Inter-governmental Working Meeting on Drug Compounding and DSCSA

U.S. Food and Drug Administration
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Update on Inspections of Sterile Drug Compounding Facilities

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Summary of Presentation

- Inspections of Facilities
- Form FDA 483 Observations
- Re-inspection
- Inspection Obstacles
- Post Inspection

Types of Inspections

- For-cause inspections
  - After receiving
    - Reports of serious adverse events
    - Reports of serious product quality issues
    - Complaints about sterile practices at the facilities
    - Request from a state for FDA assistance
- Compliance follow up re-inspection
  - Verify corrective actions or to gather additional information for regulatory action or recall
- Surveillance inspections
  - Risk-based model includes, for example:
    - History of compliance and recalls
    - History of serious adverse event reports
    - History of product quality problems

FDA Inspections of Compounding Facilities

- Between October 1, 2012 and October 19, 2015:
  - Conducted over 250 inspections of compounding facilities
  - About 100 were for cause
  - Includes 60 inspections of outsourcing facilities
  - Includes 9 re-inspections of same facility

Objective/Focus of Sterile Compounding For-Cause Inspection

- Investigate and obtain evidence of the cause of the adverse event, product quality complaint or other triggering event
- Obtain evidence of the firm's investigation of sterility failures and/or complaints
- Collect compounded sterile drug product samples for testing
- Identify all sterility failures that have occurred since the last inspection
- Look at documentation for non-sterile drugs, depending on the problem and what we observe during the inspection

Objective/Focus of Sterile Compounding Surveillance Inspections

Surveillance

- Determine the current operational status of the firm concerning sterile drug production and gather information about its current aseptic processing practices
- Focus is on sterility assurance of sterile products produced at the facility
- Identify processes and conditions that may result in drugs being produced under conditions that represent a significant risk to patient safety
  - Evaluate the firm's drug production to assure adequate controls to prevent contamination
  - Environmental samples, when warranted
- Assess the facility's conformance with Current Good Manufacturing Practice requirements (503B only)

Objective/Focus of Compliance Follow-up Inspections

- Verify corrective actions made in response to FDA 483, warning letter or injunction
- Gather information to classify or assist in a recall
- Gather additional information for an open case

Observations

Various dried material on

ISO 5 hoods where sterile operations occur.

Observations

The glove box that provides ISO 5 conditions so that aseptic processing operations can occur was located in an unclassified room without HEPA filtered air.

Observations

Unfinished doorway into controlled room

Ceiling above laminar hood which was located in an unclassified room without HEPA filtered air.

Observations

Clothing (non-sterile) of personnel in ISO 5 area not appropriate.

Observations

The HEPA filter located immediately above the ISO 5 hood was observed to have stains on the filter surface.

Stains on the work surface of the hood where sterile operations are performed.

Observations

Non-sterile cleaners used in ISO 5 area

Observations

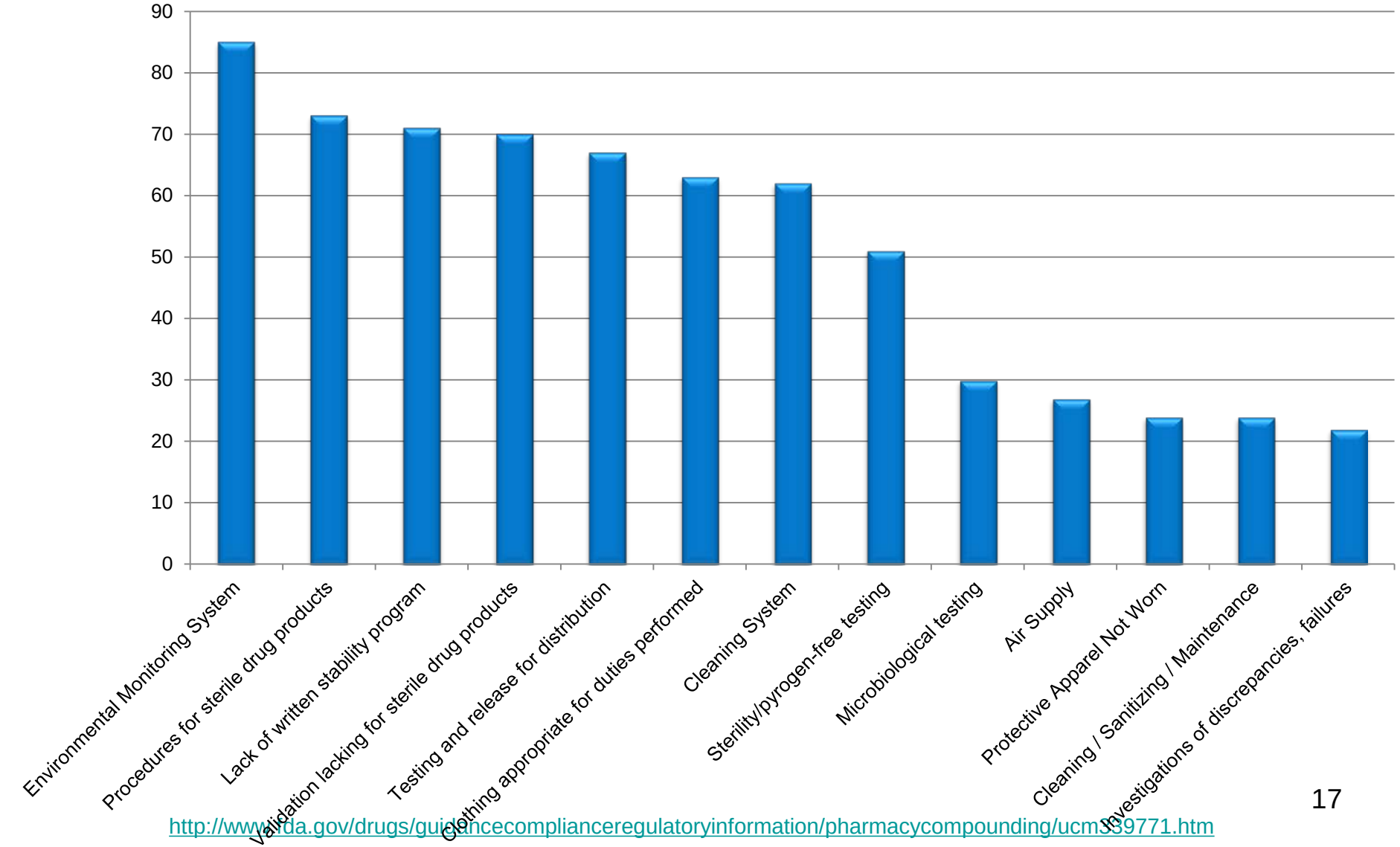
Ceiling above the ISO 6 cleanroom with exposed insulation

Observations

Freeze dryer or “lyophilizer” being used to freeze dry sterile products but is a model supposed to be used on plants and food only.

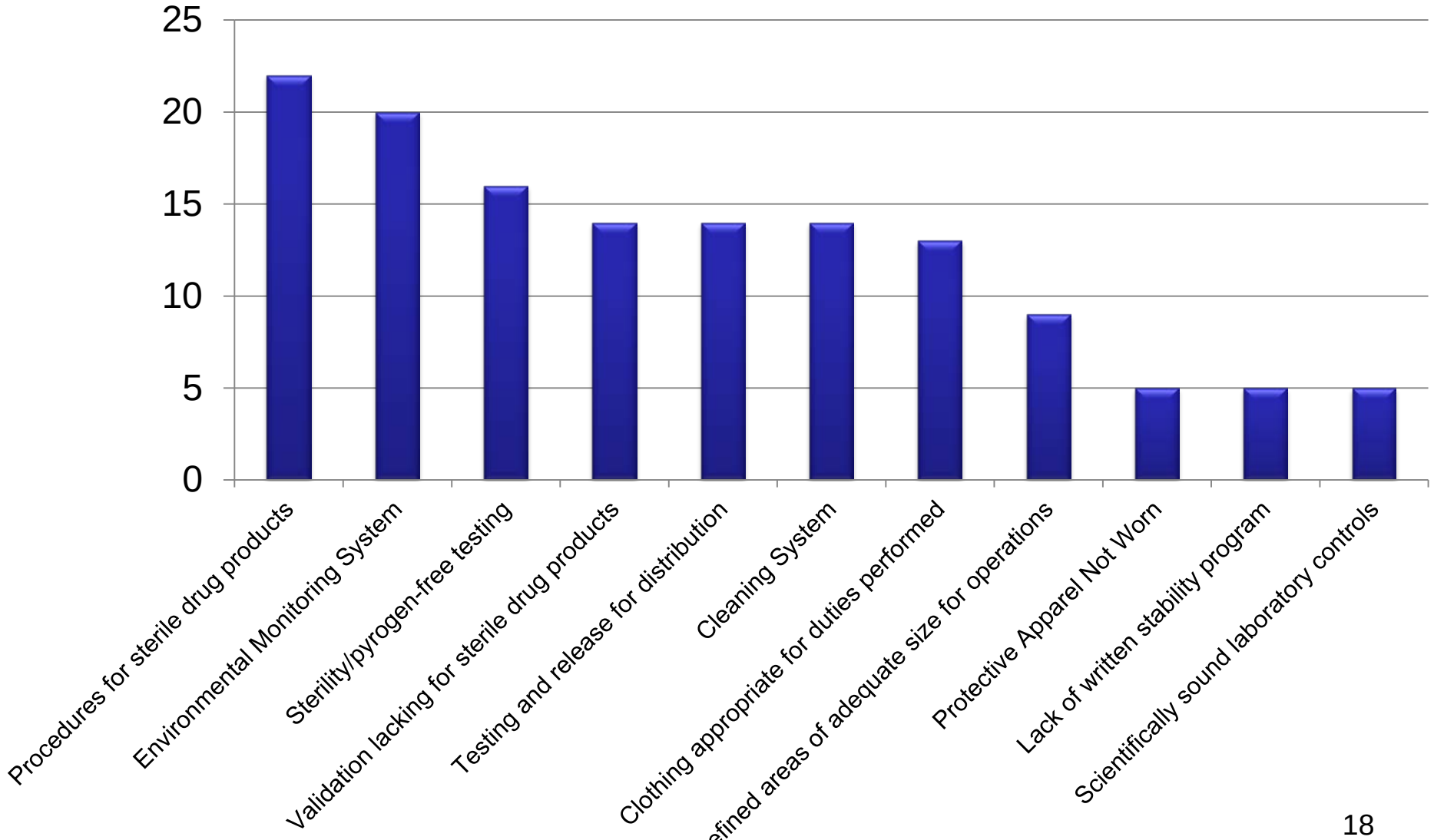
Frequently Cited Deficiencies during 503A Inspections

(when not 100% patient specific prescriptions)



http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339771.htm

Frequently Cited Deficiencies during 503B Inspections



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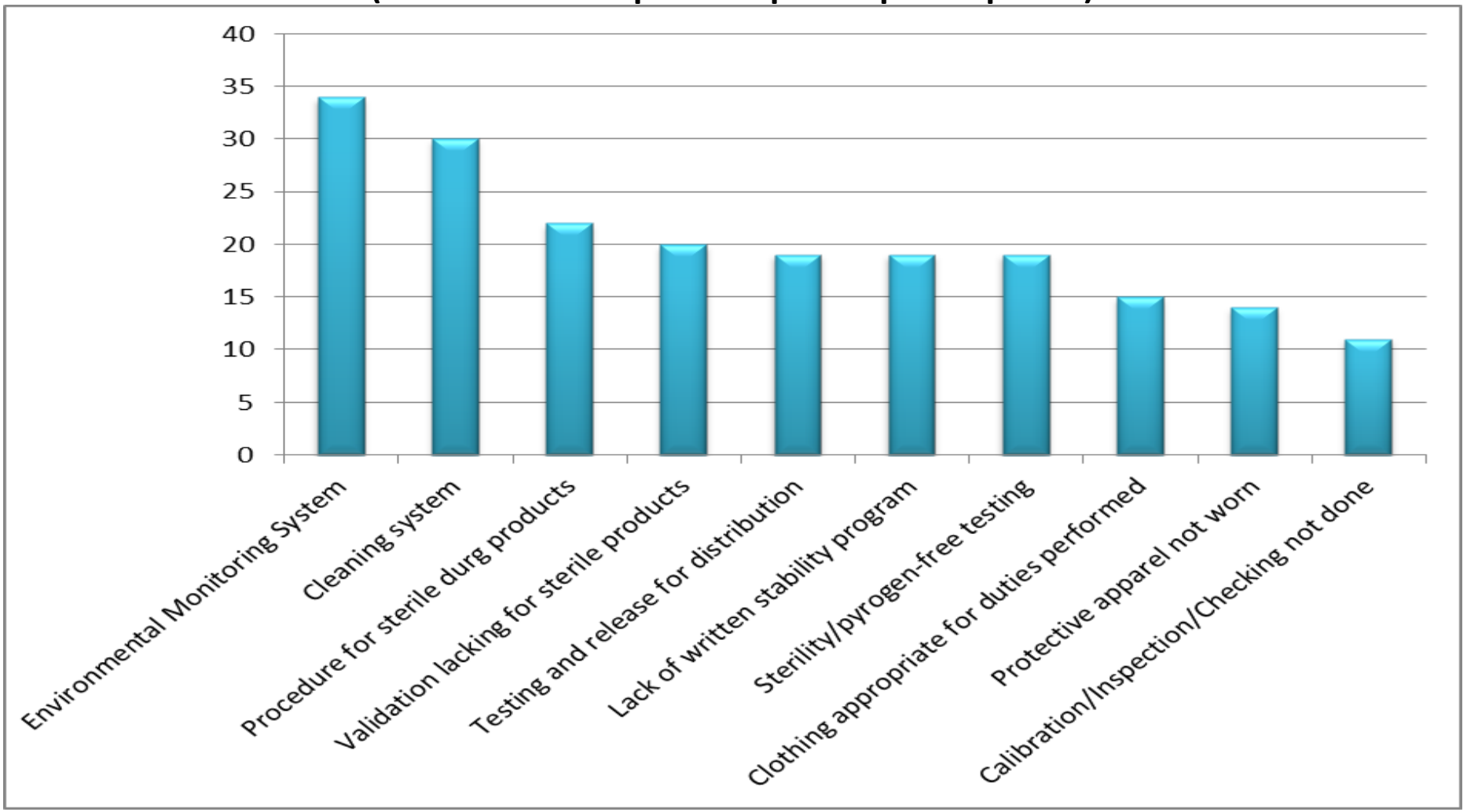
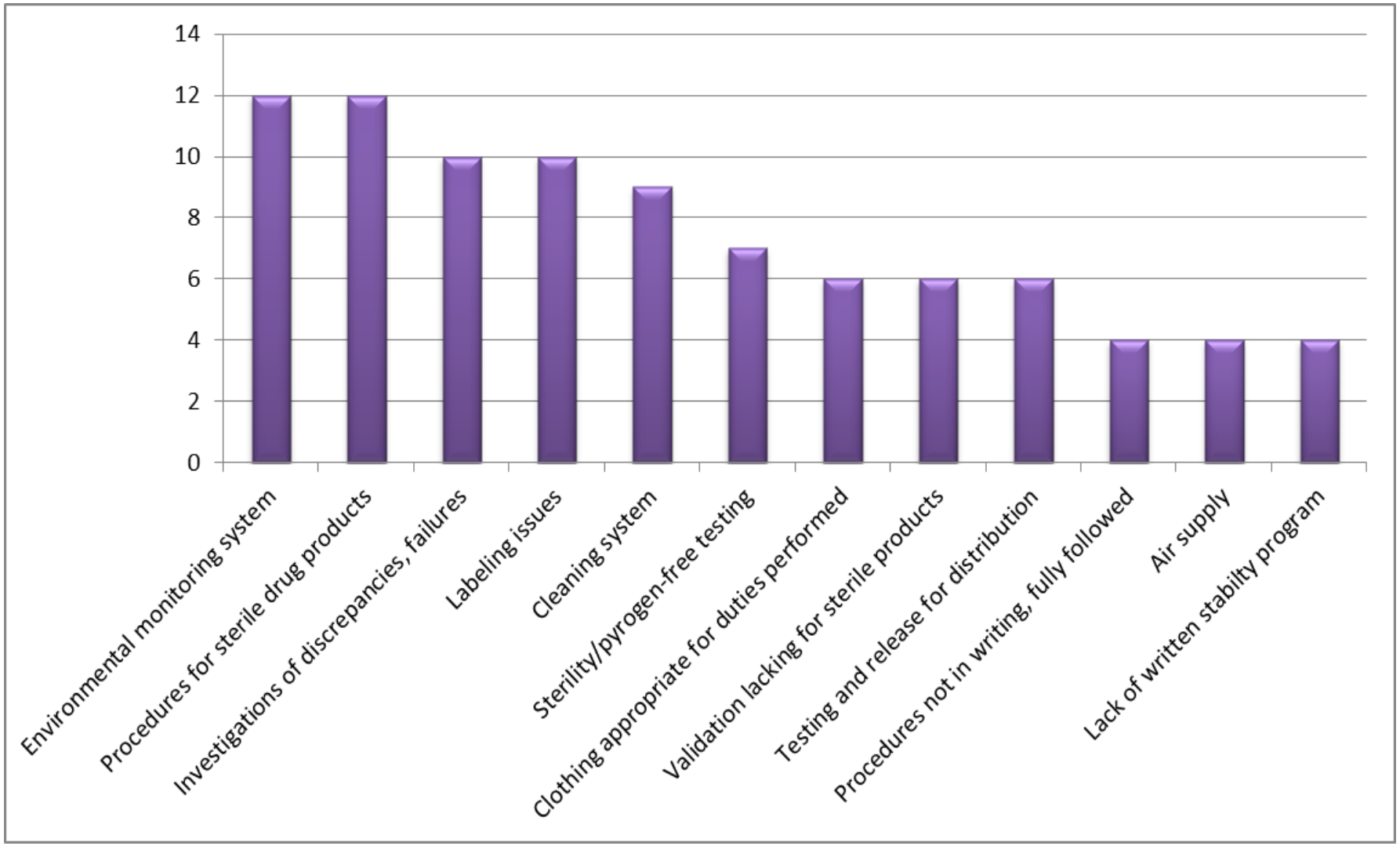
Top 10 Deficiencies since March 2015

503A Inspections

(when not 100% patient specific prescriptions)



Top 10 Deficiencies since March 2015 503B Inspections



Repeat Inspections

- Firms that were inspected multiple times did have fewer objectionable conditions on subsequent follow-up inspections, but several of the same observations recurred.

- In some cases, when the firm increased the frequency of environmental monitoring, there was an increase in the CFUs detected, which led to other objectionable conditions being noted, e.g., inadequate investigations or no investigations into excursions.

Most Common Repeat Observations

- Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed (**211.133(b))**

- Aseptic processing areas are deficient regarding the system for monitoring environmental conditions **(211.42(c)(10)(iv))**

- Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions (**211.42(c)(10)(v))**

Most Common Repeat Observations

- Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release (**211.165(a)).**

- Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements (**211.167(a)).**

- Drug products do not bear an expiration date determined by an appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use (**211.137(a)).**

Refusals Encountered

- Photography
- Observe compounding
- Sales or shipping records

Inspectional Outcome

- Initial inspection following outsourcer registration
  - 483 issued
  - FDA requested recall
  - Firm voluntary recall
  - Re-inspection

Post Inspection

- FDA Form 483 is issued at close of a violative inspection
- Documentation and evidence is prepared
- Establishment inspection report (EIR) is written
- Review and discussion between Office of Regulatory Affairs (ORA), Center for Drug Evaluation and Research (CDER) and Office of Chief Counsel (OCC) regarding potential charges, actions, and next steps

Future

- Industry Trends
- Protecting Public Health