Improved Aseptic Processes and Monitoring to Reduce FDA 483s

Abstract

In recent years, the FDA response to companies with insufficient proof of control over their production has become more aggressive, demonstrated by the rise in 483s and warning letters issued. Topics related to environmental monitoring programs are included in the most common reasons 483s are issued. By becoming aware of the regulations and reasoning backing 483 distribution, pharmaceutical companies can prepare themselves against common mistakes.

Introduction

The FDA Committee has increased warning letter distribution dramatically in recent years. Notably, there has been a significant increase in the number of warning letters referring to "data integrity" and "sterility assurance", in relation to environmental monitoring (EM). The increase is attributed to a dramatic change in the FDA regulator approach to infraction handling. Those of significance to the 2017 drug sector and relating to EM are highlighted in blue in Table 1.

For 483 topics relating to the Medical Device and Biologics sectors, see the end of the document.

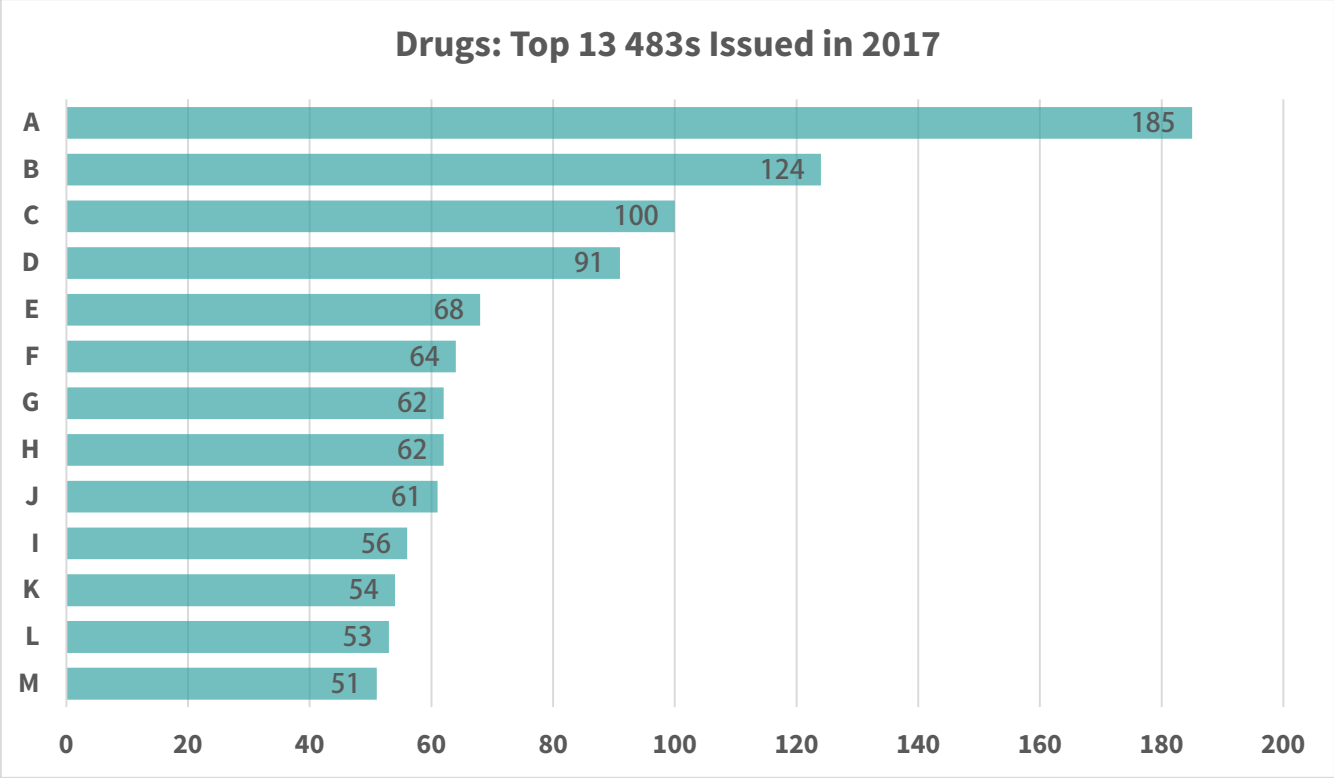

Table 1. List of 483 topics (Drug sector)	
A	21 CFR 211.22(D): The responsibilities and procedures applicable to the quality control unit are not in writing or followed
B	21 CFR 211.160(B): Inadequate scientifically sound laboratory controls
C	21 CFR 211.192: Failure to review investigations of discrepancies or batch failures
D	21 CFR 211.100(A): Absence of written procedures
E	21 CFR 211.67(B): Written procedures not established and/or followed for cleaning and maintenance of material
F	21 CFR 211.165(A): Procedures designed for testing and release for distribution are not established, written, or followed
G	21 CFR 211.68(B): Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel
H	21 CFR 211.113(B): Equipment and utensils are not maintained at appropriate intervals to prevent problems that would alter the safety, identity, strength, quality or purity of the drug product
I	21 CFR 211.68(A): Calibration, inspection, or checking is not done
J	21 CFR 211.166(A): There is no written testing program designed to assess the stability characteristics of drug products
K	21 CFR 211.110(A): Control procedures, which monitor output and validate performance, are not established
L	21 CFR 211.67(A): Equipment and utensils are not maintained or cleaned at appropriate intervals
M	21 CFR 211.25(A): Employees are not given training in operations, cGMP, written procedures

Information from https://www.fda.gov/ICECI/Inspections/ucm589892.htm#Devices. Inspections ended between 10/1/2016 and 9/30/2017.

The FDA fully expects that product bioburden be assessed and evaluated. 21 CFR 211.113(b) Control of Microbiological Contamination states that the "appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed". Such procedures should include validation of all aseptic and sterilization processes.

Warning Letters

There are several common violations found by FDA compliance officers, including a lack of quality control system, failure to establish and follow written procedures (for quality control and process validation), failure to perform cleaning practices in order to prevent contamination or malfunction, failure to exercise control over computerized access and data, and failure to investigate violations found.

Written Procedures

It is stated in several warning letters that each company did not establish or follow written procedures. These procedures should be "designed to prevent microbiological contamination of drug products purporting to be sterile", as per 21 CFR 211.113(b).

In response, the inspectors request a risk assessment "describing process failure modes, full sterility history (e.g., sterility testing, media fills), and all actions taken to evaluate and address the acceptability" of the product.

Investigation

The failure to provide a thorough batch failure investigation is frequently noted. Product specifications must be met despite whether the batch has already been distributed (21 CFR 211.192). In one letter sent in February 2011, the firm "routinely failed to thoroughly investigate and identify root causes when environmental monitoring data exceeds the action limit". As a response, one firm hired a consultant to address the infraction by assessing environmental data and repairing the facility. However, the FDA noted it was insufficient due to inadequate investigation of "disinfectant procedures, frequencies, and preparation".

In another letter dated June 2011, the infraction included microbiologists reporting plates as having no CFUs when two plates actually contained one each. Due to the action limit of the plates' sample locations, an investigation was required as per the company's SOP, but none occurred.

Several other common infractions include:

- Environmental data from past collection periods was evaluated and showed a "lack of comprehensive investigations when mold and bacteria were identified", which went above action levels. Feb. 2011
- "…routine failure to thoroughly investigate and identify root causes when environmental monitoring data exceeds the action limit." Mar. 2011
- "Environmental monitoring (EM) samples taken from manufacturing and sterility test operators were found to be positive during the time of the sterility failures, however, the isolates were not sent out for identification." Oct. 2013
- "It is imperative that you determine the identity of microorganisms found in media filled units in order to adequately understand the potential sources and scope of the contamination." Oct. 2016
- "…the inspection revealed that your maintenance personnel had documented evidence of visible discoloration and stains and "possible mold" on the "clean" side of the HEPA filters…You did not properly investigate and remediate this condition." May 2013

It is essential that the environmental monitoring program is continually maintained throughout the aseptic processing facility. Documentation of proper EM practices is essential to ensure successful investigations.

Control Systems

Warning letters often mention a failure to establish separate or defined areas necessary "to prevent contamination or mix-ups during aseptic processing" (21 CFR 211.42(c)). The following is also commonly noted:

- Due to the process relying on manual manipulations (involving personnel in close proximity to the product), the poor demonstration of environmental control could pose a significant risk to contamination.
- Sample collection from personnel was not verified to adequately represent present microcontamination.
- The SOP failed to include instructions for the "location and duration of samples collected in the critical aseptic processing area".
- The environmental monitoring program did not assure "environmental contaminants are reliably detected".
- An adequate environmental monitoring program should be established, and "capture meaningful data", in addition to acting as "an early warning system to detect possible environmental contaminants that may impact the sterility of drug products".

In a warning letter dated February 2017, the inspector noted that the company failed to "establish an adequate system for monitoring environmental conditions in aseptic processing areas" (21 CFR 211.42(c)(10)(iv). Routine personnel and surface monitoring, and air quality data were not shown to occur in any capacity, and it was requested for the company to provide a reassessment and CAPA of the environmental monitoring program to "ensure it supports robust environmental control" with guidelines such as:

- Justifying sampling locations, and associated action and alert limits

- Ensuring all locations are sampled at appropriate frequencies, with special emphasis on implementing routine sampling of aseptic processing room surfaces
- Defining circumstances under which investigation of an adverse trend or out-of-limit result is triggered, as well as appropriate responses to such occurrences in order to promptly address contamination hazards

Not only is it important to have a EM device that provides accurate and reliable data, but it is also imperative that the program dictating when and where monitoring takes place is proven to ensure product quality.

Incomplete Data

Failure to include complete data derived from all tests necessary to assure compliance was noted in several warning letters. The importance of ensuring compliance with established specifications and standards is noted in 21 CFR 211.194. Excerpts from a letter dated December 2015 include the following infractions:

- "…failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data."
- "…found that the laboratory manager had the ability to delete data."
- "…the audit trail function…was not activated, and because eight different analysts share a single username and password, you were unable to demonstrate who performed each operation on this instrument system."
- Simply preventing data deletion is not sufficient. You did not show how these steps will ensure that your firm retains and evaluates all data."

Investigators frequently specify the need for audit trails and access controls for computerized data collection (see 21 CFR Part 11).

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Microbiological Contamination Control

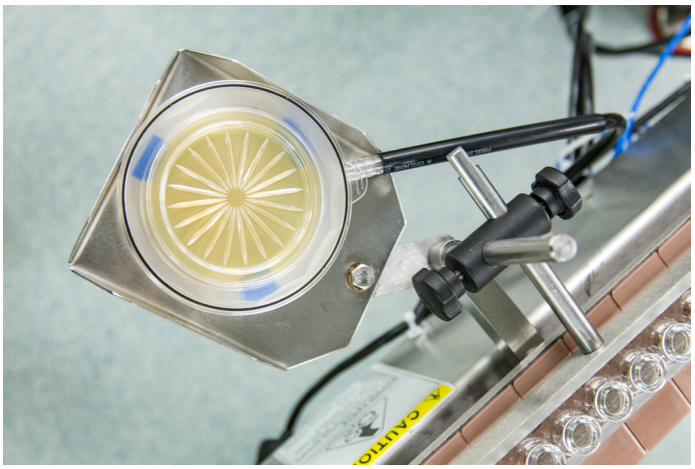
It must be established through detection testing that the product meets microbiological quality standards (see USP 37, <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms). A "specified" microorganism has several elements that require evaluation on a case-by-case basis for each drug manufacturer. The term refers to microbial contaminants that, based on microbial species, number of microorganisms dosage form, intended use, patient population and route of administration would adversely affect product safety. Most "specified" microorganisms would pose a threat of patient infection or mortality.

It is no longer possible to release products or monitor processes (especially those producing aseptically filled sterile products) using microbiological methodologies/techniques developed in the 20th century. There are four types of modern monitoring systems that offer various limitations on personnel interaction with the product.

1. In traditional cleanroom production, the presence of people in a Grade A area is allowed, with a mandatory installation of a surrounding Grade B environment.
2. In open Restricted Access Barrier Systems (oRABS), there is a physical separation of people from Grade A areas, but Grade A air is exhausted into Grade B. oRABs must be installed with a Grade B surrounding environment.
3. In closed Restricted Access Barrier Systems (cRABS), there is a physical separation between people and Grade A production areas and Grade A air recirculation. cRABS must be installed with a Grade B surrounding environment.
4. In an isolator system, the production inside the isolator is completely separated from people and air circulation in a Grade A area. The isolator can be installed in a Grade C environment.

Of the four options above, only the isolator system is able to offer complete sterility assurance. With increasing human intervention of the system, more risk is introduced and the ability to ensure a sterile final product is lessened. At most, 10% of pharmaceutical companies are able to incorporate isolators as part of their production process, with a larger minority using traditional cleanroom techniques and the majority using a form of RABS. Intervention can be mitigated with a microbiological monitoring method that offers advanced sensitivity with real-time results.

The use of outdated microbiological analytical methods (e.g., settle plates) only allows for the detection of one-third the microorganisms present in the production process. As a result, it is not possible to use these methods to completely identify areas of contamination. With a more reliable method with advanced sensitivity, improved detection of microorganisms in critical environments is possible, and can positively impact product quality.



BioCapt® Single-Use adjacent to filling line

Environmental monitoring systems are an important part of aseptic processing of sterile pharmaceuticals, in that it aids in the capability to control the presence, distribution and a result, the survival of microorganisms. Critical areas, such as process waters (deionized, RO and WFI), air and compressed gases, in addition to working surfaces (personnel, gloves, equipment) should be the primary focus in a monitoring program. Early evaluation of the surface, personnel and additional critical points of the aseptic manufacturing area aids in minimizing corrective action time.

Swabbing using the SurCapt™ Microbial Surface Detection Kit

Additional benefits to a strong EM program include undelayed product release, enhanced efficiency and productivity (labor and time), overall cost reduction and data integrity.

Industry Innovation

The FDA has recognized the need for innovation in the pharmaceutical industry. In 2002, four key initiatives were put forward to instigate this change, including the *Critical Path Initiative*, *Pharmaceutical Quality for the 21st Century - A Risk Based Approach*, *Quality by Design (QbD)* and *Process Analytical Technology (PAT)*. The collective goal of these new measures is to modernize and improve the quality of pharmaceutical manufacturing processes, and encourage the industry to implement risk-based, continuous, real-time quality assurance.

The desired attributes for a measuring system include:

- Sensitivity at the single-cell level
- Discrimination between viable and non-viable microorganisms
- Able to detect VBNCs
- Rapid: as fast as possible (days vs. hours vs. minutes)
- Qualitative and quantitative capabilities
- Able to identify in case of contamination
- Cost-effective
- Easy to use and validate
- Robust
- Usable in the manufacturing environment
- Does not contribute to contamination

Full understanding of the production and process needs are paramount to choosing the appropriate monitoring method, which is best handled with a risk assessment. Be aware that different technologies will require specialized implementation.

Different sampling tools and measuring systems will offer flexibility in the application of the appropriate technology for each sampling point. Specific methods should be registered for monitoring critical quality parameters and critical process parameters.

Conclusion

The issuing of 483s has increased significantly, becoming a growing trend of change in the pharmaceutical industry. Many of the cited infractions impact quality control, and by extension, environmental monitoring. More 483s are likely to be dispersed in coming years, and it is best prepared for with a strong understanding of industry standards and a defensible monitoring strategy that offers a complete picture of the production process.

When developing an environmental monitoring program, look to new technologies that offer advanced sensitivity and reliability, with a focus on minimizing human intervention. Choosing to do so will improve sterility assurance and mitigate risk to the final product.

Author

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Gilberto Dalmaso has over 25 years' experience in pharmaceutical microbiology and sterility assurance. His current work is focused on pharmaceutical microbiology and aseptic processes, microbiological contamination control and rapid microbiological methods, Quality by Design (QbD), and PAT in microbiology.

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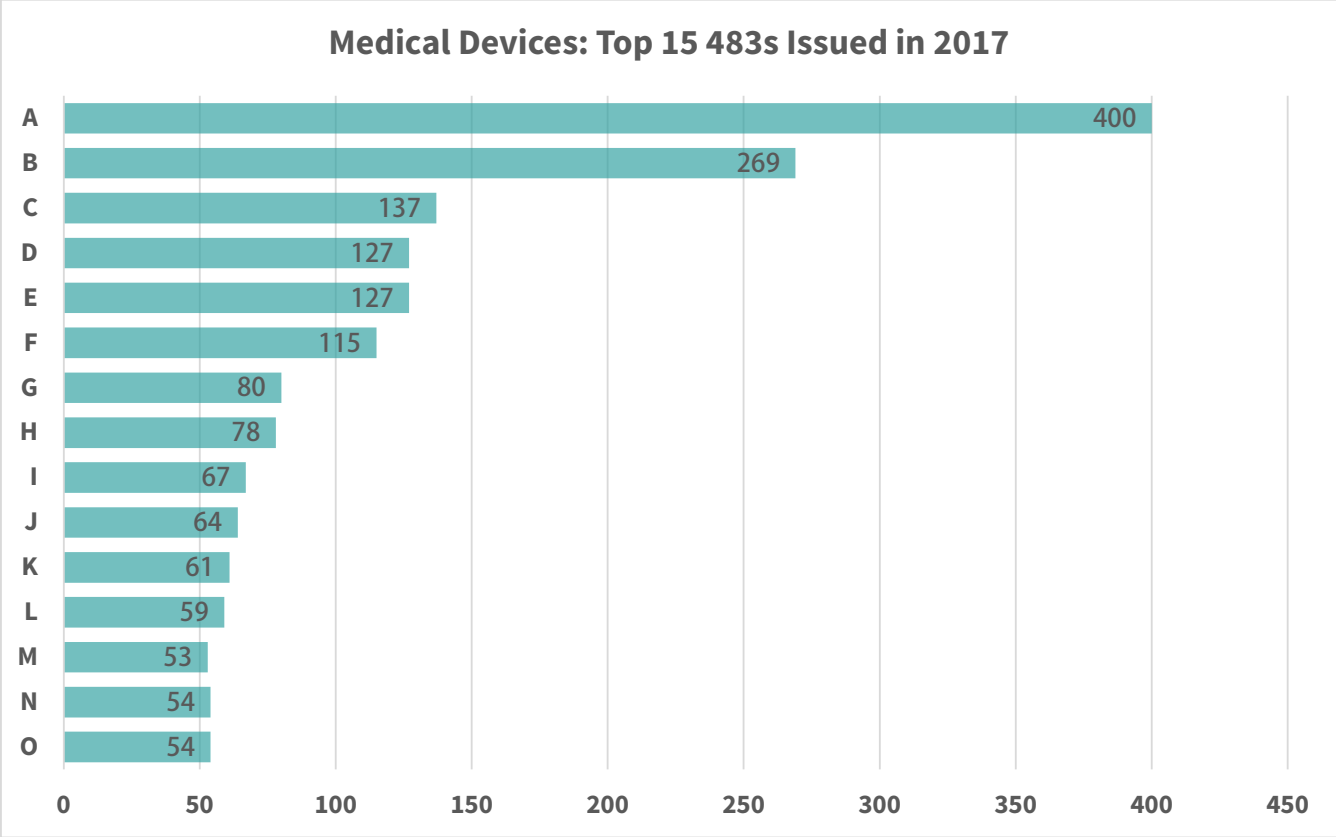

Table 2. List of 483 topics (Medical Device sector)	
A	21 CFR 820.100(A): Procedures for corrective and preventive action have not been adequately established
B	21 CFR 820.198(A): Lack of or inadequate complaint procedures
C	21 CFR 820.50: Lack of, or inadequate procedures for purchasing controls
D	21 CFR 820.75(A):Lack of or inadequate process validation
E	21 CFR 803.17: Lack of written MDR procedures
F	21 CFR 820.90(A): Procedures have not been adequately established to control product that does not conform to specified requirements
G	21 CFR 820.100(B): Corrective and preventive action activities and/or results have not been adequately documented
H	21 CFR 820.30(I): Procedures for design change have not been adequately established
I	21 CFR 820.22: Procedures for quality audits have not been adequately established
J	21 CFR 820.80(D): Procedures for finished device acceptance have not been adequately established
K	21 CFR 820.181: A device master record has not been adequately maintained
L	21 CFR 820.40: Document control procedures have not been adequately established or maintained
M	21 CFR 820.70(A): Lack of or inadequate procedures for process control
N	21 CFR 820.198(A): Complaints involving the possible failure of a device, labeling, or packaging to meet any of its specifications were not reviewed, evaluated, or investigated where necessary.
O	21 CFR 820.30(G): Risk analysis was not performed or was inadequate or was incomplete.

Information from https://www.fda.gov/ICECI/Inspections/ucm589892.htm#Devices. Inspections ended between 10/1/2016 and 9/30/2017.

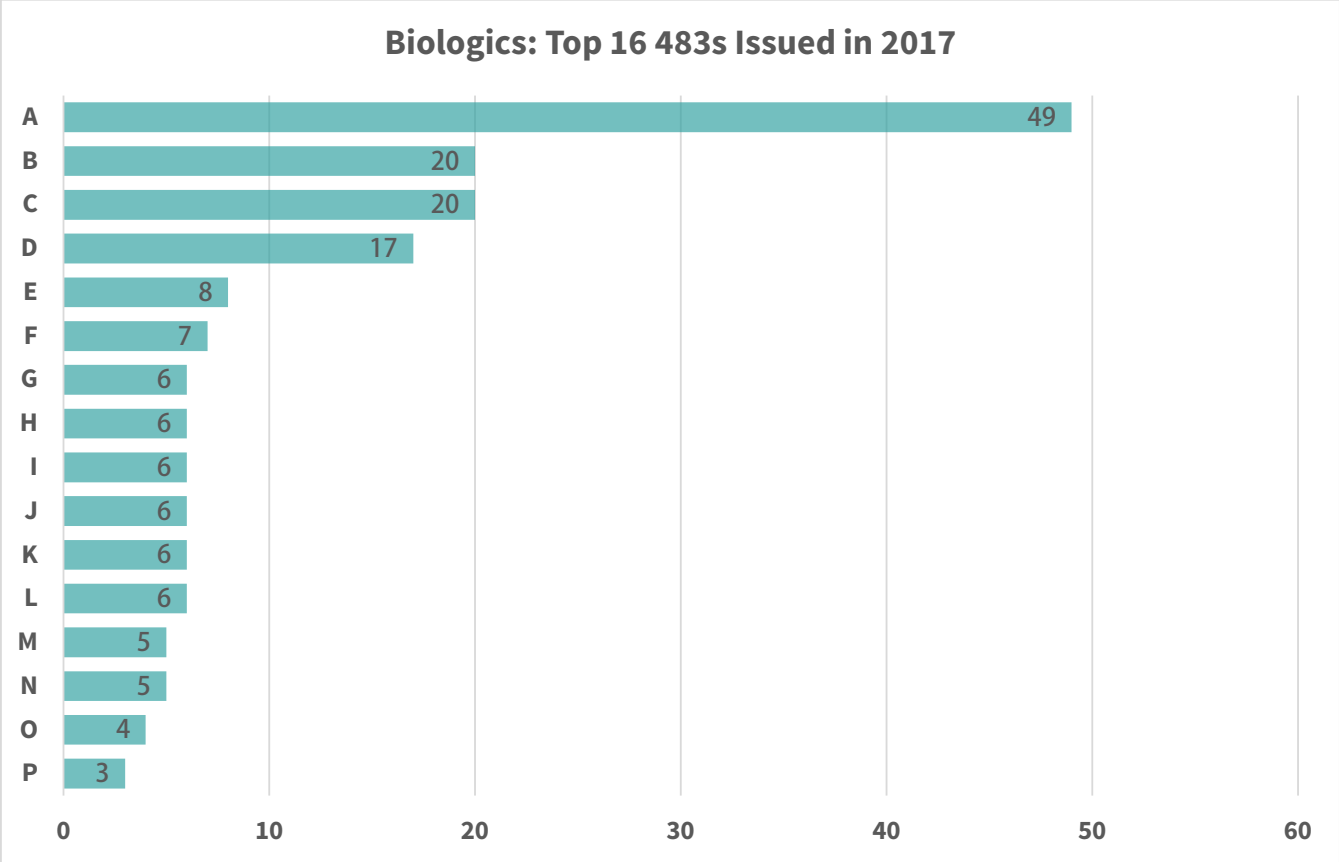

Table 3. List of 483 topics (Biologics sector)	
A	21 CFR 606.100(B): Failure to establish, maintain and follow manufacturing SOPs
B	21 CFR 606.100(C): Failure to perform a thorough investigation
C	21 CFR 606.160(B): Failure to maintain required records
D	21 CFR 606.160(A)(1): Inadequate records to identify person performing, test results, interpretation
E	21 CFR 606.60(A): Failure to maintain and clean equipment
F	21 CFR 606.60(B): Equipment not observed, standardized, calibrated on a regularly scheduled basis as prescribed in SOP manual
G	21 CFR 606.65(E): Failure to follow manufacturer's instructions
H	21 CFR 606.100(C): Failure to review records pertinent to lot or unit prior to release
I	21 CFR 606.40(A)(1):Failure to provide adequate space for examination
J	21 CFR 606.160(A)(1): Records are not legible or indelible
K	21 CFR 606.171: Failure to submit biological product deviation report
L	21 CFR 606.100(B): Written standard operating procedures for all steps in the investigation or recordkeeping process were not established, maintained, followed or available to personnel in the areas where they were performed
M	21 CFR 600.14(G)(1): Failure to obtain from the donor on the day of donation proof of identify or a postal address where the donor may be contacted for 8 weeks after donation
N	21 CFR 606.151(E): Records, including signature by the physician requesting the procedure, are not maintained of all emergency transfusions, including complete documentation justifying the emergency action
O	21 CFR 606.10(E): Medical history assessment failed to include factors that make the donor ineligible to donate
P	21 CFR 606.100(B)(15): The standard operating procedure fails to include a written description of schedules and procedures for equipment maintenance and calibration

Information from https://www.fda.gov/ICECI/EnforcementActions/ucm531890.htm#Biologics. Inspections ended between 10/1/2016 and 9/30/2017.