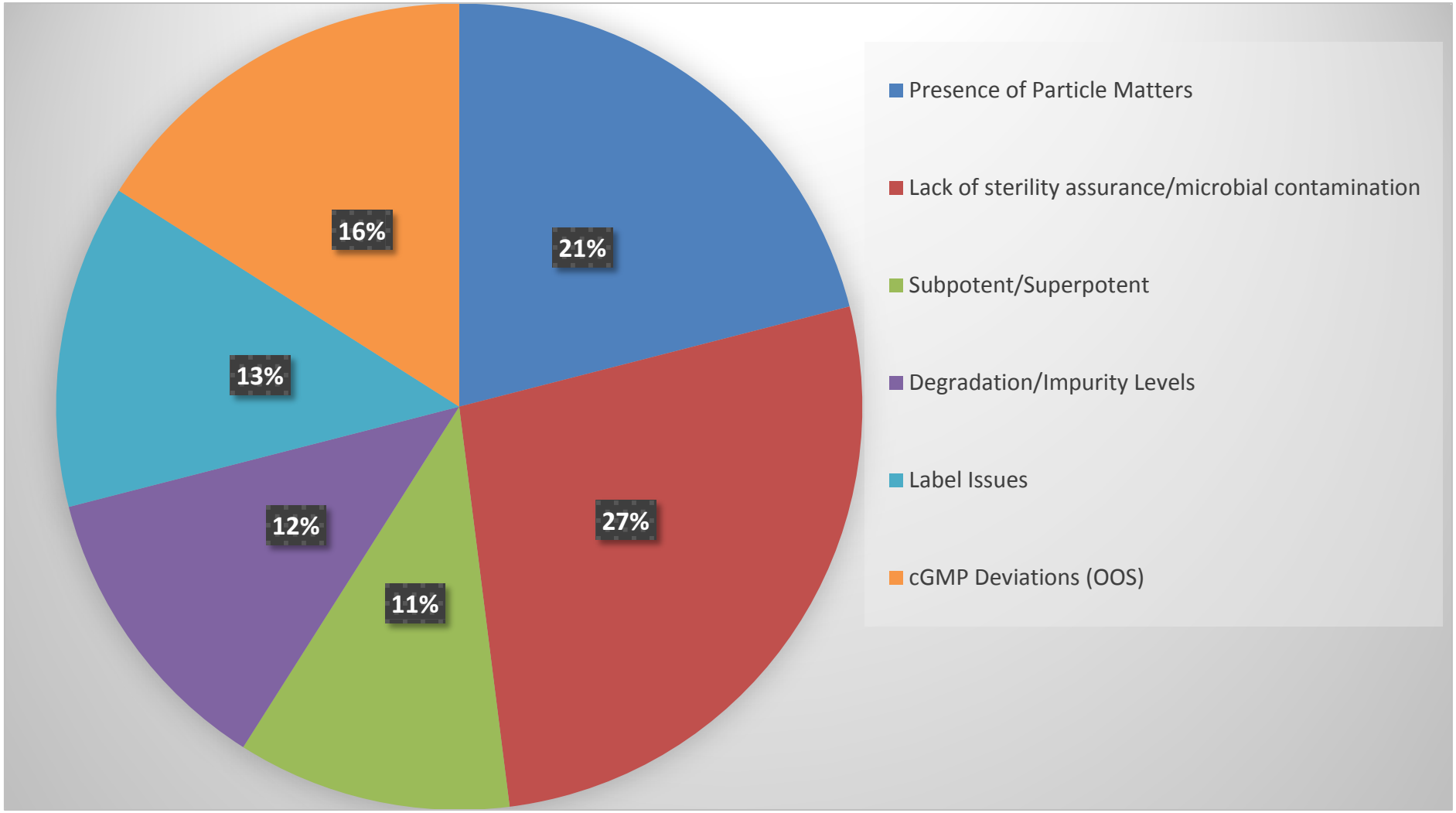
Compounding warning letters not included.

**1 October 2014 through 16 August 2019*

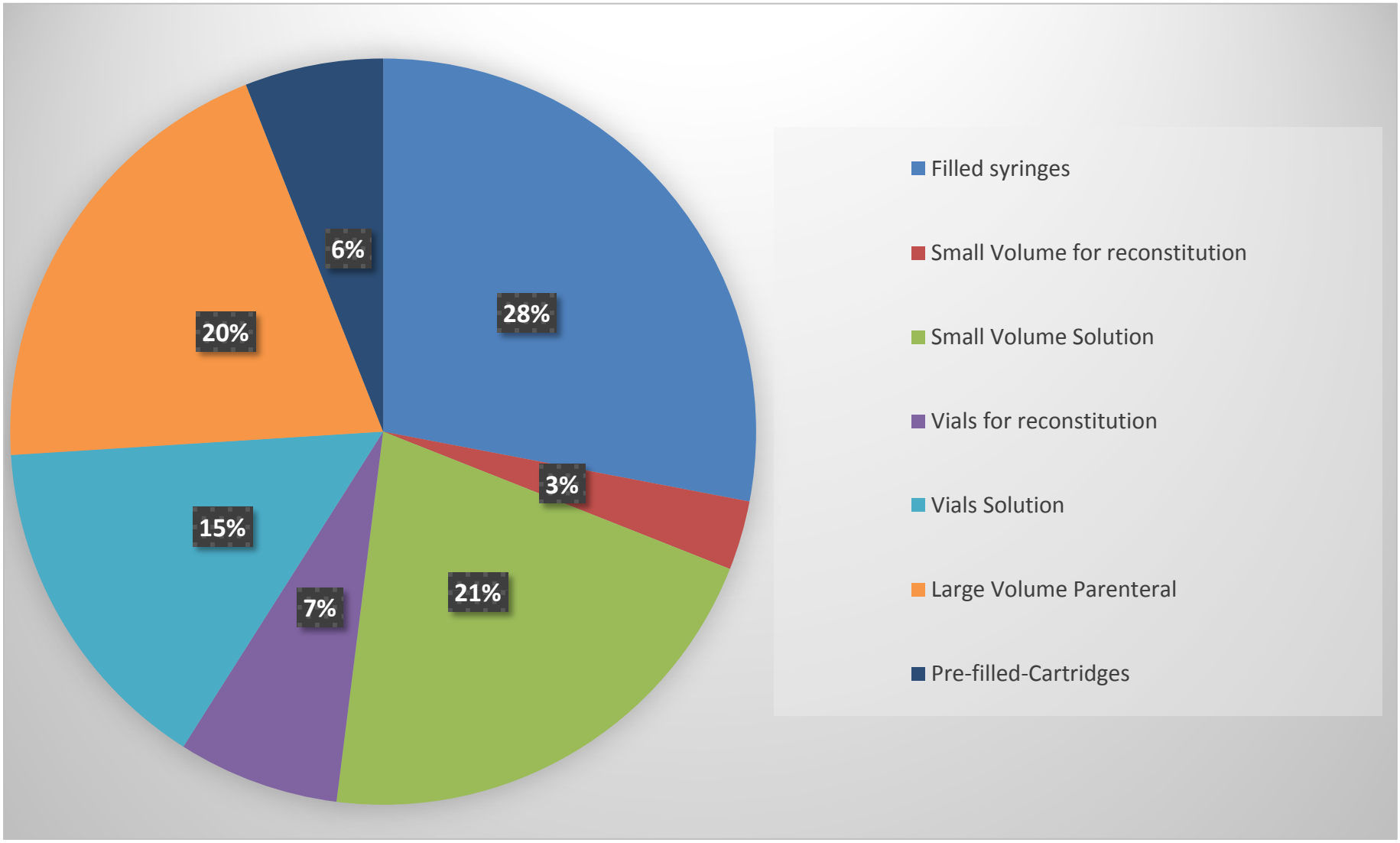
Recalls for Sterile Drug Products



Recalls for Sterile Drug Products (cumulative 2014-2018)



Recalls (%) for Sterile Dosage Forms (cumulative 2014-2018)



Notable Warning Letter Trends

1. **Supply Chain**
   - *Insufficient Impurity Profiles (e.g., genotoxic impurities)*
   - *Repacking (unknowns in the chain)*
2. **Microbial Contamination of Non-sterile Drug Products**
3. **Aseptic Processing Line Design**
4. **Data Integrity: Underlying Causes**
   - *A primary root cause is computer system vulnerabilities…*

Warning Letter & Import Alert

Supply Chain- Genotoxic Impurities

- Failure of quality unit to ensure that **quality-related customer complaints are investigated and resolved.** You received a complaint from a customer who detected an unknown peak during residual solvent testing of your **valsartan API.** The peak was NDMA. Your investigation determined is presence was caused by the convergence of three process-related factors, one factor being use of the solvent **(b)(4)).** However, FDA analyses of samples of your API, and finished drug product manufactured with your API, **identified NDMA in multiple batches manufactured with a different process**, which did not use that solvent.

- **Failure to evaluate the potential effect of changes in manufacture.** In 2011 you approved a valsartan API process change with intention to improve process, increase yield, and lower production costs. However, you failed to adequately assess **the potential formation of mutagenic impurities.** You also failed to evaluate the need for additional analytical methods to ensure detection and control of unanticipated impurities before you approved the process change. **You are responsible for developing and using suitable methods to detect impurities** when developing, and making changes to, your manufacturing processes. **If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.**

FDA Statement- Genotoxic Impurities

Lifecycle Testing and Sensitive Methods

- The potential for the development of genotoxic impurities during a manufacturing processes is an area of intense focus. We'll continue to improve our science and standards for detecting and preventing these risks.
- **Now that they are aware that certain conditions result in the formation of nitrosamines, manufacturers using processes at risk for these impurities are expected to test for them** to ensure that active ingredients and finished products…are safe for patients.
- While we're still investigating the root causes of the impurities, our ongoing effort has determined that the impurities may be generated when **specific chemicals** and **reaction conditions are present in the manufacturing process of the** drug's **API**, and may also result from the reuse of materials, such as **solvents.** We're working with API makers to ensure they fix their processes and cease distribution of affected **API.**

FDA Statement: Commissioner (former) Scott Gottlieb and CDER Director Janet Woodcock (Jan. 25, 2019)

Impurity Profiles
Supply Chain Lessons Learned

- Generate full impurity profiles.
  - *Ensure impurities with potential for high **toxicity** are identified.*
  - *Generally requires multiple capable test methods.*
- Some of these impurities are far below the typical **0.1% qualification level.** For example, a limit of 0.03ppm (e.g,, published by EMA) would be:

0.03ppm = 0.000003%

- Test batches throughout the lifecycle and monitor for changes in impurity profile (i.e., new or increased levels of impurities)

Warning Letter

Deficient Design of Aseptic Processing Line

- Inspection found multiple flaws in aseptic processing line interactions (e.g., stopper addition, jammed/fallen vials) including blocked first air during interventions. Also, poor material flow; deficient smoke studies
- "Provide the following in your response:
  - A comprehensive, independent identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Include an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.
  - A detailed corrective action and preventative action (CAPA) plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design and control and personnel qualification."

MORE WARNING LETTER EXAMPLES

WL: Media Fills

"Our review of your media fill batch records found that your firm rejected integral vials, and no justification was provided."

"Your media fill procedure does not specify that all personnel authorized to enter the aseptic processing rooms during manufacturing should participate in a media fill at least once a year."

"You lacked adequate procedures for training and qualifying personnel to examine media filled units following incubation, and you did not specify how they are to conduct this inspection. Furthermore, you did not keep adequate records that document which personnel performed the examinations."

WL: Leaking Containers

"During aseptic manufacturing of your sterile ophthalmic products, you documented numerous leaking containers and other bottle defects. To address these defects, you routinely adjusted your filling equipment and resumed production. You subsequently released these lots. Following distribution, you received customer complaints of leaking containers. In addition, you found numerous critical container-closure defects, including leaking products, during media fills studies."

"Additionally, our inspection found that your firm re-uses sterilizing filters as many as 22 times before discarding them."

WL: Laminar Air Flow

The filling line lacks unidirectional airflow in the ISO 5 aseptic filling zone. The horizontal airflow in the filling zone is not sufficiently robust to protect the sterile injectable product during interventions involving operator entry into the aseptic filling cabinet. Smoke studies demonstrated the filling line design permits turbulence above and below open vials.

Your smoke studies do not support your assertion that you maintain unidirectional airflow for all aseptic operations. At times, the smoke volume was too low to accurately demonstrate airflow. You did not inject the smoke in areas that showed the effects of operator interventions on the unidirectional air stream. These smoke studies do not demonstrate that your line is designed to prevent microbiological contamination, or to provide high assurance of product sterility.

WL: EM Program

Lack of adequate Environmental Monitoring (EM) program “Your records do not establish that during manufacturing operations, you collect environmental monitoring samples from all locations designated in your environmental monitoring procedure. The batch production records do not clearly reconcile samples you collect with the results you obtain. Also, your procedure instructed operators to record environmental monitoring data only in instances where there are "any results different from zero.”

Acknowledgements

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thank you
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Баярлалаа
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faafetai lava
mersi
kia ora
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tack
spas
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
vinaka
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blagodaram
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nanni
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maururu
hvala
gràçie
bayarlalaa
köszönöm
bedankt
enkosi
dziękuję
dankon
aćiū
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